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Sarcopenia in Systemic Sclerosis: Prevalence and Impact - A Systematic Review and Meta-analysis

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Sarcopenia in Systemic Sclerosis: Prevalence and Impact - A Systematic Review and Meta-analysis

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Abstract

Objective This review aims to provide an estimate of sarcopenia prevalence and its impact on clinical characteristics in patients with systemic sclerosis (SSc).

Design Systematic review and meta-analysis

Methods We systemically searched Embase, Medline, Web of Science, and the Cochrane Central Register of Controlled Trials from inception to May 24, 2023. Observational studies that reported the prevalence of sarcopenia in patients with SSc were included. Clinical characteristics from studies that compared SSc patients with and without sarcopenia were analyzed and expressed as mean difference (MD) or standardized mean difference (SMD) with a 95% confidence interval (CI).

Results A total of 4583 articles were screened and 9 studies with data from 815 patients were included in the analysis (8 cross-sectional studies and 1 retrospective cohort study). The overall prevalence of sarcopenia in SSc patients was 22% (95% CI 17%-28%). SSc patients with sarcopenia had a poorer quality of life (MD -12.02; 95% CI -19.11 to -4.93) and higher CRP levels (SMD 0.67; 95% CI 0.35 to 1.00).

Conclusions Our study conducted a comprehensive analysis and determined a notable prevalence of sarcopenia in patients diagnosed with SSc. SSc patients with sarcopenia had a worse quality of life and higher CRP levels, based on our findings. Given the detrimental impact of sarcopenia on quality of life, future efforts aimed at early identification of sarcopenia in the clinical assessment of patients with SSc may have significance.

PROSPERO registration number CRD42022368326

Keywords Sarcopenia; Systemic sclerosis; Meta-analysis; Prevalence

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to evaluate the prevalence and impact of sarcopenia in patients with systemic sclerosis.
- We conducted a comprehensive literature search to ensure that all eligible studies were included in the analysis.
- We could not establish a definitive causal relationship between sarcopenia and systemic sclerosis.
- Even though this review included studies from different continents (European, South America, and Asia), data on participant race were not accessible, limiting its potential applicability to specific patient subgroups.

Introduction

Systemic sclerosis (SSc) is a rare immune-mediated rheumatic disease that is characterized by inflammation, microvascular damage, and progressive fibrosis of both the skin and internal organs, such as the gastrointestinal tract, lung, heart, and kidney.[1,2] Depending on the extent of cutaneous involvement, SSc can be classified as limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc).[3] Patients with SSc are at risk for body composition abnormalities, including loss of skeletal muscle mass, due to malnutrition resulting from gastrointestinal involvement, chronic inflammation, and steroid therapy.[4–7] In addition, heart, lung, and joint involvement in SSc patients can lead to impaired exercise ability and decreased physical activity.[8] These factors are closely related to sarcopenia, which is an age-related disease characterized by progressive and generalized loss of skeletal muscle mass and strength.[9] The coexistence of sarcopenia and SSc can exacerbate the patient's health issues and increase their healthcare costs, posing significant challenges for healthcare professionals.

According to a meta-analysis, the prevalence of sarcopenia in community-dwelling elders aged over 60 years was 11% (95% CI: 8-13%) in men and 9% (95% CI: 7-11%) in women.[10] The presence of sarcopenia increases the risk of falling, functional decline, frailty, and mortality, leading to poor quality of life and significant healthcare expenses.[11] The high prevalence of sarcopenia in older adults, combined with its detrimental consequences, warrants the need for effective prevention and management strategies. In SSc patients, addressing sarcopenia may improve their functional status and overall health outcomes, highlighting the importance of early screening and intervention. Healthcare professionals need to recognize the interplay between SSc and sarcopenia to provide optimal care for these patients.

In recent years, the presence of sarcopenia in SSc has garnered attention in several studies.[4–7,12–16] The documented prevalence of sarcopenia in SSc varies widely from 10.7% to 42% among different studies, which can be attributed to several factors.[4,5] Differences in diagnostic criteria and assessment methods utilized in various studies, such as those proposed by the European Working Group of Sarcopenia in Older People (EWGSOP)[17,18] and the Asian Working Group for Sarcopenia (AWGS),[19] can result in variations in the evaluation of muscle mass in patients. Furthermore, the influence of sarcopenia on the clinical features of SSc patients has been a topic of debate. For instance, Caimmi et al.[12] suggested that individuals with SSc and sarcopenia had a longer duration of disease; the longer disease duration means that patients live longer with the disease, while Siegert et al.[6] contradicted this claim and found no difference between sarcopenia and disease duration in SSc patients.

Currently, no comprehensive systematic review or meta-analysis has examined sarcopenia in SSc. Therefore, we conducted a systematic review and meta-analysis to identify the diagnostic criteria for sarcopenia and evaluate the most reliable evidence on the prevalence of sarcopenia in SSc patients, as well as the effect of sarcopenia on the clinical features of SSc patients.

Methods

Data sources and search strategy

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline[20] and registered in PROSPERO (CRD42022368326). We systemically searched four electronic databases, including Embase, Medline, Web of Science, and the Cochrane Central Register of Controlled Trials, to identify all relevant articles relating to sarcopenia and SSc, without language

restrictions. Our search encompassed all records published from inception to May 24, 2023, utilizing the following terms: 'systemic sclerosis', 'scleroderm*', 'SSc', 'muscular atrophy', 'sarcopen*' and 'myopen*' (Supporting Information, Table S1-4). Additionally, we conducted a manual search of the reference lists of the included articles to identify potential studies that may have been overlooked by the principal search.

Inclusion and exclusion criteria

The following inclusion and exclusion criteria were employed for this systematic review and meta-analysis: (1) studies conducted exclusively on adult patients (age >18 years) diagnosed with SSc; (2) studies reporting the prevalence of sarcopenia in SSc patients; (3) studies defining sarcopenia as low muscle mass (LMM) plus low muscle strength (LMS), and/or low physical performance (LPP), or LMM alone; (4) studies measuring lean mass or muscle mass using one of the four main techniques: dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), magnetic resonance imaging (MRI) and computed tomography (CT); and (5) observational studies. Conversely, the exclusion criteria were as follows: (1) repeated studies (defined as either identical data or identical articles); (2) animal studies, case reports, reviews, editorials, comments, and letters.

Outcomes

The main outcomes of this systematic review comprise two aspects: firstly, the prevalence of sarcopenia among patients with SSc, and secondly, the clinical features of patients with SSc who suffer from sarcopenia compared to those who do not. These clinical features encompassed a range of factors, namely, the duration of disease, the quality of life assessed by the Short Form-36 (SF-36) survey[21], the pulmonary function (the forced vital capacity (FVC)

predicted value), and the C-relative protein level.

Study selection and data extraction

After removing duplicates, the studies identified through the search strategy underwent eligibility assessment by two reviewers (X.T. and T.L.), who independently screened the titles and abstracts and assigned them to one of three categories: 'include,' 'exclude,' or 'maybe.' Subsequently, the full-text articles of those categorized as 'include' or 'maybe' were reviewed to arrive at a final selection, with any discrepancies between the reviewers resolved by a third reviewer (J.Y.). Two reviewers (X.T. and X.S.) independently extracted the following variables using a pre-defined data collection form: first author, publication year, country, study design, sample size, mean age, number of females, disease subtype, mean disease duration, SSc diagnostic criteria, sarcopenia diagnostic criteria, assessment method for detecting sarcopenia, and prevalence of sarcopenia. Additionally, we also collected data on clinical features in the form of mean ± standard deviation (SD). For those studies that were not expressed as mean ± SD, we performed data conversion with the method recommended by Luo et al.[22] and Wan et al.[23]

Assessment of quality

Two authors (X.T. and T.J.) independently assessed the quality of the included studies using the Agency for Healthcare Research and Quality (AHRQ)[24] scale in cross-sectional studies. This tool consists of 11 questions, with a 'no' or 'unclear' receiving 0 points and a 'yes' receiving 1 point. Low-quality articles received scores of 0–3, moderate-quality scores of 4–7, and high-quality scores of 8–11. The Newcastle–Ottawa Scale (NOS) was used to judge the quality of the cohort study.[25] The NOS scoring system assigns points from 0 to 9. We assigned values

ranging from 0 to 3, 4 to 6, and 7 to 9 for low, moderate, and high-quality, accordingly. Any discrepancies were resolved through discussion or consensus with a third author (J.Y.).

Statistical Analysis

The prevalence of sarcopenia in SSc patients was determined by calculating the proportion of patients with sarcopenia in each study and conducting a meta-analysis of single proportions. We performed this meta-analysis using Stata/SE (Version 12.0, StataCorp, Texas, USA). Forest plots were used to illustrate the prevalence of sarcopenia, along with corresponding 95% confidence intervals (CIs) for each study and the overall estimate. Clinical characteristics such as disease duration, the SF-36 value, the FVC predicted value, and the CRP level from studies that compared SSc patients with and without sarcopenia were also analyzed using Review Manager (Version 5.4, The Cochrane Collaboration, Oxford, UK) and expressed as mean difference (MD) or standardized mean difference (SMD) with 95% CI. Heterogeneity across studies was assessed via the I^2 statistic, with values of 25% being considered low, 50% moderate, and 75% high.[26] If $I^2 > 50\%$, a random-effects model was employed.

Subgroup analyses were conducted to investigate potential sources of heterogeneity, focusing on sarcopenia definition (1 vs >1 diagnostic criteria), disease subtype, and mean age (< 60 vs ≥60 years). Meta-regressions were also conducted on sample size, mean age, percentage of female patients, and duration of SSc. However, due to limited data on the clinical characteristics of SSc patients with and without sarcopenia, subgroup analyses and meta-regressions were not conducted. To evaluate the stability of pooled results, sensitivity analysis was performed by excluding one study at a time. Publication bias was evaluated using Egger's test[27]. Statistical significance was set at $P < 0.05$ for all analyses.

Patient and public involvement

None.

Results

Search results

A comprehensive search of databases yielded 4583 articles. After eliminating duplicates (n = 1523), the remaining 3060 titles and abstracts were screened. Subsequently, 25 relevant articles underwent full-text reading, and 16 were excluded for reasons specified in the flow chart and Table S5 in the supplement. Ultimately, 9 studies were eligible for inclusion in this meta-analysis (Figure 1).

Study characteristics

Table 1 provides an overview of the characteristics of the studies included in this meta-analysis. A total of 815 SSc patients from 9 eligible studies[4–7,12–16] published between 2018 and 2022 were included. The mean age of the patients ranged from 52.5 to 64.1 years, while the mean duration of SSc ranged from 6 to 12.8 years. The majority of the studies (8 out of 9) had a cross-sectional design,[4–6,12–16] with one being a retrospective cohort study.[7] The studies were conducted in various regions, with five from Europe,[5–7,12,16] two from South America,[13,15] and two from Asia.[4,14]

Risk of bias

According to the AHRQ and NOS ratings, 8 of the eligible studies[4–7,12,14–16] were of moderate quality, with only one article[13] classified as high quality. (Table S7-8 in the supplement).

Methods used to assess sarcopenia

Table 1 provides an overview of the diagnostic criteria used to evaluate sarcopenia across the

included studies. Among them, seven studies[4–7,13,15,16] employed EWGSOP criteria (5 EWGSOP2010 and 2 EWGSOP2019) while one[14] used AWGS criteria. Three studies[5,7,12] solely relied on LMM for sarcopenia diagnosis, while six studies[4,6,13–16] utilized LMM combined with LMS and/or LPP. The sarcopenia diagnostic criteria and cutoff values in the studies are summarized in Table 2. Muscle mass was measured using dual-energy X-ray absorptiometry in seven studies[5,7,12–16] and bioelectrical impedance analysis in two studies[4,6]. Handgrip dynamometry was utilized to assess muscle strength in six studies[4,6,13–16], while gait speed (three studies[14–16]) and the short physical performance battery (SPPB) (two studies[13,16]) were used to evaluate physical performance.

Sarcopenia prevalence

Overall sarcopenia prevalence

The nine studies included in this review reported the prevalence of sarcopenia in SSc patients, ranging from 10.7% to 42% (Table 1). The pooled prevalence of sarcopenia in patients with SSc was estimated at 22% (95% CI 17%-28%), as shown in Figure 2.

Subgroup analysis of sarcopenia prevalence

The prevalence of sarcopenia differed in studies that utilized a single criterion [LMM; 28% (95% CI 16%-42%)] versus those that employed >1 criterion [LMM + LMS and/or LPP; 20% (95% CI 15%-25%)], with no statistically significant difference noted (P = 0.234, Figure S1 in the supplement). Subgroup analysis based on disease subtype revealed that sarcopenia prevalence in dcSSc [30% (95% CI 23%-37%)] was higher than that in lcSSc [23% (95% CI 12%-36%)], and the difference was not statistically significant (P = 0.339, Figure S2 in the supplement). The United Nations defines an older person as someone above the age of 60. Therefore, we

also performed a subgroup analysis stratified by the mean age of the participants, with < 60 and ≥ 60 years as the cutoff points. The prevalence of sarcopenia was lower in patients younger than 60 years [20% (95% CI 12%-29%)] vs those older than 60 years [24% (95% CI 17%-32%)], but the difference was not of statistical significance (P = 0.539, Figure S3 in the supplement).

Meta-regression analyses

The results of the meta-regression analyses indicated that there was no significant association between the prevalence of sarcopenia and sample size (P = 0.424), mean age of patients (P = 0.532), the proportion of female patients (P = 0.449), or duration of SSc (P = 0.255). These findings are summarized in Table S6 of the supplementary material.

Impact of sarcopenia on the clinical characteristics of SSc patients

Duration of SSc

Data from a total of four studies comprising 511 patients were included in the meta-analysis of SSc duration, which revealed that individuals with sarcopenia did not have a longer disease duration than those without sarcopenia [MD 2.97 (95% CI -0.13 to 6.08); I^2 = 90%, Figure 3A].

Quality of life

The meta-analysis included two studies with a total of 191 patients, which provided data on the SF-36 value. The findings of the meta-analysis indicated that patients with sarcopenia had a lower SF-36 value compared to those without sarcopenia [MD -12.02 (95% CI -19.11 to -4.93); I^2 = 71%, Figure 3B], that is, having sarcopenia was associated with poorer quality of life compared with those without sarcopenia.

Pulmonary function

The meta-analysis incorporated two studies involving a total of 320 patients that reported data on the FVC predicted value. The results indicated that patients with sarcopenia did not have a lower FVC predicted value than those without sarcopenia [MD -4.02 (95% CI -8.67 to 0.62); I^2 = 0%, Figure 3C]. Therefore, there was no significant difference in pulmonary function between sarcopenia and non-sarcopenia patients.

CRP level

Data from two studies comprising 191 patients were analyzed to investigate the relationship between sarcopenia and CRP level. The results showed that sarcopenia was associated with a higher CRP level than no sarcopenia [SMD 0.67 (95% CI 0.35 to 1.00); I^2 = 0%, Figure 3D].

Sensitivity and publication bias analysis

The sensitivity analysis revealed that the overall prevalence of sarcopenia was not significantly affected by any individual study (Figure S4 in the supplementary material). In addition, Egger's test suggested no publication bias in this review (P = 0.311, Figure S5 in the supplement).

Discussion

Primary results

In this meta-analysis encompassing nine studies, the pooled prevalence of sarcopenia among 815 patients diagnosed with systemic sclerosis (SSc) was estimated to be 22%, which was significantly greater than that in community-dwelling older adults.[28] Notably, SSc patients diagnosed with sarcopenia had poorer quality of life and a higher CRP level, while no significant difference was noted for disease duration and FVC predicted value when compared to patients without sarcopenia.

Mechanism basis

Sarcopenia, a condition characterized by loss of muscle mass and function, can be age-associated (primary sarcopenia) or secondary to chronic diseases, including malignant tumors and musculoskeletal diseases.[29–31] Compared with other chronic inflammatory rheumatic diseases, sarcopenia has not been extensively evaluated in SSc. Recently, some studies have focused on the presence of sarcopenia in SSc. Nevertheless, the pathogenesis of sarcopenia in SSc remains unclear. Possible mechanisms contributing to the development of sarcopenia in SSc include (1) malnutrition: gastrointestinal involvement is the most frequent internal complication of SSc[32]. Symptoms such as esophageal reflux, early satiety, nausea, and vomiting may lead to reduced caloric intake.[12] Additionally, fibrosis of the bowel wall and small intestine bacterial overgrowth can result in malabsorption of nutrients. Therefore, malnutrition is prevalent in SSc patients. One study in community-dwelling older adults demonstrated that malnutrition is an independent predictor of sarcopenia (OR: 2.42; 95% CI 1.04-5.60)[33]. (2) Oxidative stress and chronic inflammation: oxidative stress, which is an imbalance in oxidant and antioxidant levels, is commonly observed in SSc patients[34]. Increased oxidative stress disrupts the balance between the degradation and resynthesis of skeletal muscle proteins[35]. In addition, chronic low-grade inflammation is detrimental to skeletal muscle in humans[36]. Inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, have been reported to contribute to the pathogenesis of SSc[37]. These cytokines stimulate protein catabolism and suppress muscle synthesis, ultimately leading to muscle wasting[38]. (3) Physical inactivity: due to pain and joint involvement, physical inactivity is common in SSc patients[39], leading to faster and greater muscle loss[40]. However, the mechanism of sarcopenia in SSc patients remains to be confirmed by future research.

Interpretation of the results

This review offers unique insight into sarcopenia in patients with SSc. It describes the prevalence of sarcopenia in SSc patients and how it is impacted by the different definitions of sarcopenia. The varying prevalence of sarcopenia may be explained in part by the variety of definitions. However, there was no statistical difference between 1 and >1 diagnostic criteria. This might be due to the lack of robustness of the combined results as a result of the small number of studies using one diagnostic criterion. In addition, discrepancies in sarcopenia diagnostic cutoffs among the included studies may have resulted in differing sarcopenia prevalence. Furthermore, our meta-analysis indicated no statistically significant variation in the prevalence of sarcopenia between disease subtypes, which is consistent with the results of Sangaroon et al.[14] It is important to note that this conclusion needs to be interpreted with caution due to the limited number of studies that could be included in the analysis. Although sarcopenia commonly occurs as an age-related process in older individuals[41], it becomes more common as people get older. Our meta-analysis demonstrated that the difference in the prevalence of sarcopenia was not statistically significant between the patients over 60 years old and the patients under 60 years old. Furthermore, patients younger than 60 years old all used >1 criterion to diagnose sarcopenia, which makes the prevalence of sarcopenia in young people even lower. This suggests that, despite the influence of age on the presence of sarcopenia, the illness itself is responsible for sarcopenia onset and progression in SSc patients. Therefore, rheumatologists should screen for sarcopenia even in young SSc patients. However, this conclusion must be confirmed by a large number of high-quality clinical studies.

Our meta-analysis also revealed that SSc patients diagnosed with sarcopenia had poorer quality

of life. On the one hand, involvement of the heart, lungs, and joints in SSc patients might result in diminished exercise capacity and decreased physical activity,[8] making SSc patients vulnerable to sarcopenia. On the other hand, sarcopenia is associated with a variety of negative outcomes, including hospitalization, functional decline, falls, and death.[42,43] Therefore, it should come as no surprise that SSc patients with sarcopenia have a higher risk of having a worse quality of life. Furthermore, individuals with SSc who had sarcopenia had higher CRP levels, according to our findings. This result is not surprising given that chronic inflammation is a known contributor to secondary sarcopenia.[44] However, our review indicated that no significant difference was noted for disease duration or FVC predicted value between SSc patients with and without sarcopenia. According to the results of Caimmi et al,[12] the longer the disease duration, the greater the risk of sarcopenia. This might be due to the minimal number of studies that could extract data, resulting in false negatives in the pooled study results. Therefore, large prospective cohort studies are required to confirm this conclusion.

Clinical implications

This meta-analysis provides a comprehensive evaluation of the prevalence, diagnostic criteria, and impact of sarcopenia in SSc patients, which has not been previously done. The results of this study provide an up-to-date estimation of the prevalence of sarcopenia, which can guide sample size calculations for future research. While sarcopenia has been relatively under-studied in SSc compared to other rheumatic diseases, our findings suggested that neither sarcopenia definition, disease subtype nor age affects the prevalence of sarcopenia. SSc patients with sarcopenia had poorer quality of life, according to our findings. Therefore, early identification and intervention of sarcopenic patients by clinicians is crucial. The high prevalence of

sarcopenia in SSc patients highlights the importance of early screening and management. Standardized criteria for sarcopenia diagnosis are also essential in SSc patients to minimize variations in prevalence. These findings have important implications for future research, clinical practice, and policy development in managing sarcopenia in SSc patients, and can potentially improve outcomes for these patients.

Strengths and weaknesses

This systematic review undertook a comprehensive and meticulous literature search to ensure that all pertinent studies were included in the analysis. The selection of studies, data extraction, and quality assessments were carried out independently by two reviewers, thereby enhancing the accuracy and reliability of the results. Subgroup analyses and meta-regression analyses were also conducted to explore the possible sources of heterogeneity, while sensitivity and publication bias analyses were performed to ensure robust and dependable conclusions.

Nevertheless, we must acknowledge certain limitations of our study. Firstly, since most of the included studies were cross-sectional, it is impossible to establish a definitive causal relationship between sarcopenia and SSc. Nonetheless, this is a limitation inherent to the original literature and beyond our control. We, therefore, look forward to high-quality prospective cohort studies to provide more conclusive evidence on this matter. Secondly, there was some heterogeneity among the included studies in terms of factors such as the definition of sarcopenia, measurement approaches, and diagnostic cut-offs. Moreover, most of the studies had small sample sizes. Therefore, future studies should aim to use uniform diagnostic criteria for sarcopenia and expand the sample size to improve the quality of research. Finally, even though this review included studies from different continents (European, South America, and

Asia), data on participant race were not accessible, limiting its potential applicability to specific patient subgroups.

Conclusions

Our study conducted a comprehensive analysis and determined a notable prevalence of sarcopenia in patients diagnosed with SSc. SSc patients with sarcopenia had a worse quality of life and higher CRP levels, based on our findings. Given the detrimental impact of sarcopenia on quality of life, future efforts aimed at early identification of sarcopenia in the clinical assessment of patients with SSc may have significance.

Contributors

All authors conceived and designed this review; YJ, XPT, and JRY developed the search strategy; XPT and TPL screened studies; XPT and XYS extracted data; XPT and TTJ appraised study quality; XPT and NG conducted data analysis; XPT drafted the manuscript; all authors revised the manuscript for important intellectual content. JRY had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not required.

Ethics approval

Not applicable.

Data availability statement

The data are accessible upon reasonable request from the corresponding author.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table 1 Characteristics of the included studies

First author and year	Country	Study design	Sample size	Mean age(years)	Female, n	Disease subtype	Disease duration (years)	SSc diagnostic criteria	Sarcopenia diagnostic criteria	Criteria (assessment method of detecting sarcopenia)	Prevalence of sarcopenia	
											Total,n(%)	Diffuse,n(%)
Caimmi (2018)[12]	Italy	Cross-sectional study	140	64	118	limited 97 diffuse 43	12.8	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA)	29(20.7%)	11(7.9%)
Siegert (2018)[6]	Germany	Cross-sectional study	129	60	118	-	7	2013 ACR/EULAR	EWGSOP (2010)	LMM (BIA) LMS (HGS)	29(22.5%)	-
Corallo (2019)[5]	Italy	Cross-sectional study	62	62	54	limited 50 diffuse 12	8	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA)	26(42%)	4(6.4%)
Rincon (2019)[15]	Argentina	Cross-sectional study	27	52.5	20	limited 16 diffuse 11	7.8	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA) LMS (HGS) LPP (4mGS)	9(33.3%)	3(11.1%)

First author and year	Country	Study design	Sample size	Mean age(years)	Female, n	Disease subtype	Disease duration (years)	SSc diagnostic criteria	Sarcopenia diagnostic criteria	Criteria (assessment method of detecting sarcopenia)	Prevalence of sarcopenia	
											Total,n(%)	Diffuse,n(%)
Paolino (2020)[7]	Italy	Retrospective cohort study	43	64.1	36	-	10.2	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA)	10(23.3%)	-
Hax (2021)[13]	Brazil	Cross-sectional study	94	60.5	87	-	12.5	2013 ACR/EULAR	EWGSOP (2019)	LMM (DXA) LMS (HGS) LPP (SPPB)	15(15.9%)	-
Sari (2021)[4]	Turkey	Cross-sectional study	93	52.6	86	-	10.7	1980ACR	EWGSOP (2010)	LMM (BIA) LMS (HGS)	10(10.7%)	-
Efremova (2022)[16]	Russia	Cross-sectional study	47	53.9	47	limited 29 diffuse 18	6	2013 ACR/EULAR	EWGSOP (2019)	LMM (DXA) LMS (HGS and Chair rising test)	10(21.3%)	6(12.8%)

First author and year	Country	Study design	Sample size	Mean age(years)	Female, n	Disease subtype	Disease duration (years)	SSc diagnostic criteria	Sarcopenia diagnostic criteria	Criteria (assessment method of detecting sarcopenia)	Prevalence of sarcopenia	
											Total,n(%)	Diffuse,n(%)
Sangaroon (2022)[14]	Thailand	Cross-sectional study	180	58.8	119	limited 86 diffuse 94	6.2	-	AWGS (2019)	LPP (GS and SPPB) LMM(DXA) LMS(HGS) LPP(GS)	41(22.8%)	30(16.7%)

ACR, American College of Rheumatology; EULAR, European League against Rheumatology classification criteria; SMI, Skeletal Muscle Mass Index; EWGSOP, European Working Group on Sarcopenia in Old People; HGS, hand grip strength; 4mGS, 4 m gait speed; SPPB, Short Physical Performance Battery; GS, gait speed; AWGS, Asian Working Group for Sarcopenia.

Table 2 Criteria and cutoff points used to detect sarcopenia in each study

First author and year	Sarcopenia diagnostic criteria	Cutoff points
Caimmi (2018)[12]	SMI	LMM: ASM/height2 < 7.26 kg/m^2 for men and < 5.50 kg/m^2 for women.[45]
Siegert (2018)[6]	EWGSOP (2010)	LMM: ALM/height2 < 7.26 kg/m2 for men and <5.50 kg/m2 for women.[45] LMS: BMI ≤ 24, HGS ≤ 29 kg; 24.1 ≤ BMI ≤ 26, HGS ≤ 30 kg; 26.1 ≤ BMI ≤ 28, HGS ≤ 30 kg; BMI > 28, HGS ≤ 32 kg for men. BMI ≤ 23, HGS ≤ 17 kg; 23.1 ≤ BMI ≤ 26, HGS ≤ 17.3 kg; 26.1 ≤ BMI ≤ 29, HGS ≤ 18 kg; BMI > 29, HGS ≤ 21 kg for women.[46]
Corallo (2019)[5]	EWGSOP (2010)	LMM: RSMI < 7.26 kg/m2 for men and < 5.50 kg/m2 for women.[45]
Rincon (2019)[15]	EWGSOP (2010)	LMM: RSMI < 7.26 kg/m2 for men and < 5.50 kg/m2 for women.[45] LMS: HGS< 30 kg for men and< 20 kg for women.[47] LPP: GS< 0.8 m/s (both genders).[47]
Paolino (2020)	EWGSOP (2010)	LMM: RSMI < 7.26 kg/m2 for men and < 5.50

First author and year	Sarcopenia diagnostic criteria	Cutoff points
[7]		kg/m2 for women.[45]
Hax (2021)	EWGSOP (2019)	LMM: ASMI < 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women.[48] LMS: HGS < 27 kg for men and < 16 kg for women.[49] LPP: SPPB ≤ 8 point score.[50]
Sari (2021)[4]	EWGSOP (2010)	LMM: ASMI < 7.26 kg/m2 for men and <5.50 kg/m2 for women.[45] LMS: BMI ≤ 24, HGS ≤ 29 kg; 24.1 ≤ BMI ≤ 26, HGS ≤ 30 kg; 26.1 ≤ BMI ≤ 28, HGS ≤ 30 kg; BMI > 28, HGS ≤ 32 kg for men. BMI ≤ 23, HGS ≤ 17 kg; 23.1 ≤ BMI ≤ 26, HGS ≤ 17.3 kg; 26.1 ≤ BMI ≤ 29, HGS ≤ 18 kg; BMI > 29, HGS ≤ 21 kg for women.[46]
Efremova (2022)[16]	EWGSOP (2019)	LMM: ASMI < 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women.[48] LMS: HGS < 27 kg for men and < 16 kg for women.[49] or Chair stand > 15 s for five rises.[51]

First author and year	Sarcopenia diagnostic criteria	Cutoff points
		LPP: GS ≤ 0.8 m/s.[52] or SPPB ≤ 8 point score.[50]
Sangaroon (2022)[14]	AWGS (2019)	LMM: ASMI < 7.0 kg/m^2 for men and < 5.4 kg/m^2 for women.[53] LMS: HGS < 28 kg for men and < 18 kg for women.[53] LPP: GS< 1 m/s (both genders).[53]

SMI, Skeletal Muscle Mass Index; ASM, appendicular skeletal muscle mass; ALM, appendicular lean mass; RSMI, Relative Skeletal Muscle Mass Index; ASMI, Appendicular Skeleton Muscle Index; SPPB, Short Physical Performance Battery; GS, gait speed.

Figure 1 The flow chart of the literature selection

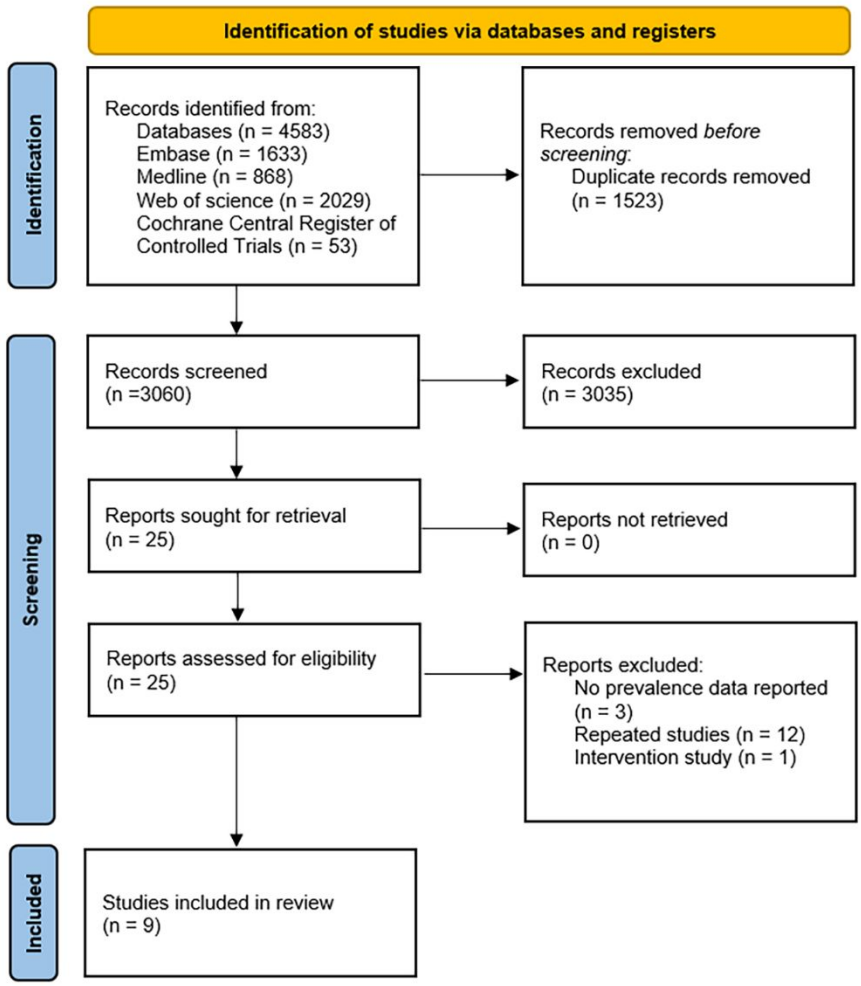
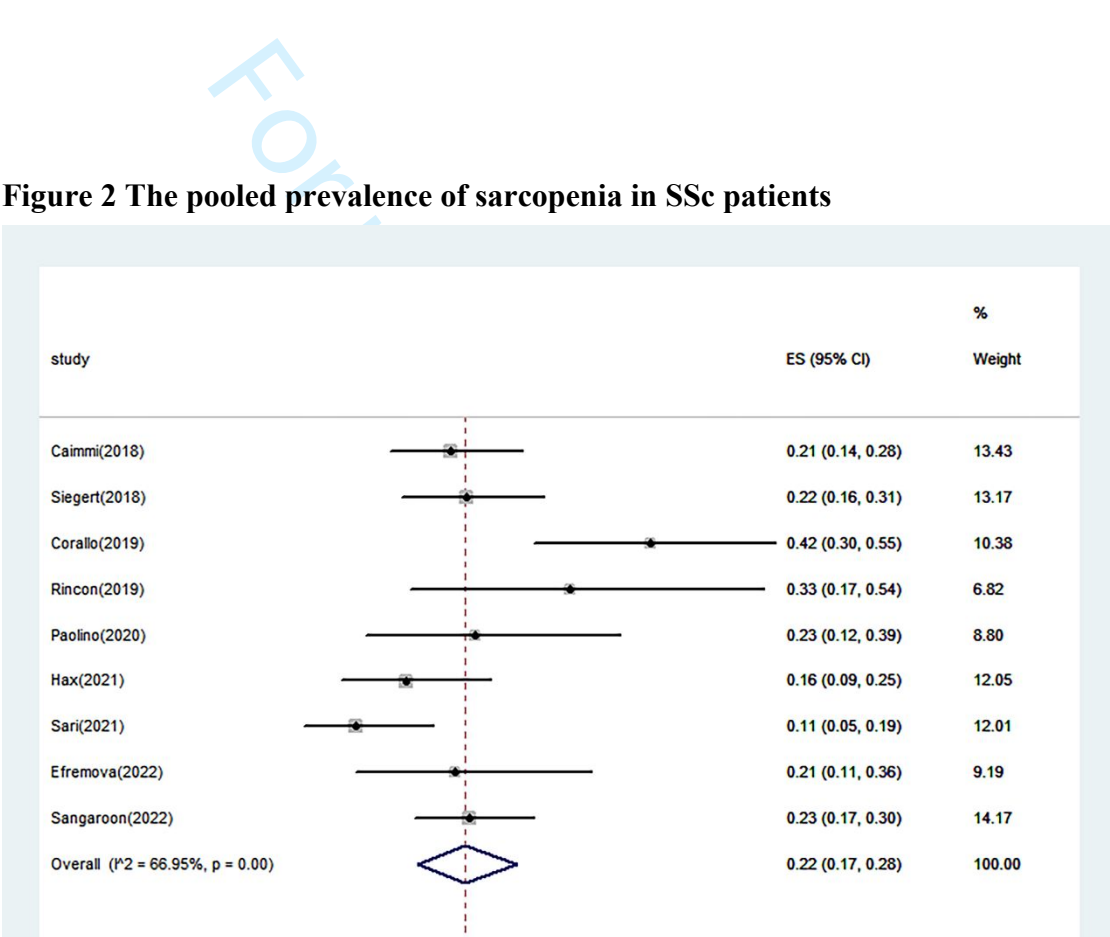


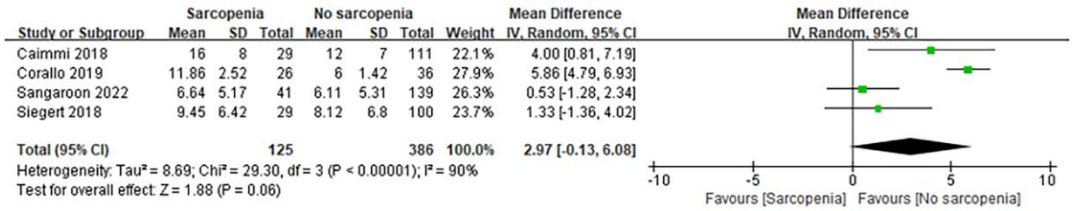
Figure 2 The pooled prevalence of sarcopenia in SSc patients



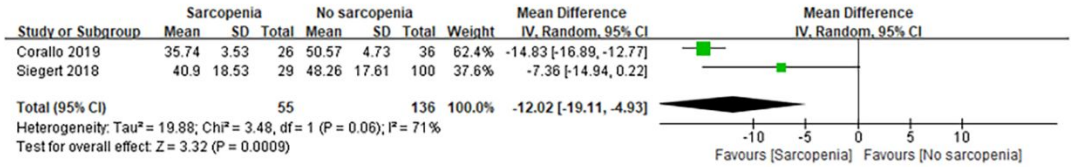
CI, confidence interval; ES, effect size (prevalence %); I^2, I^2 heterogeneity statistic. Random effects model used for analysis.

Figure 3 Impact of sarcopenia on clinical characteristics in patients with SSc

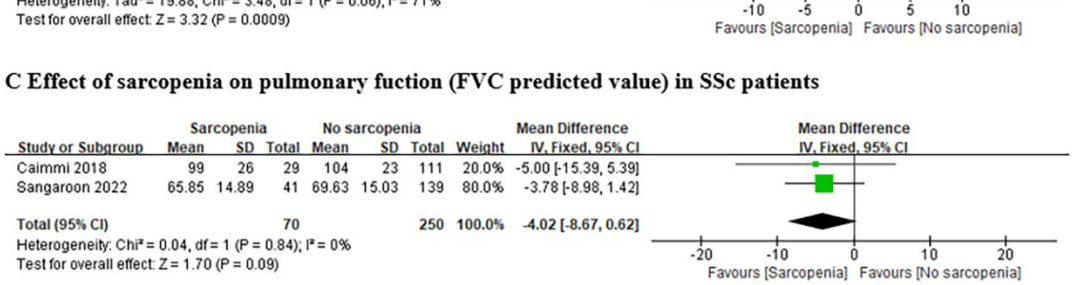
A Effect of sarcopenia on disease duration (years) of SSc patients



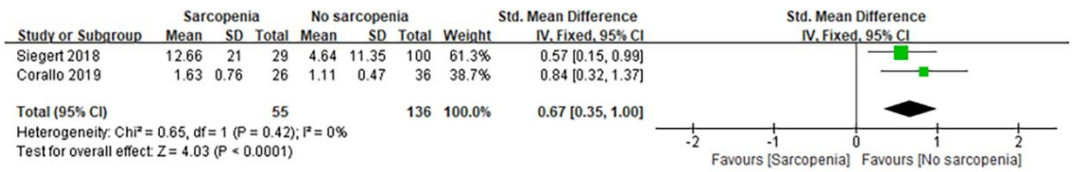
B Effect of sarcopenia on quality of life (SF-36 value) in SSc patients



C Effect of sarcopenia on pulmonary fuction (FVC predicted value) in SSc patients



D Effect of sarcopenia on CRP in SSc patients



Sarcopenia in Systemic Sclerosis: Prevalence and Impact - A Systematic Review and Meta-analysis

1. Table S1 Search strategy by Medline via Ovid SP
2. Table S2 Search strategy by Embase via Ovid SP
3. Table S3 Search strategy by Web of Science
4. Table S4 Search strategy by Cochrane Central Register of Controlled Trials via Ovid SP
5. Table S5 The reasons for the exclusion of full-text articles
6. Table S6 Meta-regression analyses of sarcopenia prevalence
7. Table S7 ARHQ Methodology Checklist for Cross-Sectional Study
8. Table S8 Newcastle-Ottawa Scale for Cohort study
9. Figure S1 Prevalence of sarcopenia by criteria
10. Figure S2 Prevalence of sarcopenia by disease subtype
11. Figure S3 Prevalence of sarcopenia by mean age
12. Figure S4 Sensitivity analysis
13. Figure S5 Egger's test for publication bias

Table S1 Search strategy by Medline via Ovid SP

1.	exp Scleroderma, Systemic/
2.	((Systemic or general* or diffus* or progress* or Limit*) adj3 sclerosis).mp.
3.	scleroderm*.tw.
4.	SSc.tw.
5.	1 or 2 or 3 or 4
6.	exp muscular atrophy/
7.	(sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat*).mp.
8.	((muscle or muscular) adj5 (atroph* or wast* or weak* or loss* or mass or degenerat*)).ti,ab.
9.	6 or 7 or 8
10.	5 and 9
11.	exp animals/ not humans.sh.
12.	10 not 11

Table S2 Search strategy by Embase via Ovid SP

1. exp systemic sclerosis/
2. ((Systemic or general* or diffus* or progress* or Limit*) adj3 sclerosis).mp.
3. scleroderm*.tw.
4. SSc.tw.
5. 1 or 2 or 3 or 4
6. exp muscle atrophy/
7. (sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat*).mp.
8. ((muscle or muscular) adj5 (atroph* or wast* or weak* or loss* or mass or degenerat*)).ti,ab.
9. 6 or 7 or 8
10. 5 and 9
11. exp animal/
12. human/
13. 11 not 12
14. 10 not 13

Table S3 Search strategy by Web of Science

Topic= (((Systemic or general* or diffus* or progress* or Limit*) near/3 sclerosis) or sclerodem or ssc) and (sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat* or ((muscle or muscular) near/5 (atroph* or wast* or weak* or loss* or mass or degenerat*)))

Table S4 Search strategy by Cochrane Central Register of Controlled Trials via Ovid SP

1.	exp Scleroderma, Systemic/
2.	((Systemic or general* or diffus* or progress* or Limit*) adj3 sclerosis).mp.
3.	scleroderm*.tw.
4.	SSc.tw.
5.	1 or 2 or 3 or 4
6.	exp muscular atrophy/
7.	(sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat*).mp.
8.	((muscle or muscular) adj5 (atroph* or wast* or weak* or loss* or mass or degenerat*)).ti,ab.
9.	6 or 7 or 8
10.	5 and 9

Table S5 The reasons for the exclusion of full-text articles

Study	Reason for the exclusion
Norman (2014)	Repeated study
Siegert (2014)	Repeated study
Caimmi (2017)	Repeated study
March (2017)	Repeated study
Doerfler (2017)	Intervention study
Paolino (2018)	Repeated study
Radic (2018)	Not reported sarcopenia prevalence data in SSc patients
Remolina (2019)	Repeated study
Sari (2019)	Repeated study
Veronica (2019)	Repeated study
Hax (2020)	Repeated study
Santo (2020)	Repeated study
Sangaroon (2020)	Repeated study
Peterson (2020)	Not reported sarcopenia prevalence data in SSc patients
Efremova (2021)	Repeated study
Sorokina (2022)	Not reported sarcopenia prevalence data in SSc patients

Table S6 Meta-regression analyses of sarcopenia prevalence

Variables	Coefficient	SE	P value	CI-Lower	CI-Upper
Sample size	-0.0022	0.0026	0.424	-0.0083	0.0039
Average age	0.0210	0.0319	0.532	-0.0545	0.0965
Proportion of female	-1.0603	1.3233	0.449	-4.1893	2.0687
Duration of SSc	-0.0606	0.0488	0.255	-0.1760	0.0549

Table S7 ARHQ Methodology Checklist for Cross-Sectional Study

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total Score
Caimmi (2018)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	Unclear	Yes	No	6
Siegert (2018)	Yes	Yes	Unclear	Yes	Unclear	Yes	No	No	No	Yes	No	5
Corallo (2019)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	No	Yes	No	6
Rincon (2019)	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	No	No	Yes	No	4
Hax (2021)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	Yes	No	8

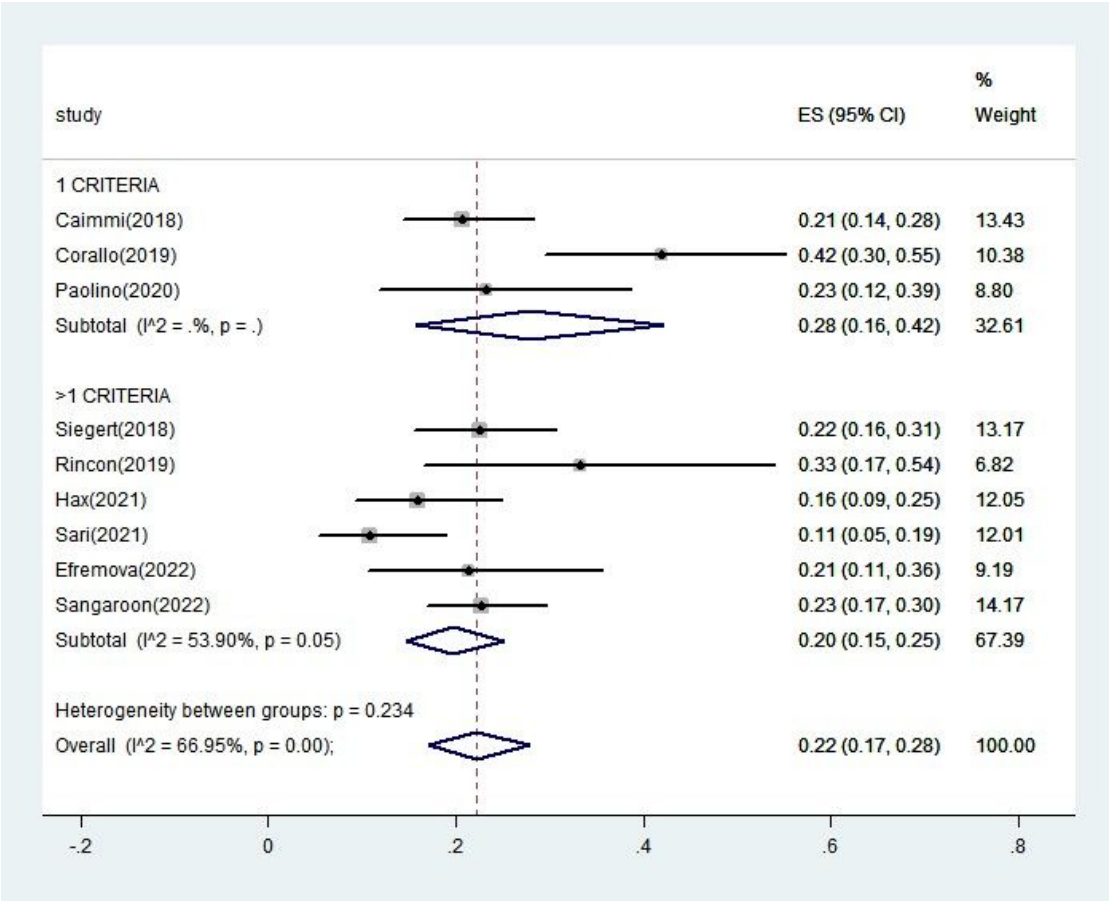
Sari (2021)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	No	Yes	No	6
Efremova (2022)	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No	No	No	Yes	No	3
Sangaroon (2022)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	No	Yes	No	6

Item 1. Define the source of information (survey, record review)
Item 2. List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications
Item 3. Indicate time period used for identifying patients
Item 4. Indicate whether or not subjects were consecutive if not population-based
Item 5. Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants
Item 6. Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)
Item 7. Explain any patient exclusions from analysis
Item 8. Describe how confounding was assessed and/or controlled
Item 9. If applicable, explain how missing data were handled in the analysis
Item 10. Summarize patient response rates and completeness of data collection
Item 11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained

Table S8 Newcastle-Ottawa Scale for Cohort study

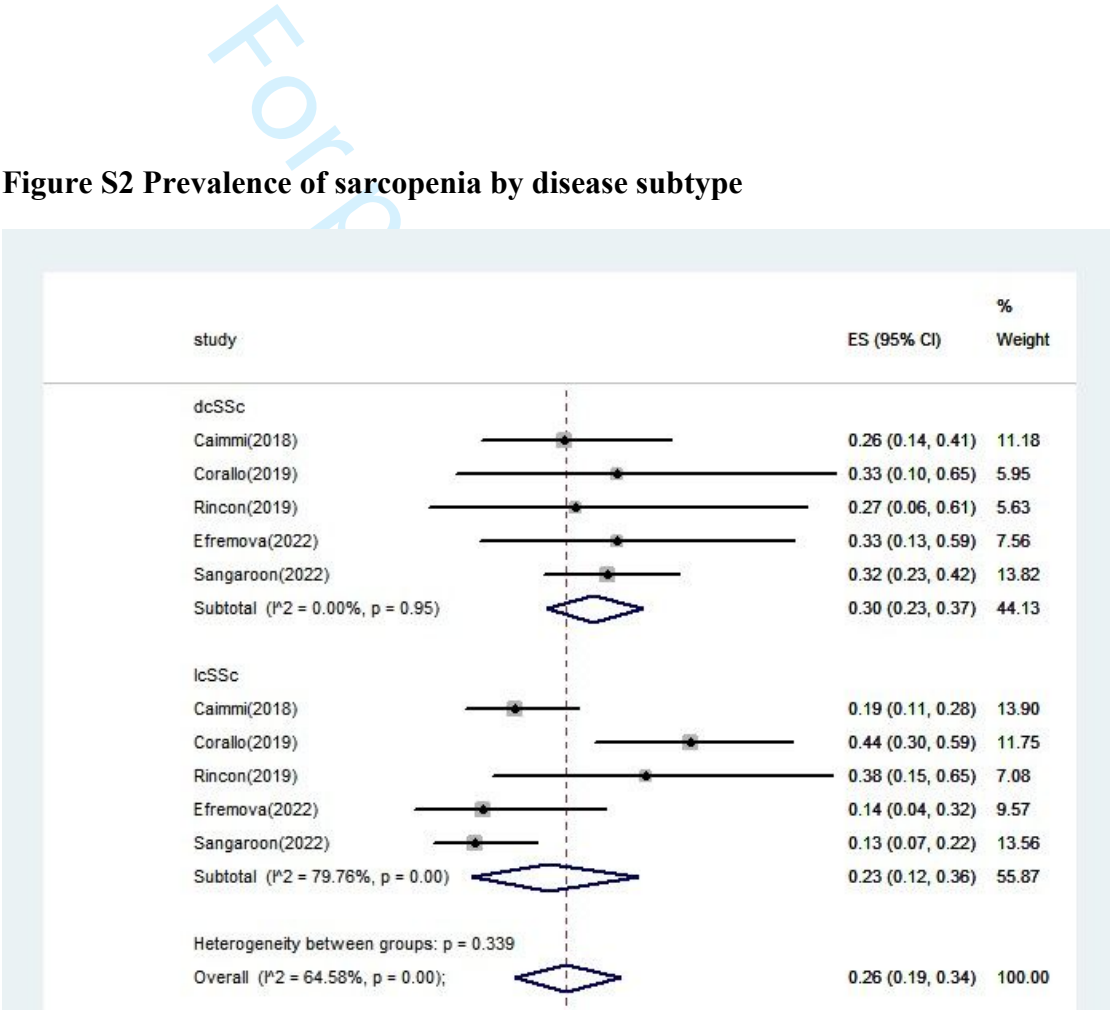
Study	Selection				Comparability	Outcome			Total Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Paolino (2020)	0	1	1	0	1	1	0	0	4

Figure S1 Prevalence of sarcopenia by criteria



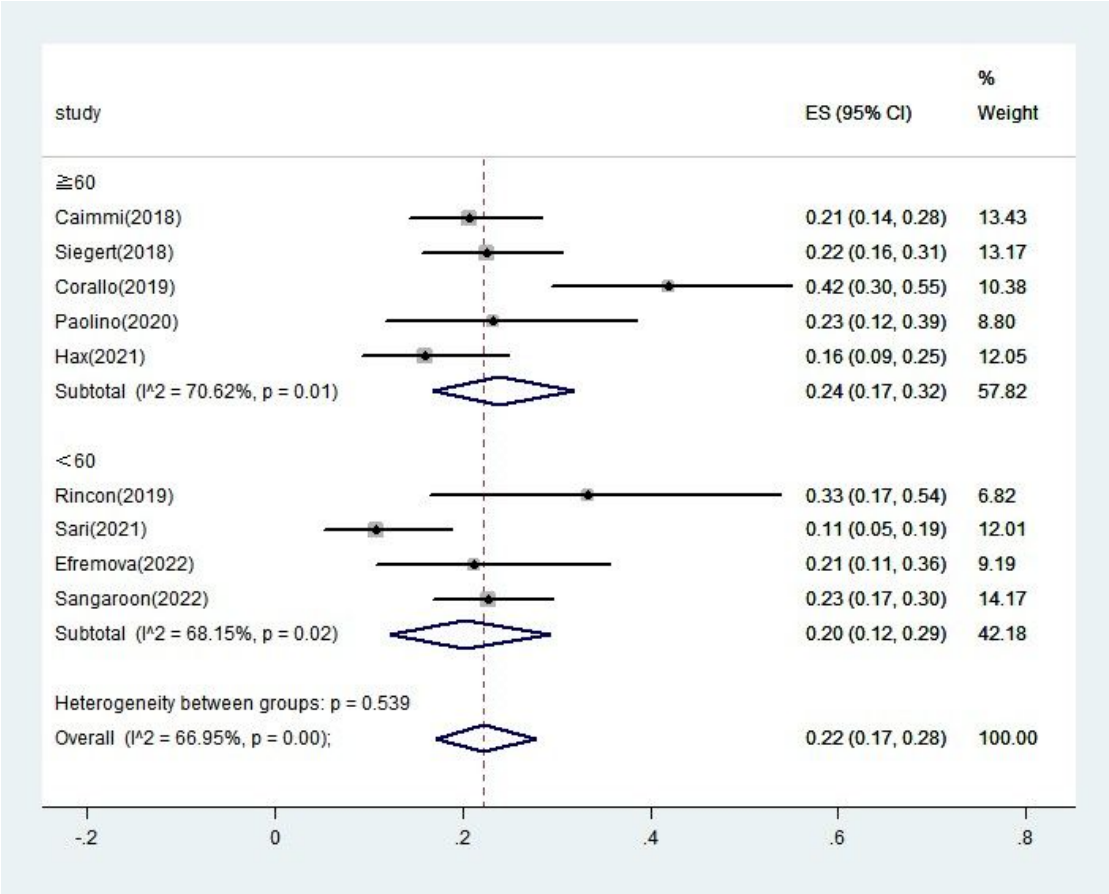
ES = effect size (prevalence); I^2 = I^2 heterogeneity statistic. A random effects model was used for analysis, and there was no significant difference between subgroups (P = 0.234).

Figure S2 Prevalence of sarcopenia by disease subtype



ES = effect size (prevalence); I^2 = I^2 heterogeneity statistic. The random effects model was used for the analysis, and there was no significant difference between the subgroups (P = 0.339).

Figure S3 Prevalence of sarcopenia by mean age



ES = effect size (prevalence); I^2 = I^2 heterogeneity statistic. The random effects model was used for the analysis, and there was no significant difference between the subgroups (P = 0.539).

Figure S4 Sensitivity analysis

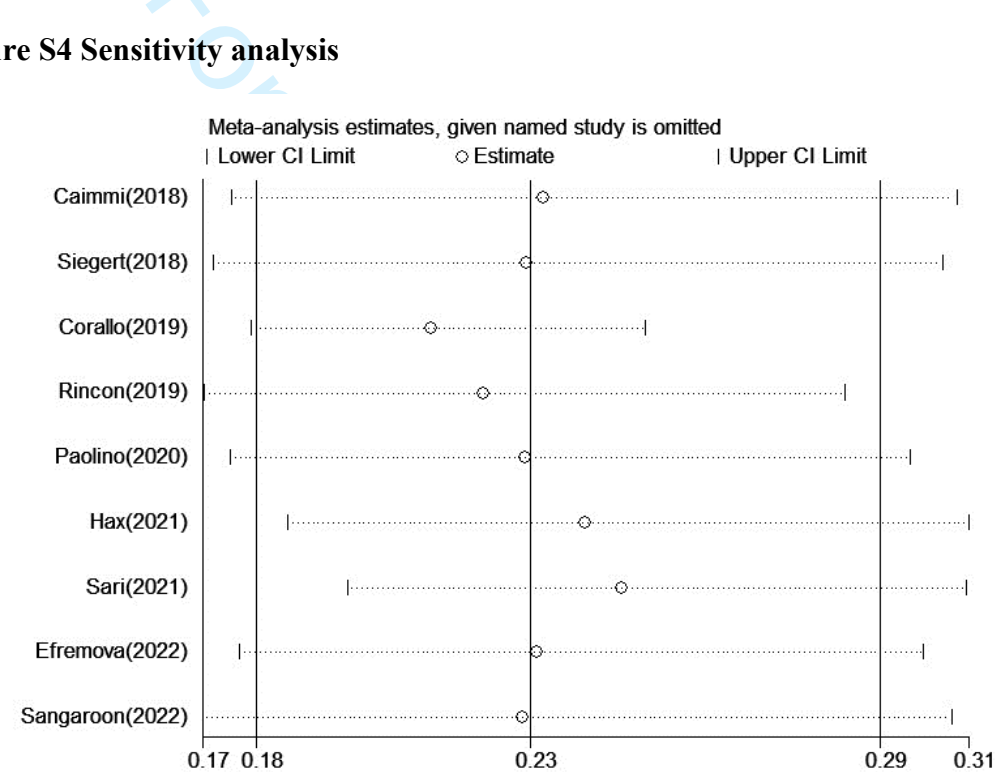
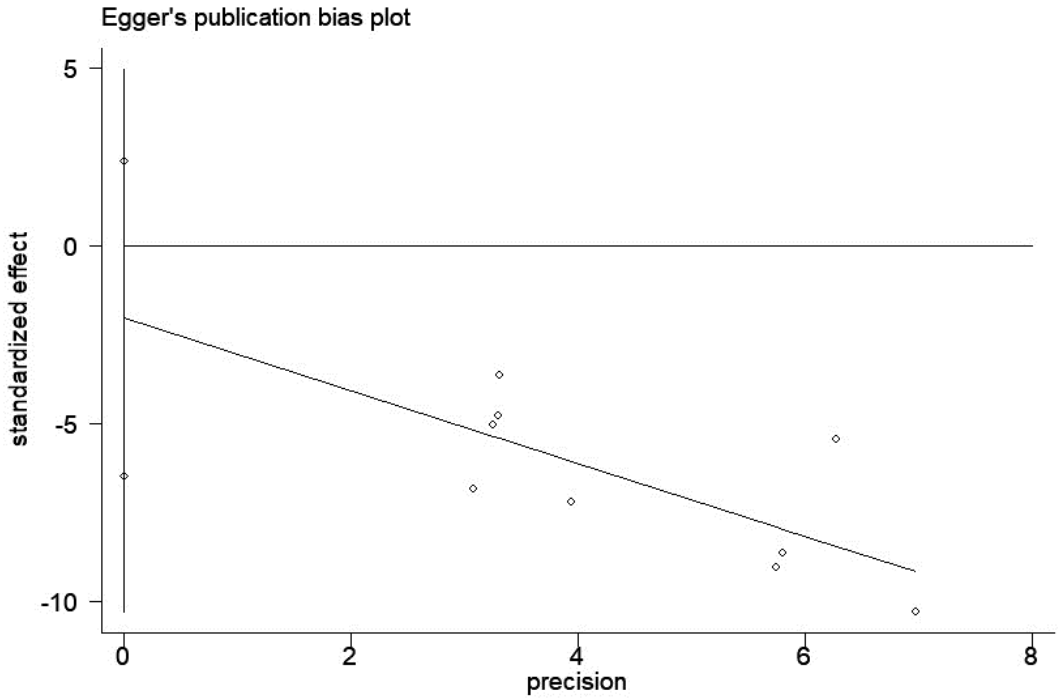


Figure S5 Egger's test for publication bias



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg. 1, lines 1-2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 5, lines 1-11
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 5, lines 13-15
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg. 6, lines 6-16
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg. 5, lines 18-22; Pg. 6, lines 1-5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S1-4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 7, lines 3-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg. 7, lines 8-15
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 6, lines 18-22
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Table 1 and Figure 3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 7, lines 17-22; Pg. 8 lines 1-2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg. 8, lines 6-12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Figure 2-3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg. 7, lines 13-15
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg. 8, lines 6-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the	Pg. 8, lines

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4-12
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg. 8, lines 15-18
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg. 8, lines 20-21
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg. 8, lines 21-22
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	None
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1, Table S5
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table s7-8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-3, Figure s1-3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Figure 2-3, Figure S1-3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg. 10, lines 11-22; Pg.11, lines 1-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figure S1-3, Table 6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg. 12, lines 11-12, Figure S4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg. 12, lines 12-13
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	None
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg. 14, lines 1-22; Pg. 15,

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			lines 1-13
	23b	Discuss any limitations of the evidence included in the review.	Pg. 16, lines 17-20
	23c	Discuss any limitations of the review processes used.	Pg. 16, lines 13-22; Pg.17 lines 1-2
	23d	Discuss implications of the results for practice, policy, and future research.	Pg. 15, lines 15-22; Pg. 16 lines 1-5
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg. 5, lines 18-20
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg. 5, lines 18-20
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 17, lines 17-22; Pg. 18 lines 1-3
Competing interests	26	Declare any competing interests of review authors.	Page 18, lines 4-5
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Table 1, Figure 2-3, Figure S1-3

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Sarcopenia in Systemic Sclerosis: Prevalence and Impact - A Systematic Review and Meta-analysis

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Sarcopenia in Systemic Sclerosis: Prevalence and Impact - A Systematic Review and Meta-analysis

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Abstract

Objective This review aims to provide an estimate of sarcopenia prevalence and its impact on clinical characteristics in patients with systemic sclerosis (SSc).

Design Systematic review and meta-analysis.

Data sources Embase, Medline, Web of Science, and the Cochrane Central Register of Controlled Trials were systemically searched from inception to May 24, 2023.

Eligibility criteria for selecting studies We included observational studies that reported the prevalence of sarcopenia in patients with SSc.

Data extraction and synthesis Two reviewers independently performed study selection and data extraction using standardized methods. Risk of bias was assessed using the Agency for Healthcare Research and Quality (AHRQ) scale and the Newcastle–Ottawa Scale (NOS). Meta-analysis was conducted using random effects models.

Results A total of 4583 articles were screened and 9 studies with data from 815 patients were included in the analysis (8 cross-sectional studies and 1 retrospective cohort study). The overall prevalence of sarcopenia in SSc patients was 22% (95% CI 17% to 28%). SSc patients with sarcopenia had a poorer quality of life (MD -12.02; 95% CI -19.11 to -4.93) and higher CRP levels (SMD 0.67 mg/L; 95% CI 0.35 to 1.00).

Conclusions Sarcopenia is common in patients with SSc. SSc patients with sarcopenia had a worse quality of life and higher CRP levels, based on our findings. Given the detrimental impact of sarcopenia on quality of life, future efforts aimed at early identification of sarcopenia in the clinical assessment of patients with SSc may have significance.

PROSPERO registration number CRD42022368326

Keywords Sarcopenia; Systemic sclerosis; Meta-analysis; Prevalence

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to evaluate the prevalence and impact of sarcopenia in patients with systemic sclerosis.
- We conducted a comprehensive literature search to ensure that all eligible studies were included in the analysis.
- We could not establish a definitive causal relationship between sarcopenia and systemic sclerosis.
- Even though this review included studies from different continents (Europe, South America, and Asia), data on participant race were not accessible, limiting its potential applicability to specific patient subgroups.

Introduction

Systemic sclerosis (SSc) is a rare immune-mediated rheumatic disease that is characterized by inflammation, microvascular damage, and progressive fibrosis of both the skin and internal organs, such as the gastrointestinal tract, lung, heart, and kidney.[1,2] Depending on the extent of cutaneous involvement, SSc can be classified as limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc).[3] Patients with SSc are at risk for body composition abnormalities, including loss of skeletal muscle mass, due to malnutrition resulting from gastrointestinal involvement, chronic inflammation, and steroid therapy.[4–7] In addition, heart, lung, and joint involvement in SSc patients can lead to impaired exercise ability and decreased physical activity.[8] These factors are closely related to sarcopenia, which is an age-related disease characterized by progressive and generalized loss of skeletal muscle mass and strength.[9] The coexistence of sarcopenia and SSc can exacerbate the patient's health issues and increase their healthcare costs, posing significant challenges for healthcare professionals.

According to a meta-analysis, the prevalence of sarcopenia in community-dwelling elders aged over 60 years was 11% (95% CI: 8 to 13%) in men and 9% (95% CI: 7 to 11%) in women.[10] The presence of sarcopenia increases the risk of falling, functional decline, frailty, and mortality, leading to poor quality of life and significant healthcare expenses.[11] The high prevalence of sarcopenia in older adults, combined with its detrimental consequences, warrants the need for effective prevention and management strategies. In SSc patients, addressing sarcopenia may improve their functional status and overall health outcomes, highlighting the importance of early screening and intervention. Healthcare professionals need to recognize the interplay between SSc and sarcopenia to provide optimal care for these patients.

In recent years, the presence of sarcopenia in SSc has garnered attention in several studies.[4–7,12–16] The documented prevalence of sarcopenia in SSc varies widely from 10.7% to 42% among different studies, which can be attributed to several factors.[4,5] Differences in diagnostic criteria and assessment methods utilized in various studies, such as those proposed by the European Working Group of Sarcopenia in Older People (EWGSOP)[9,17] and the Asian Working Group for Sarcopenia (AWGS),[18] can result in variations in the evaluation of muscle mass in patients. Furthermore, the influence of sarcopenia on the clinical features of SSc patients has been a topic of debate. For instance, Caimmi et al.[12] suggested that individuals with SSc and sarcopenia had a longer duration of disease; the longer disease duration means that patients live longer with the disease, while Siegert et al.[6] contradicted this claim and found no difference between sarcopenia and disease duration in SSc patients. Currently, no comprehensive systematic review or meta-analysis has examined sarcopenia in SSc. Therefore, we conducted a systematic review and meta-analysis to identify the diagnostic criteria for sarcopenia and evaluate the most reliable evidence on the prevalence of sarcopenia in SSc patients, as well as the effect of sarcopenia on the clinical features of SSc patients.

Methods

Data sources and search strategy

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline[19] and registered in PROSPERO (CRD42022368326). We systemically searched four electronic databases, including Embase, Medline, Web of Science, and the Cochrane Central Register of Controlled Trials, to identify all relevant articles relating to sarcopenia and SSc, without language

restrictions. Our search encompassed all records published from inception to May 24, 2023, utilizing the following terms: 'systemic sclerosis', 'scleroderm*', 'SSc', 'muscular atrophy', 'sarcopen*' and 'myopen*' (Supporting Information, Table S1-4). Additionally, we conducted a manual search of the reference lists of the included articles to identify potential studies that may have been overlooked by the principal search.

Inclusion and exclusion criteria

The following inclusion and exclusion criteria were employed for this systematic review and meta-analysis: (1) studies conducted exclusively on adult patients (age >18 years) diagnosed with SSc; (2) studies reporting the prevalence of sarcopenia in SSc patients; (3) studies defining sarcopenia as low muscle mass (LMM) plus low muscle strength (LMS), and/or low physical performance (LPP), or LMM alone; LMM was evaluated by dividing appendicular skeletal muscle mass (in kilograms) by height in meters squared, LMS by hand grip strength, LPP by gait speed or short physical performance battery, and diagnostic cutoffs varied depending on the criterion[9,17,18,20]; (4) studies measuring lean mass or muscle mass using one of the four main techniques: dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), magnetic resonance imaging (MRI) and computed tomography (CT); and (5) observational studies. Conversely, the exclusion criteria were as follows: repeated studies (defined as either identical data or identical articles).

Outcomes

The main outcomes of this systematic review comprise two aspects: firstly, the prevalence of sarcopenia among patients with SSc, and secondly, the clinical features of patients with SSc who suffer from sarcopenia compared to those who do not. These clinical features

encompassed a range of factors, namely, the duration of disease, the quality of life assessed by the Short Form-36 (SF-36) survey[21], the pulmonary function (the forced vital capacity (FVC) predicted value), and the C-relative protein level. These features are frequently the focus of clinical studies in patients with SSc, and it is of significant interest to understand how sarcopenia impacts them.

Study selection and data extraction

After removing duplicates, the studies identified through the search strategy underwent eligibility assessment by two reviewers (X.T. and T.L.), who independently screened the titles and abstracts and assigned them to one of three categories: 'include,' 'exclude,' or 'maybe.' Subsequently, the full-text articles of those categorized as 'include' or 'maybe' were reviewed to arrive at a final selection, with any discrepancies between the reviewers resolved by a third reviewer (J.Y.). Two reviewers (X.T. and X.S.) independently extracted the following variables using a pre-defined data collection form: first author, publication year, country, study design, sample size, mean age, number of females, disease subtype, mean disease duration, SSc diagnostic criteria, sarcopenia diagnostic criteria, assessment method for detecting sarcopenia, and prevalence of sarcopenia. Additionally, we also collected data on clinical features in the form of mean ± standard deviation (SD). For those studies that were not expressed as mean ± SD, we performed data conversion with the method recommended by Luo et al.[22] and Wan et al.[23]

Assessment of quality

Two authors (X.T. and T.J.) independently assessed the quality of the included studies using the Agency for Healthcare Research and Quality (AHRQ)[24] scale in cross-sectional studies.

This tool consists of 11 questions, with a 'no' or 'unclear' receiving 0 points and a 'yes' receiving 1 point. Low-quality articles received scores of 0–3, moderate-quality scores of 4–7, and high-quality scores of 8–11. The Newcastle–Ottawa Scale (NOS) was used to judge the quality of the cohort study.[25] The NOS scoring system assigns points from 0 to 9. We assigned values ranging from 0 to 3, 4 to 6, and 7 to 9 for low, moderate, and high-quality, accordingly. Any discrepancies were resolved through discussion or consensus with a third author (J.Y.).

Statistical Analysis

The prevalence of sarcopenia in SSc patients was determined by calculating the proportion of patients with sarcopenia in each study and conducting a meta-analysis of single proportions. We performed this meta-analysis using Stata/SE (Version 12.0, StataCorp, Texas, USA). Forest plots were used to illustrate the prevalence of sarcopenia, along with corresponding 95% confidence intervals (CIs) for each study and the overall estimate. Clinical characteristics such as disease duration, the SF-36 value, the FVC predicted value, and the CRP level from studies that compared SSc patients with and without sarcopenia were also analyzed using Review Manager (Version 5.4, The Cochrane Collaboration, Oxford, UK) and expressed as mean difference (MD) or standardized mean difference (SMD) with 95% CI. Heterogeneity across studies was assessed via the I^2 statistic, with values of 25% being considered low, 50% moderate, and 75% high.[26] Considering the variation in the definition of sarcopenia, diagnostic criteria, and population characteristics among the included studies, this study employed a random-effects model.

Subgroup analyses were conducted to investigate potential sources of heterogeneity, focusing on sarcopenia definition (1 vs >1 diagnostic criteria), disease subtype, and mean age (< 60 vs

≥60 years). The reasons for grouping in subgroup analysis are as follows. Firstly, variability in the definition of sarcopenia will result in varied prevalence estimates for patients with SSc. Unsurprisingly, increasing the number of necessary criteria in a sarcopenia definition will eventually diminish sarcopenia prevalence. Additionally, the disease subtype is an important factor that affects the prevalence of sarcopenia. Patients with dcSSc are more prone to develop sarcopenia.[14] Moreover, age is an essential factor that influences the onset and course of sarcopenia, with the prevalence of sarcopenia increasing with age. Meta-regressions were also conducted on sample size, mean age, percentage of female patients, and duration of SSc. However, due to limited data on the clinical characteristics of SSc patients with and without sarcopenia, subgroup analyses and meta-regressions were not conducted. To evaluate the stability of pooled results, sensitivity analysis was performed by excluding one study at a time. Publication bias was evaluated using Egger's test[27]. Statistical significance was set at $P < 0.05$ for all analyses.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Results

Search results

A comprehensive search of databases yielded 4583 articles. After eliminating duplicates (n = 1523), the remaining 3060 titles and abstracts were screened. Subsequently, 25 relevant articles underwent full-text reading, and 16 were excluded for reasons specified in the flow chart and Table S5 in the supplement. Ultimately, 9 studies were eligible for inclusion in this meta-

analysis (Figure 1).

Study characteristics

Table S6 provides an overview of the characteristics of the studies included in this meta-analysis. A total of 815 SSc patients from 9 eligible studies[4–7,12–16] published between 2018 and 2022 were included. The mean age of the patients ranged from 52.5 to 64.1 years, while the mean duration of SSc ranged from 6 to 12.8 years. The majority of the studies (8 out of 9) had a cross-sectional design,[4–6,12–16] with one being a retrospective cohort study.[7] The studies were conducted in various regions, with five from Europe,[5–7,12,16] two from South America,[13,15], and two from Asia.[4,14]

Risk of bias

According to the AHRQ and NOS ratings, 8 of the eligible studies[4–7,12,14–16] were of moderate quality, with only one article[13] classified as high quality. (Table S7-8 in the supplement).

Methods used to assess sarcopenia

Table S6 provides an overview of the diagnostic criteria used to evaluate sarcopenia across the included studies. Among them, seven studies[4–7,13,15,16] employed EWGSOP criteria (5 EWGSOP2010 and 2 EWGSOP2019) while one[14] used AWGS criteria. Three studies[5,7,12] solely relied on LMM for sarcopenia diagnosis, while six studies[4,6,13–16] utilized LMM combined with LMS and/or LPP. The sarcopenia diagnostic criteria and cutoff values in the studies are summarized in Table 1. Muscle mass was measured using dual-energy X-ray absorptiometry in seven studies[5,7,12–16] and bioelectrical impedance analysis in two studies[4,6]. Handgrip dynamometry was utilized to assess muscle strength in six

studies[4,6,13–16], while gait speed (three studies[14–16]) and the short physical performance battery (SPPB) (two studies[13,16]) were used to evaluate physical performance.

Sarcopenia prevalence

Overall sarcopenia prevalence

The nine studies included in this review reported the prevalence of sarcopenia in SSc patients, ranging from 10.7% to 42% (Table S6). The pooled prevalence of sarcopenia in patients with SSc was estimated at 22% (95% CI 17% to 28%), as shown in Figure 2.

Subgroup analysis of sarcopenia prevalence

The prevalence of sarcopenia differed in studies that utilized a single criterion [LMM; 28% (95% CI 16% to 42%)] versus those that employed >1 criterion [LMM + LMS and/or LPP; 20% (95% CI 15% to 25%)], with no statistically significant difference noted (P = 0.234, Figure S1 in the supplement). Subgroup analysis based on disease subtype revealed that sarcopenia prevalence in dcSSc [30% (95% CI 23% to 37%)] was higher than that in lcSSc [23% (95% CI 12% to 36%)], and the difference was not statistically significant (P = 0.339, Figure S2 in the supplement). The United Nations defines an older person as someone above the age of 60. Therefore, we also performed a subgroup analysis stratified by the mean age of the participants, with < 60 and ≥ 60 years as the cutoff points. The prevalence of sarcopenia was lower in patients younger than 60 years [20% (95% CI 12% to 29%)] vs those older than 60 years [24% (95% CI 17% to 32%)], but the difference was not of statistical significance (P = 0.539, Figure S3 in the supplement).

Meta-regression analyses

The results of the meta-regression analyses indicated that there was no significant association

between the prevalence of sarcopenia and sample size (P = 0.424), mean age of patients (P = 0.532), the proportion of female patients (P = 0.449), or duration of SSc (P = 0.255). These findings are summarized in Table S9 of the supplementary material.

Impact of sarcopenia on the clinical characteristics of SSc patients

Duration of SSc

Data from a total of four studies comprising 511 patients were included in the meta-analysis of SSc duration, which revealed that individuals with sarcopenia did not have a longer disease duration than those without sarcopenia [MD 2.97 years (95% CI -0.13 to 6.08); I^2 = 90%, Figure 3A].

Quality of life

The meta-analysis included two studies with a total of 191 patients, which provided data on the SF-36 value. The findings of the meta-analysis indicated that patients with sarcopenia had a lower SF-36 value compared to those without sarcopenia [MD -12.02 (95% CI -19.11 to -4.93); I^2 = 71%, Figure 3B], that is, having sarcopenia was associated with poorer quality of life compared with those without sarcopenia.

Pulmonary function

The meta-analysis incorporated two studies involving a total of 320 patients that reported data on the FVC predicted value. The results indicated that patients with sarcopenia did not have a lower FVC predicted value than those without sarcopenia [MD -4.02% (95% CI -8.67 to 0.62); I^2 = 0%, Figure 3C]. Therefore, there was no significant difference in pulmonary function between sarcopenia and non-sarcopenia patients.

CRP level

Data from two studies comprising 191 patients were analyzed to investigate the relationship between sarcopenia and CRP level. The results showed that sarcopenia was associated with a higher CRP level than no sarcopenia [SMD 0.67 mg/L (95% CI 0.35 to 1.00); $I^2 = 0\%$, Figure 3D].

Sensitivity and publication bias analysis

The sensitivity analysis revealed that the overall prevalence of sarcopenia was not significantly affected by any individual study (Figure S4 in the supplementary material). In addition, Egger's test suggested no publication bias in this review (P = 0.311, Figure S5 in the supplement).

Discussion

Primary results

In this meta-analysis encompassing nine studies, the pooled prevalence of sarcopenia among 815 patients diagnosed with systemic sclerosis (SSc) was estimated to be 22%, which was significantly greater than that in community-dwelling older adults.[28] Notably, SSc patients diagnosed with sarcopenia had poorer quality of life and a higher CRP level, while no significant difference was noted for disease duration and FVC predicted value when compared to patients without sarcopenia.

Mechanism basis

Sarcopenia, a condition characterized by loss of muscle mass and function, can be age-associated (primary sarcopenia) or secondary to chronic diseases, including malignant tumors and musculoskeletal diseases.[29–31] Compared with other chronic inflammatory rheumatic diseases, sarcopenia has not been extensively evaluated in SSc. Recently, some studies have focused on the presence of sarcopenia in SSc. Nevertheless, the pathogenesis of sarcopenia in

SSc remains unclear. Possible mechanisms contributing to the development of sarcopenia in SSc include (1) malnutrition: gastrointestinal involvement is the most frequent internal complication of SSc[32]. Symptoms such as esophageal reflux, early satiety, nausea, and vomiting may lead to reduced caloric intake.[12] Additionally, fibrosis of the bowel wall and small intestine bacterial overgrowth can result in malabsorption of nutrients. Therefore, malnutrition is prevalent in SSc patients. One study in community-dwelling older adults demonstrated that malnutrition is an independent predictor of sarcopenia (OR: 2.42; 95% CI 1.04 to 5.60)[33]. (2) Oxidative stress and chronic inflammation: oxidative stress, which is an imbalance in oxidant and antioxidant levels, is commonly observed in SSc patients[34]. Increased oxidative stress disrupts the balance between the degradation and resynthesis of skeletal muscle proteins[35]. In addition, chronic low-grade inflammation is detrimental to skeletal muscle in humans[36]. Inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, have been reported to contribute to the pathogenesis of SSc[37]. These cytokines stimulate protein catabolism and suppress muscle synthesis, ultimately leading to muscle wasting[38]. (3) Physical inactivity: due to pain and joint involvement, physical inactivity is common in SSc patients[39], leading to faster and greater muscle loss[11]. However, the mechanism of sarcopenia in SSc patients remains to be confirmed by future research.

Interpretation of the results

This review offers unique insight into sarcopenia in patients with SSc. It describes the prevalence of sarcopenia in SSc patients and how it is impacted by the different definitions of sarcopenia. The varying prevalence of sarcopenia may be explained in part by the variety of definitions. However, there was no statistical difference between 1 and >1 diagnostic criteria.

This might be due to the lack of robustness of the combined results as a result of the small number of studies using one diagnostic criterion. In addition, discrepancies in sarcopenia diagnostic cutoffs among the included studies may have resulted in differing sarcopenia prevalence. Furthermore, our meta-analysis indicated no statistically significant variation in the prevalence of sarcopenia between disease subtypes, which is consistent with the results of Sangaroon et al.[14] It is important to note that this conclusion needs to be interpreted with caution due to the limited number of studies that could be included in the analysis. Although sarcopenia commonly occurs as an age-related process in older individuals[11], it becomes more common as people get older. Our meta-analysis demonstrated that the difference in the prevalence of sarcopenia was not statistically significant between the patients over 60 years old and the patients under 60 years old. Furthermore, patients younger than 60 years old all used >1 criterion to diagnose sarcopenia, which makes the prevalence of sarcopenia in young people even lower. This suggests that, despite the influence of age on the presence of sarcopenia, the illness itself is responsible for sarcopenia onset and progression in SSc patients. Therefore, rheumatologists should screen for sarcopenia even in young SSc patients. However, this conclusion must be confirmed by a large number of high-quality clinical studies.

Our meta-analysis also revealed that SSc patients diagnosed with sarcopenia had a poorer quality of life. On the one hand, involvement of the heart, lungs, and joints in SSc patients might result in diminished exercise capacity and decreased physical activity,[8] making SSc patients vulnerable to sarcopenia. On the other hand, sarcopenia is associated with a variety of negative outcomes, including hospitalization, functional decline, falls, and death.[40,41] Therefore, it should come as no surprise that SSc patients with sarcopenia have a higher risk

of having a worse quality of life. Furthermore, individuals with SSc who had sarcopenia had higher CRP levels, according to our findings. This result is not surprising given that chronic inflammation is a known contributor to secondary sarcopenia.[42] However, our review indicated that no significant difference was noted for disease duration or FVC predicted value between SSc patients with and without sarcopenia. According to the results of Caimmi et al,[12] the longer the disease duration, the greater the risk of sarcopenia. This might be due to the minimal number of studies that could extract data, resulting in false negatives in the pooled study results. Therefore, large prospective cohort studies are required to confirm this conclusion.

Clinical implications

This meta-analysis provides a comprehensive evaluation of the prevalence, diagnostic criteria, and impact of sarcopenia in SSc patients, which has not been previously done. The results of this study provide an up-to-date estimation of the prevalence of sarcopenia, which can guide sample size calculations for future research. While sarcopenia has been relatively under-studied in SSc compared to other rheumatic diseases, our findings suggested that neither sarcopenia definition, disease subtype nor age affects the prevalence of sarcopenia. SSc patients with sarcopenia had a poorer quality of life, according to our findings. Therefore, early identification and intervention of sarcopenic patients by clinicians is crucial. The high prevalence of sarcopenia in SSc patients highlights the importance of early screening and management. Standardized criteria for sarcopenia diagnosis are also essential in SSc patients to minimize variations in prevalence. These findings have important implications for future research, clinical practice, and policy development in managing sarcopenia in SSc patients, and can

potentially improve outcomes for these patients.

Strengths and weaknesses

This systematic review undertook a comprehensive and meticulous literature search to ensure that all pertinent studies were included in the analysis. The selection of studies, data extraction, and quality assessments were carried out independently by two reviewers, thereby enhancing the accuracy and reliability of the results. Subgroup analyses and meta-regression analyses were also conducted to explore the possible sources of heterogeneity, while sensitivity and publication bias analyses were performed to ensure robust and dependable conclusions.

Nevertheless, we must acknowledge certain limitations of our study. Firstly, since most of the included studies were cross-sectional, it is impossible to establish a definitive causal relationship between sarcopenia and SSc. Nonetheless, this is a limitation inherent to the original literature and beyond our control. We, therefore, look forward to high-quality prospective cohort studies to provide more conclusive evidence on this matter. Secondly, there was some heterogeneity among the included studies in terms of factors such as the definition of sarcopenia, measurement approaches, and diagnostic cut-offs. Moreover, most of the studies had small sample sizes. Therefore, future studies should aim to use uniform diagnostic criteria for sarcopenia and expand the sample size to improve the quality of research. Finally, even though this review included studies from different continents (Europe, South America, and Asia), data on participant race were not accessible, limiting its potential applicability to specific patient subgroups.

Conclusions

Sarcopenia is common in patients with SSc. SSc patients with sarcopenia had a worse quality

of life and higher CRP levels, based on our findings. Given the detrimental impact of sarcopenia on quality of life, future efforts aimed at early identification of sarcopenia in the clinical assessment of patients with SSc may have significance.

Contributors

All authors conceived and designed this review; YJ, XPT, and JRY developed the search strategy; XPT and TPL screened studies; XPT and XYS extracted data; XPT and TTJ appraised study quality; XPT and NG conducted data analysis; XPT drafted the manuscript; all authors revised the manuscript for important intellectual content. JRY had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

Not applicable.

Data availability statement

The data are accessible upon reasonable request from the corresponding author.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table 1 Criteria and cutoff points used to detect sarcopenia in each study

First author and year	Sarcopenia diagnostic criteria	Cutoff points
Caimmi (2018)[12]	SMI	LMM: ASM/height2 < 7.26 kg/m^2 for men and < 5.50 kg/m^2 for women.[43]
Siegert (2018)[6]	EWGSOP (2010)	LMM: ALM/height2 < 7.26 kg/m2 for men and <5.50 kg/m2 for women.[43] LMS: BMI ≤ 24, HGS ≤ 29 kg; 24.1 ≤ BMI ≤ 26, HGS ≤ 30 kg; 26.1 ≤ BMI ≤ 28, HGS ≤ 30 kg; BMI > 28, HGS ≤ 32 kg for men. BMI ≤ 23, HGS ≤ 17 kg; 23.1 ≤ BMI ≤ 26, HGS ≤ 17.3 kg; 26.1 ≤ BMI ≤ 29, HGS ≤ 18 kg; BMI > 29, HGS ≤ 21 kg for women.[44]
Corallo (2019)[5]	EWGSOP (2010)	LMM: RSMI < 7.26 kg/m2 for men and < 5.50 kg/m2 for women.[43]
Rincon (2019)[15]	EWGSOP (2010)	LMM: RSMI < 7.26 kg/m2 for men and < 5.50 kg/m2 for women.[43] LMS: HGS< 30 kg for men and< 20 kg for women.[45] LPP: GS< 0.8 m/s (both genders).[45]
Paolino (2020) [7]	EWGSOP (2010)	LMM: RSMI < 7.26 kg/m2 for men and < 5.50 kg/m2 for women.[43]
Hax (2021)	EWGSOP (2019)	LMM: ASMI < 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women.[46] LMS: HGS < 27 kg for men and < 16 kg for women.[47] LPP: SPPB ≤ 8 point score.[48]

First author and year	Sarcopenia diagnostic criteria	Cutoff points
Sari (2021)[4]	EWGSOP (2010)	LMM: ASMI < 7.26 kg/m2 for men and <5.50 kg/m2 for women.[43] LMS: BMI ≤ 24, HGS ≤ 29 kg; 24.1 ≤ BMI ≤ 26, HGS ≤ 30 kg; 26.1 ≤ BMI ≤ 28, HGS ≤ 30 kg; BMI > 28, HGS ≤ 32 kg for men. BMI ≤ 23, HGS ≤ 17 kg; 23.1 ≤ BMI ≤ 26, HGS ≤ 17.3 kg; 26.1 ≤ BMI ≤ 29, HGS ≤ 18 kg; BMI > 29, HGS ≤ 21 kg for women.[44]
Efremova (2022)[16]	EWGSOP (2019)	LMM: ASMI < 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women.[46] LMS: HGS < 27 kg for men and < 16 kg for women.[47] or Chair stand > 15 s for five rises.[49] LPP: GS ≤ 0.8 m/s.[50] or SPPB ≤ 8 point score.[48]
Sangaroon (2022)[14]	AWGS (2019)	LMM: ASMI < 7.0 kg/m^2 for men and < 5.4 kg/m^2 for women.[20] LMS: HGS < 28 kg for men and < 18 kg for women.[20] LPP: GS< 1 m/s (both genders).[20]

SMI, Skeletal Muscle Mass Index; ASM, appendicular skeletal muscle mass; ALM, appendicular lean mass; RSMI, Relative Skeletal Muscle Mass Index; ASMI, Appendicular Skeleton Muscle Index; SPPB, Short Physical Performance Battery; GS, gait speed.

Figure legend

1. Figure 1 The flow chart of the literature selection

2. Figure 2 The pooled prevalence of sarcopenia in SSc patients

3. **Figure 3 Impact of sarcopenia on clinical characteristics in patients with SSc**

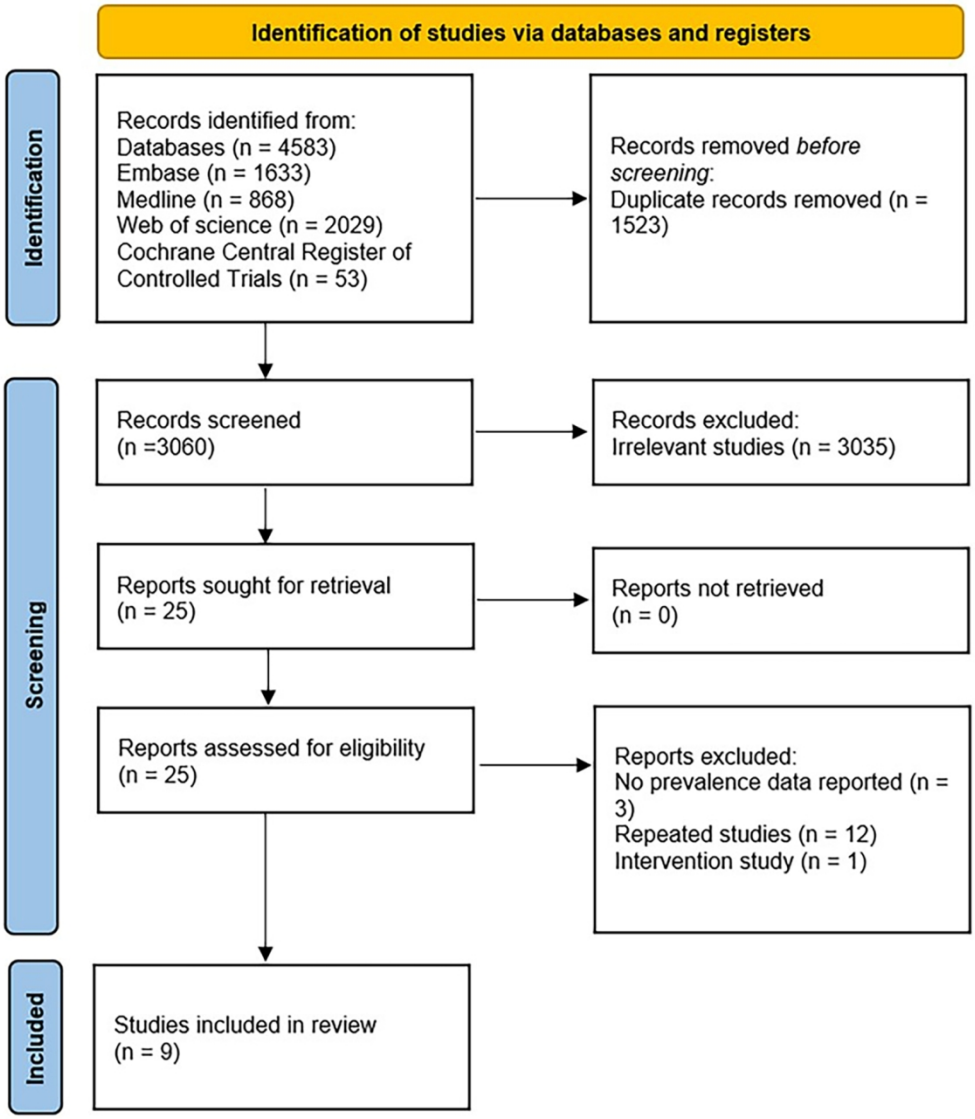

Figure 1 The flow chart of the literature selection

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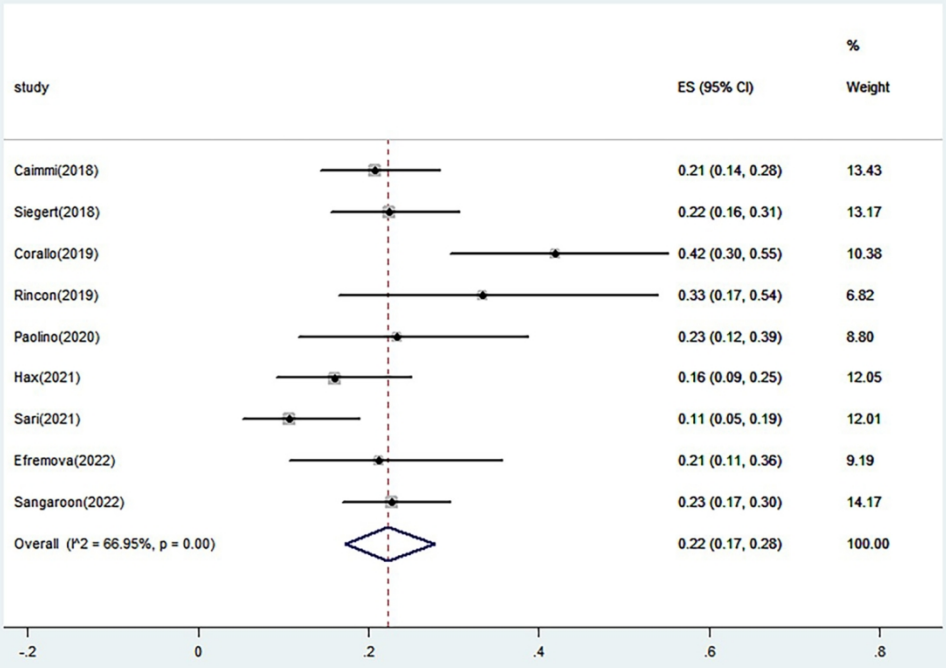

Figure 2 The pooled prevalence of sarcopenia in SSc patients

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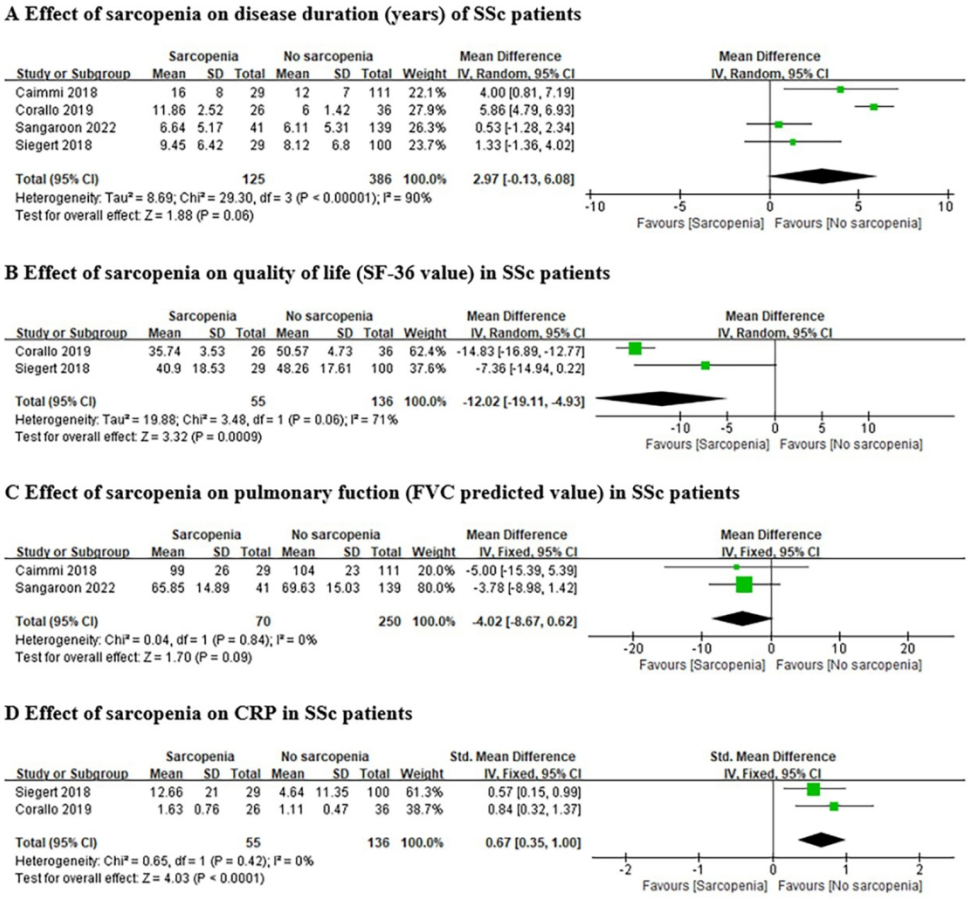

Figure 3 Impact of sarcopenia on clinical characteristics in patients with SSc

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Sarcopenia in Systemic Sclerosis: Prevalence and Impact - A Systematic Review and Meta-analysis

1. Table S1 Search strategy by Medline via Ovid SP
2. Table S2 Search strategy by Embase via Ovid SP
3. Table S3 Search strategy by Web of Science
4. Table S4 Search strategy by Cochrane Central Register of Controlled Trials via Ovid SP
5. Table S5 The reasons for the exclusion of full-text articles
6. Table S6 Characteristics of the included studies
7. Table S7 ARHQ Methodology Checklist for Cross-Sectional Study
8. Table S8 Newcastle-Ottawa Scale for Cohort study
9. Table S9 Meta-regression analyses of sarcopenia prevalence
10. Figure S1 Prevalence of sarcopenia by criteria
11. Figure S2 Prevalence of sarcopenia by disease subtype
12. Figure S3 Prevalence of sarcopenia by mean age
13. Figure S4 Sensitivity analysis
14. Figure S5 Egger's test for publication bias

Table S1 Search strategy by Medline via Ovid SP

1.	exp Scleroderma, Systemic/
2.	((Systemic or general* or diffus* or progress* or Limit*) adj3 sclerosis).mp.
3.	scleroderm*.tw.
4.	SSc.tw.
5.	1 or 2 or 3 or 4
6.	exp muscular atrophy/
7.	(sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat*).mp.
8.	((muscle or muscular) adj5 (atroph* or wast* or weak* or loss* or mass or degenerat*)).ti,ab.
9.	6 or 7 or 8
10.	5 and 9
11.	exp animals/ not humans.sh.
12.	10 not 11

Table S2 Search strategy by Embase via Ovid SP

1.	exp systemic sclerosis/
2.	((Systemic or general* or diffus* or progress* or Limit*) adj3 sclerosis).mp.
3.	scleroderm*.tw.
4.	SSc.tw.
5.	1 or 2 or 3 or 4
6.	exp muscle atrophy/
7.	(sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat*).mp.
8.	((muscle or muscular) adj5 (atroph* or wast* or weak* or loss* or mass or degenerat*)).ti,ab.
9.	6 or 7 or 8
10.	5 and 9
11.	exp animal/
12.	human/
13.	11 not 12
14.	10 not 13

Table S3 Search strategy by Web of Science

Topic= (((Systemic or general* or diffus* or progress* or Limit*) near/3 sclerosis) or sclerodem or ssc) and (sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat* or ((muscle or muscular) near/5 (atroph* or wast* or weak* or loss* or mass or degenerat*)))

Table S4 Search strategy by Cochrane Central Register of Controlled Trials via Ovid SP

1.	exp Scleroderma, Systemic/
2.	((Systemic or general* or diffus* or progress* or Limit*) adj3 sclerosis).mp.
3.	scleroderm*.tw.
4.	SSc.tw.
5.	1 or 2 or 3 or 4
6.	exp muscular atrophy/
7.	(sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat*).mp.
8.	((muscle or muscular) adj5 (atroph* or wast* or weak* or loss* or mass or degenerat*)).ti,ab.
9.	6 or 7 or 8
10.	5 and 9

Table S5 The reasons for the exclusion of full-text articles

Study	Reason for the exclusion
Norman (2014)	Repeated study
Siegert (2014)	Repeated study
Caimmi (2017)	Repeated study
March (2017)	Repeated study
Doerfler (2017)	Intervention study
Paolino (2018)	Repeated study
Radic (2018)	Not reported sarcopenia prevalence data in SSc patients
Remolina (2019)	Repeated study
Sari (2019)	Repeated study
Veronica (2019)	Repeated study
Hax (2020)	Repeated study
Santo (2020)	Repeated study
Sangaroon (2020)	Repeated study
Peterson (2020)	Not reported sarcopenia prevalence data in SSc patients
Efremova (2021)	Repeated study
Sorokina (2022)	Not reported sarcopenia prevalence data in SSc patients

Table S6 Characteristics of the included studies

First author and year	Country	Study design	Sample size	Mean age(years)	Female, n	Disease subtype	Disease duration (years)	SSc diagnostic criteria	Sarcopenia diagnostic criteria	Criteria (assessment method of detecting sarcopenia)	Prevalence of sarcopenia	
											Total,n(%)	Diffuse,n(%)
Caimmi (2018)	Italy	Cross-sectional study	140	64	118	limited 97 diffuse 43	12.8	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA)	29(20.7%)	11(7.9%)
Siegert (2018)	Germany	Cross-sectional study	129	60	118	-	7	2013 ACR/EULAR	EWGSOP (2010)	LMM（BIA） LMS（HGS）	29(22.5%)	-
Corallo (2019)	Italy	Cross-sectional study	62	62	54	limited 50 diffuse 12	8	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA)	26(42%)	4(6.4%)
Rincon (2019)	Argentina	Cross-sectional study	27	52.5	20	limited 16 diffuse 11	7.8	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA) LMS（HGS） LPP (4mGS)	9(33.3%)	3(11.1%)
Paolino (2020)	Italy	Retrospective cohort study	43	64.1	36	-	10.2	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA)	10(23.3%)	-
Hax (2021)	Brazil	Cross-sectional study	94	60.5	87	-	12.5	2013 ACR/EULAR	EWGSOP (2019)	LMM (DXA) LMS（HGS） LPP (SPPB)	15(15.9%)	-
Sari (2021)	Turkey	Cross-sectional	93	52.6	86	-	10.7	1980ACR	EWGSOP	LMM（BIA）	10(10.7%)	-

First author and year	Country	Study design	Sample size	Mean age(years)	Female, n	Disease subtype	Disease duration (years)	SSc diagnostic criteria	Sarcopenia diagnostic criteria	Criteria (assessment method of detecting sarcopenia)	Prevalence of sarcopenia	
											Total,n(%)	Diffuse,n(%)
Efremova (2022)	Russia	study Cross-sectional study	47	53.9	47	limited 29 diffuse 18	6	2013 ACR/EULAR	EWGSOP (2018)	LMS（HGS） LMM (DXA) LMS (HGS and Chair rising test) LPP (GS and SPPB)	10(21.3%)	6(12.8%)
Sangaroon (2022)	Thailand	Cross-sectional study	180	58.8	119	limited 86 diffuse 94	6.2	-	AWGS (2019)	LMM(DXA) LMS(HGS) LPP(GS)	41(22.8%)	30(16.7%)

ACR, American College of Rheumatology; EULAR, European League against Rheumatology classification criteria; SMI, Skeletal Muscle Mass Index; EWGSOP, European Working Group on Sarcopenia in Old People; HGS, hand grip strength; 4mGS, 4 m gait speed; SPPB, Short Physical Performance Battery; GS, gait speed; AWGS, Asian Working Group for Sarcopenia.

Table S7 ARHQ Methodology Checklist for Cross-Sectional Study

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total Score
Caimmi (2018)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	Unclear	Yes	No	6
Siegert (2018)	Yes	Yes	Unclear	Yes	Unclear	Yes	No	No	No	Yes	No	5
Corallo (2019)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	No	Yes	No	6
Rincon (2019)	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	No	No	Yes	No	4
Hax (2021)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	Yes	No	8
Sari (2021)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	No	Yes	No	6
Efremova (2022)	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No	No	No	Yes	No	3
Sangaroon (2022)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	No	Yes	No	6

Item 1. Define the source of information (survey, record review)
Item 2. List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications
Item 3. Indicate time period used for identifying patients
Item 4. Indicate whether or not subjects were consecutive if not population-based
Item 5. Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants
Item 6. Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)
Item 7. Explain any patient exclusions from analysis
Item 8. Describe how confounding was assessed and/or controlled
Item 9. If applicable, explain how missing data were handled in the analysis
Item 10. Summarize patient response rates and completeness of data collection
Item 11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained

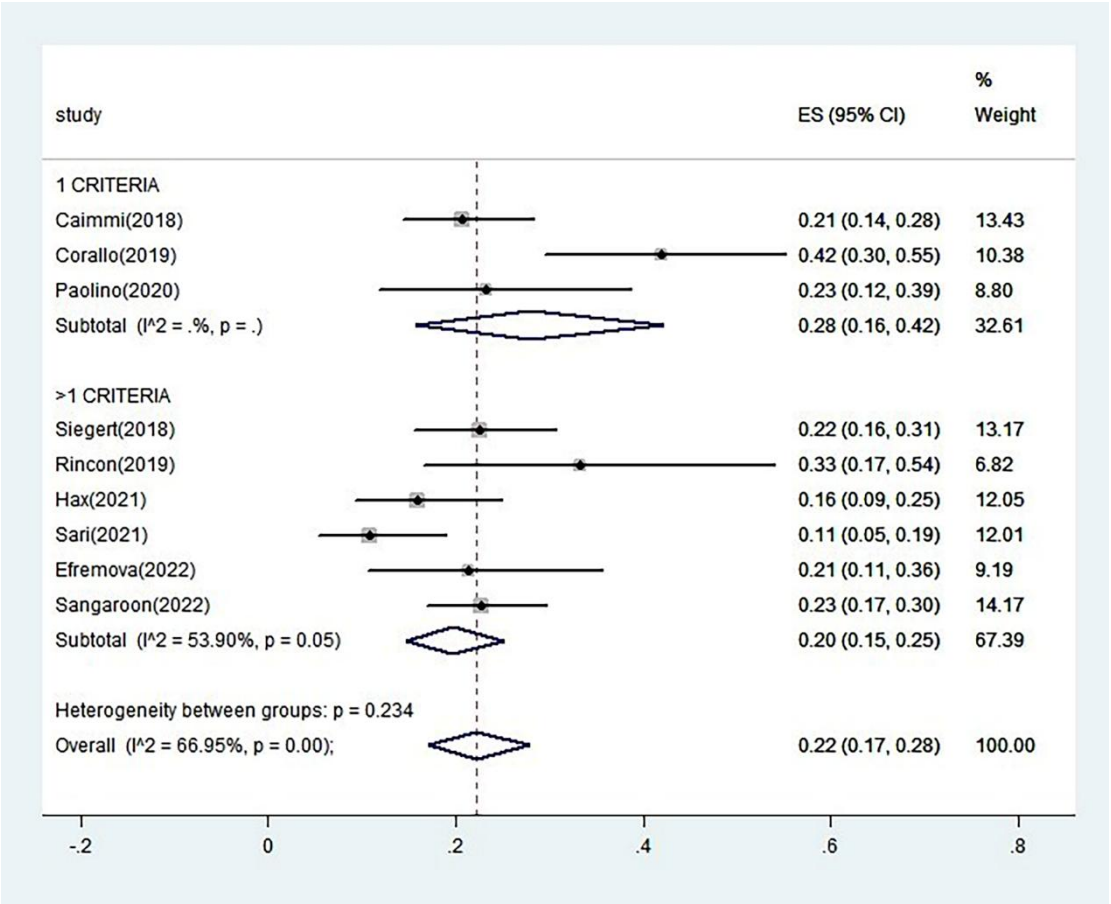
Table S8 Newcastle-Ottawa Scale for Cohort study

Study	Selection				Comparability	Outcome			Total Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Paolino (2020)	0	1	1	0	1	1	0	0	4

Table S9 Meta-regression analyses of sarcopenia prevalence

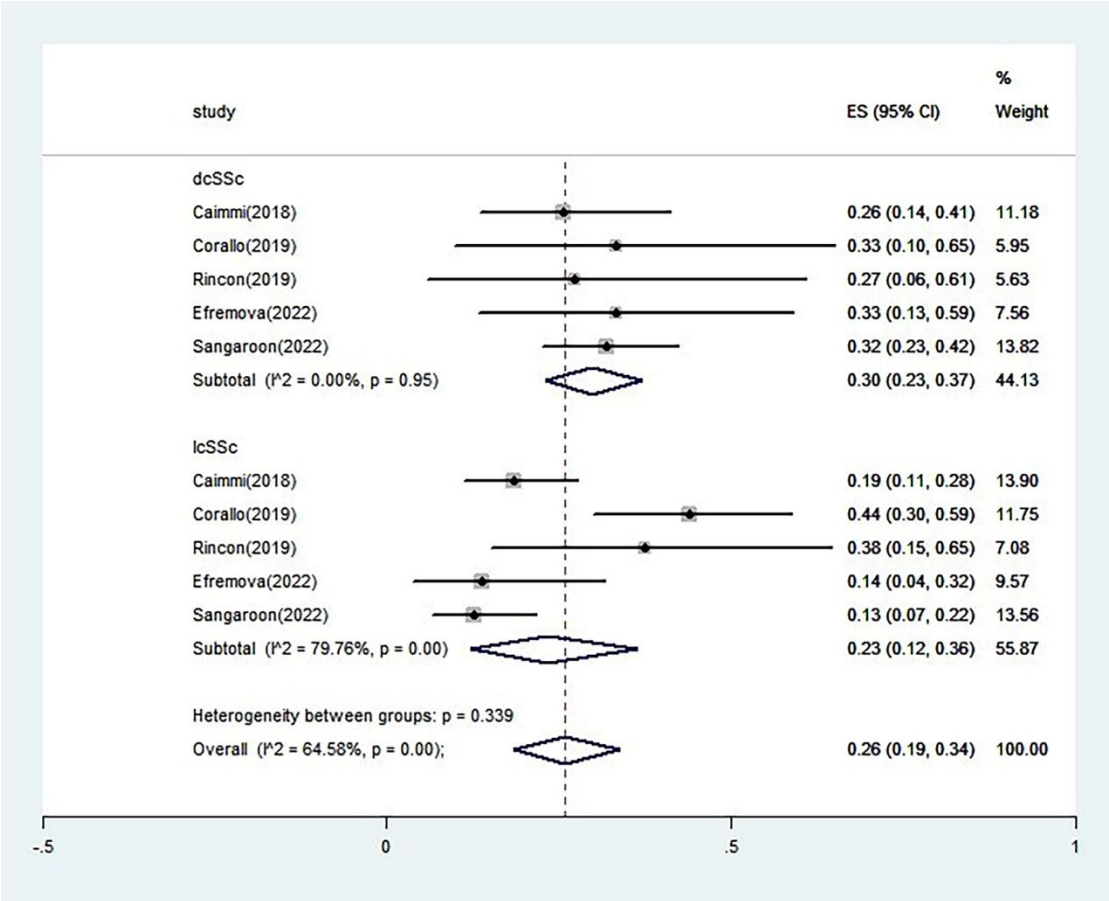
Variables	Coefficient	SE	P value	CI-Lower	CI-Upper
Sample size	-0.0022	0.0026	0.424	-0.0083	0.0039
Average age	0.0210	0.0319	0.532	-0.0545	0.0965
Proportion of female	-1.0603	1.3233	0.449	-4.1893	2.0687
Duration of SSc	-0.0606	0.0488	0.255	-0.1760	0.0549

Figure S1 Prevalence of sarcopenia by criteria



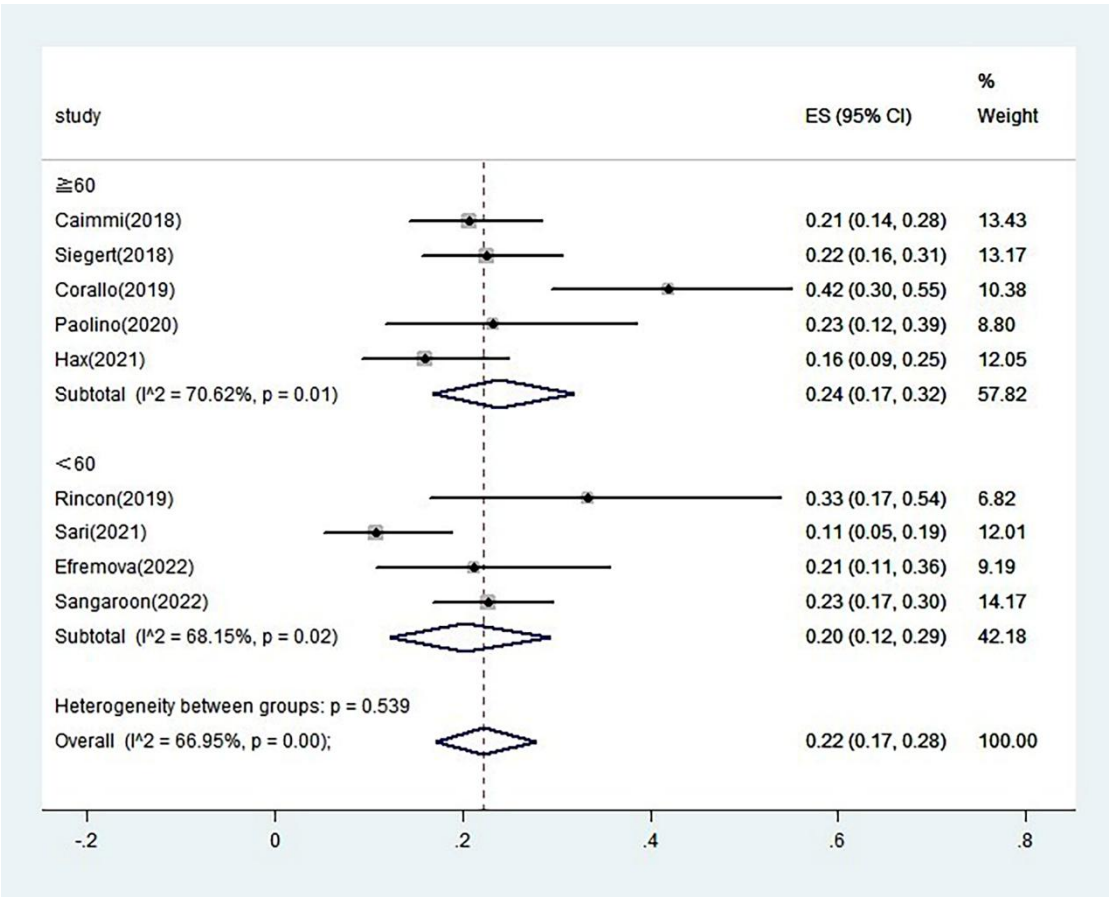
ES = effect size (prevalence); I^2 = I^2 heterogeneity statistic. A random effects model was used for analysis, and there was no significant difference between subgroups (P = 0.234).

Figure S2 Prevalence of sarcopenia by disease subtype



ES = effect size (prevalence); I^2 = I^2 heterogeneity statistic. The random effects model was used for the analysis, and there was no significant difference between the subgroups (P = 0.339).

Figure S3 Prevalence of sarcopenia by mean age



ES = effect size (prevalence); I^2 = I^2 heterogeneity statistic. The random effects model was used for the analysis, and there was no significant difference between the subgroups (P = 0.539).

Figure S4 Sensitivity analysis

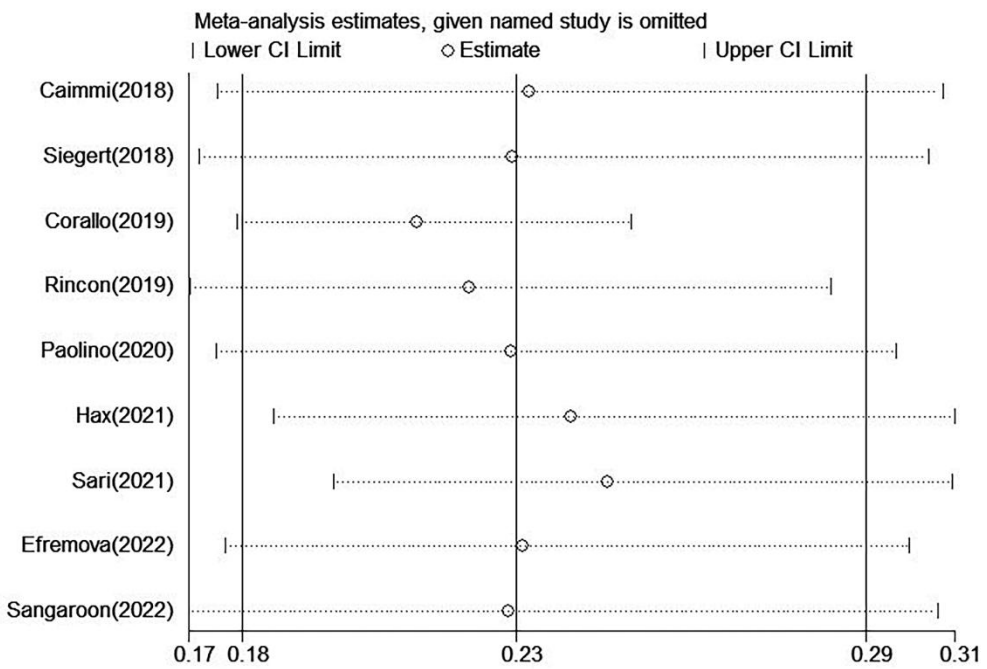
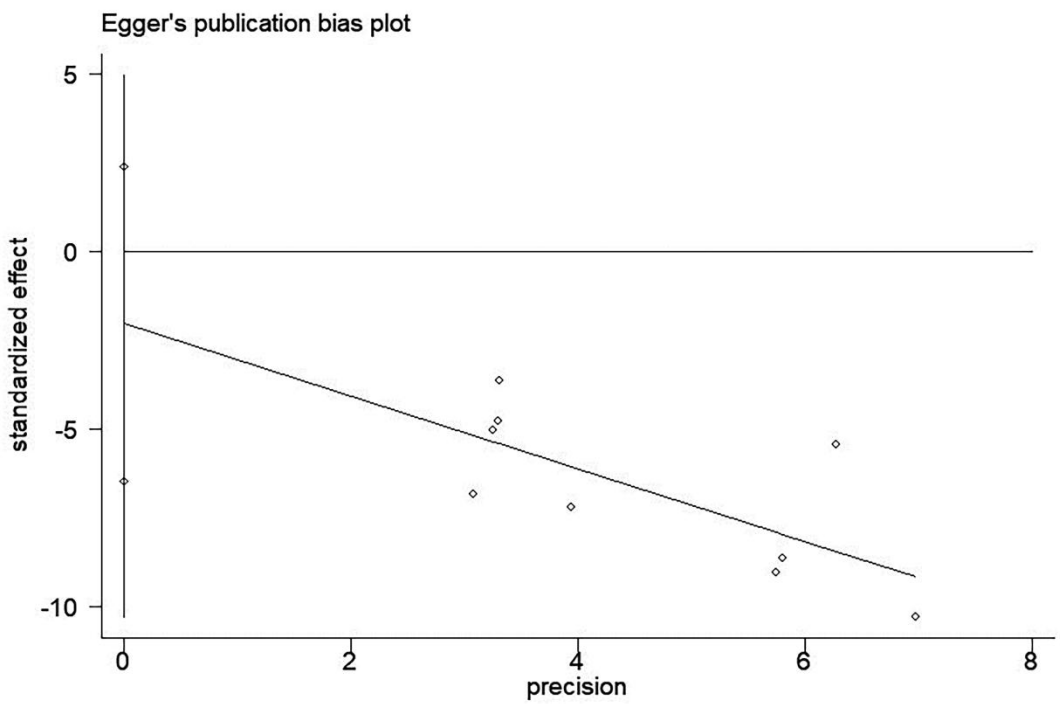


Figure S5 Egger's test for publication bias



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg. 1, lines 1-2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 5, lines 1-11
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 5, lines 13-15
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg. 6, lines 7-18
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg. 5, lines 18-22; Pg. 6, lines 1-5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S1-4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 7, lines 7-12
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg. 7, lines 12-19
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 6, lines 20-22; Pg. 7 lines 1-3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Table S6 and Figure 3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 7, lines 21-22; Pg. 8 lines 1-6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg. 8, lines 12-16
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Figure 2-3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg. 7, lines 17-19
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg. 8, lines

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			10-12
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg. 8, lines 8-16
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg. 8, lines 21-22; Pg. 9 lines 7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg. 9, lines 10-11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg. 9, lines 12-13
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	None
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1, Table S5
Study characteristics	17	Cite each included study and present its characteristics.	Table S6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S7-8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-3, Figure S1-3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Figure 2-3, Figure S1-3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg. 11, lines 3-20
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figure S1-3, Table S9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg. 13, lines 6-7, Figure S4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg. 13, lines 6-7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	None
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg. 14,

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			lines 19-22; Pg. 15, lines 1-22; Pg. 16 lines 1-9
	23b	Discuss any limitations of the evidence included in the review.	Pg. 15, lines 6-7
	23c	Discuss any limitations of the review processes used.	Pg. 17, lines 9-20
	23d	Discuss implications of the results for practice, policy, and future research.	Pg. 16, lines 11-22; Pg. 17 line 1
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg. 5, lines 18-20
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg. 5, lines 18-20
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 18, lines 11-20
Competing interests	26	Declare any competing interests of review authors.	Page 18, lines 21-22
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Table S6, Figure 2-3, Figure S1-3

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Sarcopenia in Systemic Sclerosis: Prevalence and Impact - A Systematic Review and Meta-analysis

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Sarcopenia in Systemic Sclerosis: Prevalence and Impact - A Systematic Review and Meta-analysis

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Abstract

Objective This review aims to provide an estimate of sarcopenia prevalence and its impact on clinical characteristics in patients with systemic sclerosis (SSc).

Design Systematic review and meta-analysis.

Data sources Embase, Medline, Web of Science, and the Cochrane Central Register of Controlled Trials were systemically searched from inception to May 24, 2023.

Eligibility criteria for selecting studies We included observational studies that reported the prevalence of sarcopenia in patients with SSc.

Data extraction and synthesis Two reviewers independently performed study selection and data extraction using standardized methods. Risk of bias was assessed using the Agency for Healthcare Research and Quality (AHRQ) scale and the Newcastle–Ottawa Scale (NOS). Meta-analysis was conducted using random effects models.

Results A total of 4583 articles were screened and 9 studies with data from 815 patients were included in the analysis (8 cross-sectional studies and 1 retrospective cohort study). The overall prevalence of sarcopenia in SSc patients was 22% [95% confidence interval (CI) 17% to 28%]. SSc patients with sarcopenia had a poorer quality of life [mean difference (MD) -12.02; 95% CI -19.11 to -4.93] and higher CRP levels [standardized mean difference (SMD) 0.67; 95% CI 0.35 to 1.00].

Conclusions Sarcopenia is common in patients with SSc. SSc patients with sarcopenia had a worse quality of life and higher CRP levels, based on our findings. Given the detrimental impact of sarcopenia on quality of life, future efforts aimed at early identification of sarcopenia in the clinical assessment of patients with SSc may have significance.

PROSPERO registration number CRD42022368326

Keywords Sarcopenia; Systemic sclerosis; Meta-analysis; Prevalence

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to evaluate the prevalence and impact of sarcopenia in patients with systemic sclerosis.
- We conducted a comprehensive literature search to ensure that all eligible studies were included in the analysis.
- We could not establish a definitive causal relationship between sarcopenia and systemic sclerosis.
- Even though this review included studies from different continents (Europe, South America, and Asia), data on participant race were not accessible, limiting its potential applicability to specific patient subgroups.

Introduction

Systemic sclerosis (SSc) is a rare immune-mediated rheumatic disease that is characterized by inflammation, microvascular damage, and progressive fibrosis of both the skin and internal organs, such as the gastrointestinal tract, lung, heart, and kidney.[1,2] Depending on the extent of cutaneous involvement, SSc can be classified as limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc).[3] Patients with SSc are at risk for body composition abnormalities, including loss of skeletal muscle mass, due to malnutrition resulting from gastrointestinal involvement, chronic inflammation, and steroid therapy.[4–7] In addition, heart, lung, and joint involvement in SSc patients can lead to impaired exercise ability and decreased physical activity.[8] These factors are closely related to sarcopenia, which is an age-related disease characterized by progressive and generalized loss of skeletal muscle mass and strength.[9] The coexistence of sarcopenia and SSc can exacerbate the patient's health issues and increase their healthcare costs, posing significant challenges for healthcare professionals.

According to a meta-analysis, the prevalence of sarcopenia in community-dwelling elders aged over 60 years was 11% [95% confidence interval (CI) 8% to 13%] in men and 9% (95% CI 7% to 11%) in women.[10] The presence of sarcopenia increases the risk of falling, functional decline, frailty, and mortality, leading to poor quality of life and significant healthcare expenses.[11] The high prevalence of sarcopenia in older adults, combined with its detrimental consequences, warrants the need for effective prevention and management strategies. In SSc patients, addressing sarcopenia may improve their functional status and overall health outcomes, highlighting the importance of early screening and intervention. Healthcare professionals need to recognize the interplay between SSc and sarcopenia to provide optimal

care for these patients.

In recent years, the presence of sarcopenia in SSc has garnered attention in several studies.[4–7,12–16] The documented prevalence of sarcopenia in SSc varies widely from 10.7% to 42% among different studies, which can be attributed to several factors.[4,5] Differences in diagnostic criteria and assessment methods utilized in various studies, such as those proposed by the European Working Group of Sarcopenia in Older People (EWGSOP)[9,17] and the Asian Working Group for Sarcopenia (AWGS),[18] can result in variations in the evaluation of muscle mass in patients. Furthermore, the influence of sarcopenia on the clinical features of SSc patients has been a topic of debate. For instance, Caimmi et al.[12] suggested that individuals with SSc and sarcopenia had a longer duration of disease; the longer disease duration means that patients live longer with the disease, while Siegert et al.[6] contradicted this claim and found no difference between sarcopenia and disease duration in SSc patients. Currently, no comprehensive systematic review or meta-analysis has examined sarcopenia in SSc. Therefore, we conducted a systematic review and meta-analysis to identify the diagnostic criteria for sarcopenia and evaluate the most reliable evidence on the prevalence of sarcopenia in SSc patients, as well as the effect of sarcopenia on the clinical features of SSc patients.

Methods

Data sources and search strategy

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline[19] and registered in PROSPERO (CRD42022368326). We systemically searched four electronic databases, including Embase, Medline, Web of Science, and the Cochrane Central Register of Controlled

Trials, to identify all relevant articles relating to sarcopenia and SSc, without language restrictions. Our search encompassed all records published from inception to May 24, 2023, utilizing the following terms: 'systemic sclerosis', 'scleroderm*', 'SSc', 'muscular atrophy', 'sarcopen*' and 'myopen*' (Supporting Information, Table S1-4). Additionally, we conducted a manual search of the reference lists of the included articles to identify potential studies that may have been overlooked by the principal search.

Inclusion and exclusion criteria

The following inclusion and exclusion criteria were employed for this systematic review and meta-analysis: (1) studies conducted exclusively on adult patients (age >18 years) diagnosed with SSc; (2) studies reporting the prevalence of sarcopenia in SSc patients; (3) studies defining sarcopenia as low muscle mass (LMM) plus low muscle strength (LMS), and/or low physical performance (LPP), or LMM alone; LMM was evaluated by dividing appendicular skeletal muscle mass (in kilograms) by height in meters squared, LMS by hand grip strength, LPP by gait speed or short physical performance battery, and diagnostic cutoffs varied depending on the criterion[9,17,18,20]; (4) studies measuring lean mass or muscle mass using one of the four main techniques: dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), magnetic resonance imaging (MRI) and computed tomography (CT); and (5) observational studies. Conversely, the exclusion criteria were as follows: repeated studies (defined as either identical data or identical articles).

Outcomes

The main outcomes of this systematic review comprise two aspects: firstly, the prevalence of sarcopenia among patients with SSc, and secondly, the clinical features of patients with SSc

who suffer from sarcopenia compared to those who do not. These clinical features encompassed a range of factors, namely, the duration of disease, the quality of life assessed by the Short Form-36 (SF-36) survey[21], the pulmonary function (the forced vital capacity (FVC) predicted value), and the C-reactive protein (CRP) level. These features are frequently the focus of clinical studies in patients with SSc, and it is of significant interest to understand how sarcopenia impacts them.

Study selection and data extraction

After removing duplicates, the studies identified through the search strategy underwent eligibility assessment by two reviewers (X.T. and T.L.), who independently screened the titles and abstracts and assigned them to one of three categories: 'include,' 'exclude,' or 'maybe.' Subsequently, the full-text articles of those categorized as 'include' or 'maybe' were reviewed to arrive at a final selection, with any discrepancies between the reviewers resolved by a third reviewer (J.Y.). Two reviewers (X.T. and X.S.) independently extracted the following variables using a pre-defined data collection form: first author, publication year, country, study design, sample size, mean age, number of females, disease subtype, mean disease duration, SSc diagnostic criteria, sarcopenia diagnostic criteria, assessment method for detecting sarcopenia, and prevalence of sarcopenia. Additionally, we also collected data on clinical features in the form of mean ± standard deviation (SD). For those studies that were not expressed as mean ± SD, we performed data conversion with the method recommended by Luo et al.[22] and Wan et al.[23]

Assessment of quality

Two authors (X.T. and T.J.) independently assessed the quality of the included studies using

the Agency for Healthcare Research and Quality (AHRQ)[24] scale in cross-sectional studies. This tool consists of 11 questions, with a 'no' or 'unclear' receiving 0 points and a 'yes' receiving 1 point. Low-quality articles received scores of 0–3, moderate-quality scores of 4–7, and high-quality scores of 8–11. The Newcastle–Ottawa Scale (NOS) was used to judge the quality of the cohort study.[25] The NOS scoring system assigns points from 0 to 9. We assigned values ranging from 0 to 3, 4 to 6, and 7 to 9 for low, moderate, and high-quality, accordingly. Any discrepancies were resolved through discussion or consensus with a third author (J.Y.).

Statistical Analysis

The prevalence of sarcopenia in SSc patients was determined by calculating the proportion of patients with sarcopenia in each study and conducting a meta-analysis of single proportions. We performed this meta-analysis using Stata/SE (Version 12.0, StataCorp, Texas, USA). Forest plots were used to illustrate the prevalence of sarcopenia, along with corresponding 95% confidence intervals (CIs) for each study and the overall estimate. Clinical characteristics such as disease duration, the SF-36 value, the FVC predicted value, and the CRP level from studies that compared SSc patients with and without sarcopenia were also analyzed using Review Manager (Version 5.4, The Cochrane Collaboration, Oxford, UK) and expressed as mean difference (MD) or standardized mean difference (SMD) with 95% CI. Heterogeneity across studies was assessed via the I^2 statistic, with values of 25% being considered low, 50% moderate, and 75% high.[26] Considering the variation in the definition of sarcopenia, diagnostic criteria, and population characteristics among the included studies, this study employed a random-effects model.

Subgroup analyses were conducted to investigate potential sources of heterogeneity, focusing

on sarcopenia definition (1 vs >1 diagnostic criteria), disease subtype, and mean age (< 60 vs ≥60 years). The reasons for grouping in subgroup analysis are as follows. Firstly, variability in the definition of sarcopenia will result in varied prevalence estimates for patients with SSc. Unsurprisingly, increasing the number of necessary criteria in a sarcopenia definition will eventually diminish sarcopenia prevalence. Additionally, the disease subtype is an important factor that affects the prevalence of sarcopenia. Patients with dcSSc are more prone to develop sarcopenia.[14] Moreover, age is an essential factor that influences the onset and course of sarcopenia, with the prevalence of sarcopenia increasing with age. Meta-regressions were also conducted on sample size, mean age, percentage of female patients, and duration of SSc. However, due to limited data on the clinical characteristics of SSc patients with and without sarcopenia, subgroup analyses and meta-regressions were not conducted. To evaluate the stability of pooled results, sensitivity analysis was performed by excluding one study at a time. Publication bias was evaluated using Egger's test[27]. Statistical significance was set at $P < 0.05$ for all analyses.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Results

Search results

A comprehensive search of databases yielded 4583 articles. After eliminating duplicates (n = 1523), the remaining 3060 titles and abstracts were screened. Subsequently, 25 relevant articles underwent full-text reading, and 16 were excluded for reasons specified in the flow chart and

Table S5 in the supplement. Ultimately, 9 studies were eligible for inclusion in this meta-analysis (Figure 1).

Study characteristics

Table S6 provides an overview of the characteristics of the studies included in this meta-analysis. A total of 815 SSc patients from 9 eligible studies[4–7,12–16] published between 2018 and 2022 were included. The mean age of the patients ranged from 52.5 to 64.1 years, while the mean duration of SSc ranged from 6 to 12.8 years. The majority of the studies (8 out of 9) had a cross-sectional design,[4–6,12–16] with one being a retrospective cohort study.[7] The studies were conducted in various regions, with five from Europe,[5–7,12,16] two from South America,[13,15], and two from Asia.[4,14]

Risk of bias

According to the AHRQ and NOS ratings, 8 of the eligible studies[4–7,12,14–16] were of moderate quality, with only one article[13] classified as high quality. (Table S7-8 in the supplement).

Methods used to assess sarcopenia

Table S6 provides an overview of the diagnostic criteria used to evaluate sarcopenia across the included studies. Among them, seven studies[4–7,13,15,16] employed EWGSOP criteria (5 EWGSOP 2010 and 2 EWGSOP 2019) while one[14] used AWGS criteria. Three studies[5,7,12] solely relied on LMM for sarcopenia diagnosis, while six studies[4,6,13–16] utilized LMM combined with LMS and/or LPP. The sarcopenia diagnostic criteria and cutoff values in the studies are summarized in Table 1. Muscle mass was measured using dual-energy X-ray absorptiometry in seven studies[5,7,12–16] and bioelectrical impedance analysis in two

studies[4,6]. Handgrip dynamometry was utilized to assess muscle strength in six studies[4,6,13–16], while gait speed (three studies[14–16]) and the short physical performance battery (SPPB) (two studies[13,16]) were used to evaluate physical performance.

Sarcopenia prevalence

Overall sarcopenia prevalence

The nine studies included in this review reported the prevalence of sarcopenia in SSc patients, ranging from 10.7% to 42% (Table S6). The pooled prevalence of sarcopenia in patients with SSc was estimated at 22% (95% CI 17% to 28%), as shown in Figure 2.

Subgroup analysis of sarcopenia prevalence

The prevalence of sarcopenia differed in studies that utilized a single criterion [LMM; 28% (95% CI 16% to 42%)] versus those that employed >1 criterion [LMM + LMS and/or LPP; 20% (95% CI 15% to 25%)], with no statistically significant difference noted (P = 0.234, Figure S1 in the supplement). Subgroup analysis based on disease subtype revealed that sarcopenia prevalence in dcSSc [30% (95% CI 23% to 37%)] was higher than that in lcSSc [23% (95% CI 12% to 36%)], and the difference was not statistically significant (P = 0.339, Figure S2 in the supplement). The United Nations defines an older person as someone above the age of 60. Therefore, we also performed a subgroup analysis stratified by the mean age of the participants, with < 60 and ≥ 60 years as the cutoff points. The prevalence of sarcopenia was lower in patients younger than 60 years [20% (95% CI 12% to 29%)] vs those older than 60 years [24% (95% CI 17% to 32%)], but the difference was not of statistical significance (P = 0.539, Figure S3 in the supplement).

Meta-regression analyses

The results of the meta-regression analyses indicated that there was no significant association between the prevalence of sarcopenia and sample size (P = 0.424), mean age of patients (P = 0.532), the proportion of female patients (P = 0.449), or duration of SSc (P = 0.255). These findings are summarized in Table S9 of the supplementary material.

Impact of sarcopenia on the clinical characteristics of SSc patients

Duration of SSc

Data from a total of four studies comprising 511 patients were included in the meta-analysis of SSc duration, which revealed that individuals with sarcopenia did not have a longer disease duration than those without sarcopenia [MD 2.97 years (95% CI -0.13 to 6.08); I^2 = 90%, Figure 3A].

Quality of life

The meta-analysis included two studies with a total of 191 patients, which provided data on the SF-36 value. The findings of the meta-analysis indicated that patients with sarcopenia had a lower SF-36 value compared to those without sarcopenia [MD -12.02 (95% CI -19.11 to -4.93); I^2 = 71%, Figure 3B], that is, having sarcopenia was associated with poorer quality of life compared with those without sarcopenia.

Pulmonary function

The meta-analysis incorporated two studies involving a total of 320 patients that reported data on the FVC predicted value. The results indicated that patients with sarcopenia did not have a lower FVC predicted value than those without sarcopenia [MD -4.02% (95% CI -8.67 to 0.62); I^2 = 0%, Figure 3C]. Therefore, there was no significant difference in pulmonary function between sarcopenia and non-sarcopenia patients.

CRP level

Data from two studies comprising 191 patients were analyzed to investigate the relationship between sarcopenia and CRP level. The results showed that sarcopenia was associated with a higher CRP level than no sarcopenia [SMD 0.67 (95% CI 0.35 to 1.00); $I^2 = 0\%$, Figure 3D].

Sensitivity and publication bias analysis

The sensitivity analysis revealed that the overall prevalence of sarcopenia was not significantly affected by any individual study (Figure S4 in the supplementary material). In addition, Egger's test suggested no publication bias in this review (P = 0.311, Figure S5 in the supplement).

Discussion

Primary results

In this meta-analysis encompassing nine studies, the pooled prevalence of sarcopenia among 815 patients diagnosed with systemic sclerosis (SSc) was estimated to be 22%, which was significantly greater than that in community-dwelling older adults.[28] Notably, SSc patients diagnosed with sarcopenia had poorer quality of life and a higher CRP level, while no significant difference was noted for disease duration and FVC predicted value when compared to patients without sarcopenia.

Mechanism basis

Sarcopenia, a condition characterized by loss of muscle mass and function, can be age-associated (primary sarcopenia) or secondary to chronic diseases, including malignant tumors and musculoskeletal diseases.[29–31] Compared with other chronic inflammatory rheumatic diseases, sarcopenia has not been extensively evaluated in SSc. Recently, some studies have focused on the presence of sarcopenia in SSc. Nevertheless, the pathogenesis of sarcopenia in

SSc remains unclear. Possible mechanisms contributing to the development of sarcopenia in SSc include (1) malnutrition: gastrointestinal involvement is the most frequent internal complication of SSc[32]. Symptoms such as esophageal reflux, early satiety, nausea, and vomiting may lead to reduced caloric intake.[12] Additionally, fibrosis of the bowel wall and small intestine bacterial overgrowth can result in malabsorption of nutrients. Therefore, malnutrition is prevalent in SSc patients. One study in community-dwelling older adults demonstrated that malnutrition is an independent predictor of sarcopenia [odds ratio (OR) 2.42; 95% CI 1.04 to 5.60][33]. (2) Oxidative stress and chronic inflammation: oxidative stress, which is an imbalance in oxidant and antioxidant levels, is commonly observed in SSc patients[34]. Increased oxidative stress disrupts the balance between the degradation and resynthesis of skeletal muscle proteins[35]. In addition, chronic low-grade inflammation is detrimental to skeletal muscle in humans[36]. Inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, have been reported to contribute to the pathogenesis of SSc[37]. These cytokines stimulate protein catabolism and suppress muscle synthesis, ultimately leading to muscle wasting[38]. (3) Physical inactivity: due to pain and joint involvement, physical inactivity is common in SSc patients[39], leading to faster and greater muscle loss[11]. However, the mechanism of sarcopenia in SSc patients remains to be confirmed by future research.

Interpretation of the results

This review offers unique insight into sarcopenia in patients with SSc. It describes the prevalence of sarcopenia in SSc patients and how it is impacted by the different definitions of sarcopenia. The varying prevalence of sarcopenia may be explained in part by the variety of

definitions. However, there was no statistical difference between 1 and >1 diagnostic criteria. This might be due to the lack of robustness of the combined results as a result of the small number of studies using one diagnostic criterion. In addition, discrepancies in sarcopenia diagnostic cutoffs among the included studies may have resulted in differing sarcopenia prevalence. Furthermore, our meta-analysis indicated no statistically significant variation in the prevalence of sarcopenia between disease subtypes, which is consistent with the results of Sangaroon et al.[14] It is important to note that this conclusion needs to be interpreted with caution due to the limited number of studies that could be included in the analysis. Although sarcopenia commonly occurs as an age-related process in older individuals[11], it becomes more common as people get older. Our meta-analysis demonstrated that the difference in the prevalence of sarcopenia was not statistically significant between the patients over 60 years old and the patients under 60 years old. Furthermore, patients younger than 60 years old all used >1 criterion to diagnose sarcopenia, which makes the prevalence of sarcopenia in young people even lower. This suggests that, despite the influence of age on the presence of sarcopenia, the illness itself is responsible for sarcopenia onset and progression in SSc patients. Therefore, rheumatologists should screen for sarcopenia even in young SSc patients. However, this conclusion must be confirmed by a large number of high-quality clinical studies.

Our meta-analysis also revealed that SSc patients diagnosed with sarcopenia had a poorer quality of life. On the one hand, involvement of the heart, lungs, and joints in SSc patients might result in diminished exercise capacity and decreased physical activity,[8] making SSc patients vulnerable to sarcopenia. On the other hand, sarcopenia is associated with a variety of negative outcomes, including hospitalization, functional decline, falls, and death.[40,41]

Therefore, it should come as no surprise that SSc patients with sarcopenia have a higher risk of having a worse quality of life. Furthermore, individuals with SSc who had sarcopenia had higher CRP levels, according to our findings. This result is not surprising given that chronic inflammation is a known contributor to secondary sarcopenia.[42] However, our review indicated that no significant difference was noted for disease duration or FVC predicted value between SSc patients with and without sarcopenia. According to the results of Caimmi et al,[12] the longer the disease duration, the greater the risk of sarcopenia. This might be due to the minimal number of studies that could extract data, resulting in false negatives in the pooled study results. Therefore, large prospective cohort studies are required to confirm this conclusion.

Clinical implications

This meta-analysis provides a comprehensive evaluation of the prevalence, diagnostic criteria, and impact of sarcopenia in SSc patients, which has not been previously done. The results of this study provide an up-to-date estimation of the prevalence of sarcopenia, which can guide sample size calculations for future research. While sarcopenia has been relatively under-studied in SSc compared to other rheumatic diseases, our findings suggested that neither sarcopenia definition, disease subtype nor age affects the prevalence of sarcopenia. SSc patients with sarcopenia had a poorer quality of life, according to our findings. Therefore, early identification and intervention of sarcopenic patients by clinicians is crucial. The high prevalence of sarcopenia in SSc patients highlights the importance of early screening and management. Standardized criteria for sarcopenia diagnosis are also essential in SSc patients to minimize variations in prevalence. These findings have important implications for future research,

clinical practice, and policy development in managing sarcopenia in SSc patients, and can potentially improve outcomes for these patients.

Strengths and weaknesses

This systematic review undertook a comprehensive and meticulous literature search to ensure that all pertinent studies were included in the analysis. The selection of studies, data extraction, and quality assessments were carried out independently by two reviewers, thereby enhancing the accuracy and reliability of the results. Subgroup analyses and meta-regression analyses were also conducted to explore the possible sources of heterogeneity, while sensitivity and publication bias analyses were performed to ensure robust and dependable conclusions.

Nevertheless, we must acknowledge certain limitations of our study. Firstly, since most of the included studies were cross-sectional, it is impossible to establish a definitive causal relationship between sarcopenia and SSc. Nonetheless, this is a limitation inherent to the original literature and beyond our control. We, therefore, look forward to high-quality prospective cohort studies to provide more conclusive evidence on this matter. Secondly, there was some heterogeneity among the included studies in terms of factors such as the definition of sarcopenia, measurement approaches, and diagnostic cut-offs. Moreover, most of the studies had small sample sizes. Therefore, future studies should aim to use uniform diagnostic criteria for sarcopenia and expand the sample size to improve the quality of research. Finally, even though this review included studies from different continents (Europe, South America, and Asia), data on participant race were not accessible, limiting its potential applicability to specific patient subgroups.

Conclusions

Sarcopenia is common in patients with SSc. SSc patients with sarcopenia had a worse quality of life and higher CRP levels, based on our findings. Given the detrimental impact of sarcopenia on quality of life, future efforts aimed at early identification of sarcopenia in the clinical assessment of patients with SSc may have significance.

Contributors

All authors conceived and designed this review; YJ, XPT, and JRY developed the search strategy; XPT and TPL screened studies; XPT and XYS extracted data; XPT and TTJ appraised study quality; XPT and NG conducted data analysis; XPT drafted the manuscript; all authors revised the manuscript for important intellectual content. JRY had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

Not applicable.

Data availability statement

The data are accessible upon reasonable request from the corresponding author.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table 1 Criteria and cutoff points used to detect sarcopenia in each study

First author and year	Country	Sarcopenia diagnostic criteria	Cutoff points
Caimmi (2018)[12]	Italy	SMI	LMM: ASM/height2 < 7.26 kg/m^2 for men and < 5.50 kg/m^2 for women.[43]
Siegert (2018)[6]	Germany	EWGSOP (2010)	LMM: ALM/height2 < 7.26 kg/m2 for men and <5.50 kg/m2 for women.[43] LMS: BMI ≤ 24, HGS ≤ 29 kg; 24.1 ≤ BMI ≤ 26, HGS ≤ 30 kg; 26.1 ≤ BMI ≤ 28, HGS ≤ 30 kg; BMI > 28, HGS ≤ 32 kg for men. BMI ≤ 23, HGS ≤ 17 kg; 23.1 ≤ BMI ≤ 26, HGS ≤ 17.3 kg; 26.1 ≤ BMI ≤ 29, HGS ≤ 18 kg; BMI > 29, HGS ≤ 21 kg for women.[44]
Corallo (2019)[5]	Italy	EWGSOP (2010)	LMM: RSMI < 7.26 kg/m2 for men and < 5.50 kg/m2 for women.[43]
Rincon (2019)[15]	Argentina	EWGSOP (2010)	LMM: RSMI < 7.26 kg/m2 for men and < 5.50 kg/m2 for women.[43] LMS: HGS< 30 kg for men and< 20 kg for women.[45] LPP: GS< 0.8 m/s (both genders).[45]
Paolino (2020) [7]	Italy	EWGSOP (2010)	LMM: RSMI < 7.26 kg/m2 for men and < 5.50 kg/m2 for women.[43]
Hax (2021)	Brazil	EWGSOP (2019)	LMM: ASMI < 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women.[46] LMS: HGS < 27 kg for men and < 16 kg for women.[47]

First author and year	Country	Sarcopenia diagnostic criteria	Cutoff points
			LPP: SPPB ≤ 8 point score.[48]
Sari (2021)[4]	Turkey	EWGSOP (2010)	LMM: ASMI < 7.26 kg/m2 for men and <5.50 kg/m2 for women.[43] LMS: BMI ≤ 24, HGS ≤ 29 kg; 24.1 ≤ BMI ≤ 26, HGS ≤ 30 kg; 26.1 ≤ BMI ≤ 28, HGS ≤ 30 kg; BMI > 28, HGS ≤ 32 kg for men. BMI ≤ 23, HGS ≤ 17 kg; 23.1 ≤ BMI ≤ 26, HGS ≤ 17.3 kg; 26.1 ≤ BMI ≤ 29, HGS ≤ 18 kg; BMI > 29, HGS ≤ 21 kg for women.[44]
Efremova (2022)[16]	Russia	EWGSOP (2019)	LMM: ASMI < 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women.[46] LMS: HGS < 27 kg for men and < 16 kg for women.[47] or Chair stand > 15 s for five rises.[49] LPP: GS ≤ 0.8 m/s.[50] or SPPB ≤ 8 point score.[48]
Sangaroon (2022)[14]	Thailand	AWGS (2019)	LMM: ASMI < 7.0 kg/m^2 for men and < 5.4 kg/m^2 for women.[20] LMS: HGS < 28 kg for men and < 18 kg for women.[20] LPP: GS< 1 m/s (both genders).[20]

SMI, Skeletal Muscle Mass Index; ASM, appendicular skeletal muscle mass; ALM, appendicular lean mass; RSMI, Relative Skeletal Muscle Mass Index; ASMI, Appendicular Skeleton Muscle Index; SPPB, Short Physical Performance Battery; GS, gait speed.

Figure legend

1. **Figure 1 The flow chart of the literature selection**

2. **Figure 2 The pooled prevalence of sarcopenia in SSc patients**

3. **Figure 3 Impact of sarcopenia on clinical characteristics in patients with SSc**

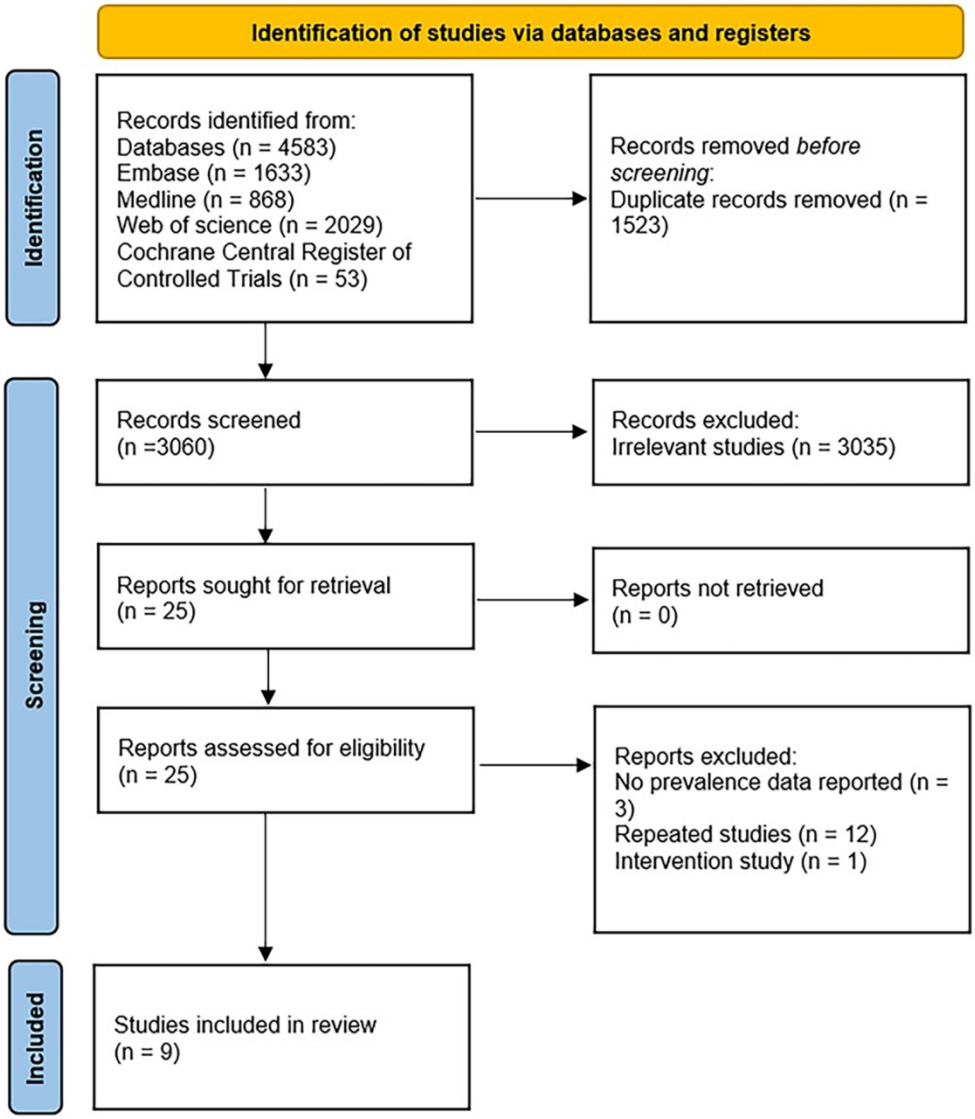

Figure 1 The flow chart of the literature selection

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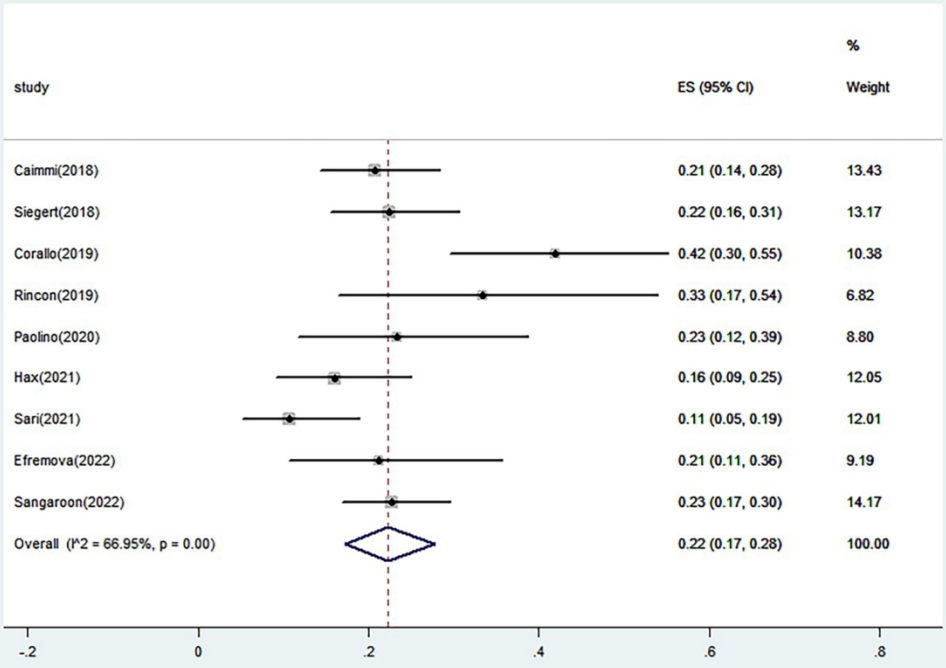


Figure 2 The pooled prevalence of sarcopenia in SSc patients

146x107mm (300 x 300 DPI)

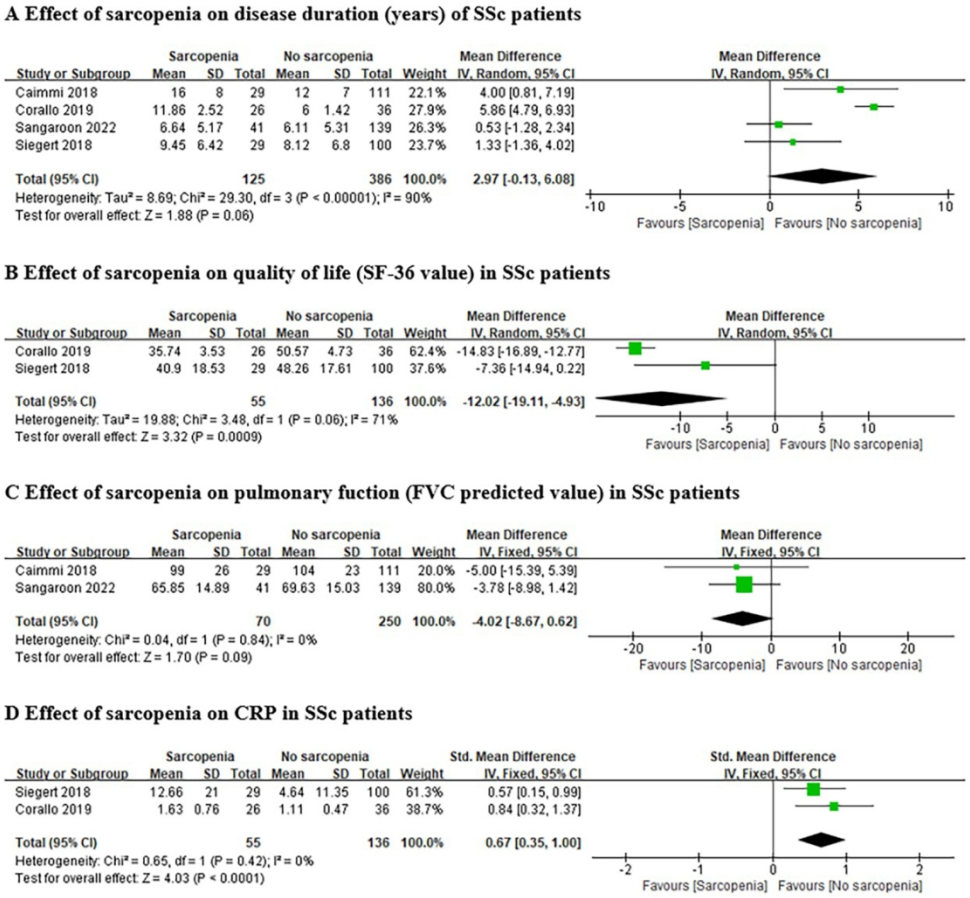


Figure 3 Impact of sarcopenia on clinical characteristics in patients with SSc

146x136mm (300 x 300 DPI)

Sarcopenia in Systemic Sclerosis: Prevalence and Impact - A Systematic Review and Meta-analysis

1. Table S1 Search strategy by Medline via Ovid SP
2. Table S2 Search strategy by Embase via Ovid SP
3. Table S3 Search strategy by Web of Science
4. Table S4 Search strategy by Cochrane Central Register of Controlled Trials via Ovid SP
5. Table S5 The reasons for the exclusion of full-text articles
6. Table S6 Characteristics of the included studies
7. Table S7 ARHQ Methodology Checklist for Cross-Sectional Study
8. Table S8 Newcastle-Ottawa Scale for Cohort study
9. Table S9 Meta-regression analyses of sarcopenia prevalence
10. Figure S1 Prevalence of sarcopenia by criteria
11. Figure S2 Prevalence of sarcopenia by disease subtype
12. Figure S3 Prevalence of sarcopenia by mean age
13. Figure S4 Sensitivity analysis
14. Figure S5 Egger's test for publication bias

Table S1 Search strategy by Medline via Ovid SP

1.	exp Scleroderma, Systemic/
2.	((Systemic or general* or diffus* or progress* or Limit*) adj3 sclerosis).mp.
3.	scleroderm*.tw.
4.	SSc.tw.
5.	1 or 2 or 3 or 4
6.	exp muscular atrophy/
7.	(sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat*).mp.
8.	((muscle or muscular) adj5 (atroph* or wast* or weak* or loss* or mass or degenerat*)).ti,ab.
9.	6 or 7 or 8
10.	5 and 9
11.	exp animals/ not humans.sh.
12.	10 not 11

Table S2 Search strategy by Embase via Ovid SP

1.	exp systemic sclerosis/
2.	((Systemic or general* or diffus* or progress* or Limit*) adj3 sclerosis).mp.
3.	scleroderm*.tw.
4.	SSc.tw.
5.	1 or 2 or 3 or 4
6.	exp muscle atrophy/
7.	(sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat*).mp.
8.	((muscle or muscular) adj5 (atroph* or wast* or weak* or loss* or mass or degenerat*)).ti,ab.
9.	6 or 7 or 8
10.	5 and 9
11.	exp animal/
12.	human/
13.	11 not 12
14.	10 not 13

Table S3 Search strategy by Web of Science

Topic= (((Systemic or general* or diffus* or progress* or Limit*) near/3 sclerosis) or sclerodem or ssc) and (sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat* or ((muscle or muscular) near/5 (atroph* or wast* or weak* or loss* or mass or degenerat*)))

Table S4 Search strategy by Cochrane Central Register of Controlled Trials via Ovid SP

1.	exp Scleroderma, Systemic/
2.	((Systemic or general* or diffus* or progress* or Limit*) adj3 sclerosis).mp.
3.	scleroderm*.tw.
4.	SSc.tw.
5.	1 or 2 or 3 or 4
6.	exp muscular atrophy/
7.	(sarcopen* or myopen* or dynapon* or amyotroph* or myoatroph* or myophagis* or myodegenerat*).mp.
8.	((muscle or muscular) adj5 (atroph* or wast* or weak* or loss* or mass or degenerat*)).ti,ab.
9.	6 or 7 or 8
10.	5 and 9

Table S5 The reasons for the exclusion of full-text articles

Study	Reason for the exclusion
Norman (2014)	Repeated study
Siegert (2014)	Repeated study
Caimmi (2017)	Repeated study
March (2017)	Repeated study
Doerfler (2017)	Intervention study
Paolino (2018)	Repeated study
Radic (2018)	Not reported sarcopenia prevalence data in SSc patients
Remolina (2019)	Repeated study
Sari (2019)	Repeated study
Veronica (2019)	Repeated study
Hax (2020)	Repeated study
Santo (2020)	Repeated study
Sangaroon (2020)	Repeated study
Peterson (2020)	Not reported sarcopenia prevalence data in SSc patients
Efremova (2021)	Repeated study
Sorokina (2022)	Not reported sarcopenia prevalence data in SSc patients

Table S6 Characteristics of the included studies

First author and year	Country	Study design	Sample size	Mean age(years)	Female, n	Disease subtype	Disease duration (years)	SSc diagnostic criteria	Sarcopenia diagnostic criteria	Criteria (assessment method of detecting sarcopenia)	Prevalence of sarcopenia	
											Total,n(%)	Diffuse,n(%)
Caimmi (2018)	Italy	Cross-sectional study	140	64	118	limited 97 diffuse 43	12.8	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA)	29(20.7%)	11(7.9%)
Siegert (2018)	Germany	Cross-sectional study	129	60	118	-	7	2013 ACR/EULAR	EWGSOP (2010)	LMM（BIA） LMS（HGS）	29(22.5%)	-
Corallo (2019)	Italy	Cross-sectional study	62	62	54	limited 50 diffuse 12	8	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA)	26(42%)	4(6.4%)
Rincon (2019)	Argentina	Cross-sectional study	27	52.5	20	limited 16 diffuse 11	7.8	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA) LMS（HGS） LPP (4mGS)	9(33.3%)	3(11.1%)
Paolino (2020)	Italy	Retrospective cohort study	43	64.1	36	-	10.2	2013 ACR/EULAR	EWGSOP (2010)	LMM (DXA)	10(23.3%)	-
Hax (2021)	Brazil	Cross-sectional study	94	60.5	87	-	12.5	2013 ACR/EULAR	EWGSOP (2019)	LMM (DXA) LMS（HGS） LPP (SPPB)	15(15.9%)	-
Sari (2021)	Turkey	Cross-sectional	93	52.6	86	-	10.7	1980ACR	EWGSOP	LMM（BIA）	10(10.7%)	-

First author and year	Country	Study design	Sample size	Mean age(years)	Female, n	Disease subtype	Disease duration (years)	SSc diagnostic criteria	Sarcopenia diagnostic criteria	Criteria (assessment method of detecting sarcopenia)	Prevalence of sarcopenia	
											Total,n(%)	Diffuse,n(%)
Efremova (2022)	Russia	study Cross-sectional study	47	53.9	47	limited 29 diffuse 18	6	2013 ACR/EULAR	EWGSOP (2018)	LMS（HGS） LMM (DXA) LMS (HGS and Chair rising test) LPP (GS and SPPB)	10(21.3%)	6(12.8%)
Sangaroon (2022)	Thailand	Cross-sectional study	180	58.8	119	limited 86 diffuse 94	6.2	-	AWGS (2019)	LMM(DXA) LMS(HGS) LPP(GS)	41(22.8%)	30(16.7%)

ACR, American College of Rheumatology; EULAR, European League against Rheumatology classification criteria; SMI, Skeletal Muscle Mass Index; EWGSOP, European Working Group on Sarcopenia in Old People; HGS, hand grip strength; 4mGS, 4 m gait speed; SPPB, Short Physical Performance Battery; GS, gait speed; AWGS, Asian Working Group for Sarcopenia.

Table S7 ARHQ Methodology Checklist for Cross-Sectional Study

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total Score
Caimmi (2018)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	Unclear	Yes	No	6
Siegert (2018)	Yes	Yes	Unclear	Yes	Unclear	Yes	No	No	No	Yes	No	5
Corallo (2019)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	No	Yes	No	6
Rincon (2019)	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	No	No	Yes	No	4
Hax (2021)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	Yes	No	8
Sari (2021)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	No	Yes	No	6
Efremova (2022)	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No	No	No	Yes	No	3
Sangaroon (2022)	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	No	Yes	No	6

Item 1. Define the source of information (survey, record review)
Item 2. List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications
Item 3. Indicate time period used for identifying patients
Item 4. Indicate whether or not subjects were consecutive if not population-based
Item 5. Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants
Item 6. Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)
Item 7. Explain any patient exclusions from analysis
Item 8. Describe how confounding was assessed and/or controlled
Item 9. If applicable, explain how missing data were handled in the analysis
Item 10. Summarize patient response rates and completeness of data collection
Item 11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained

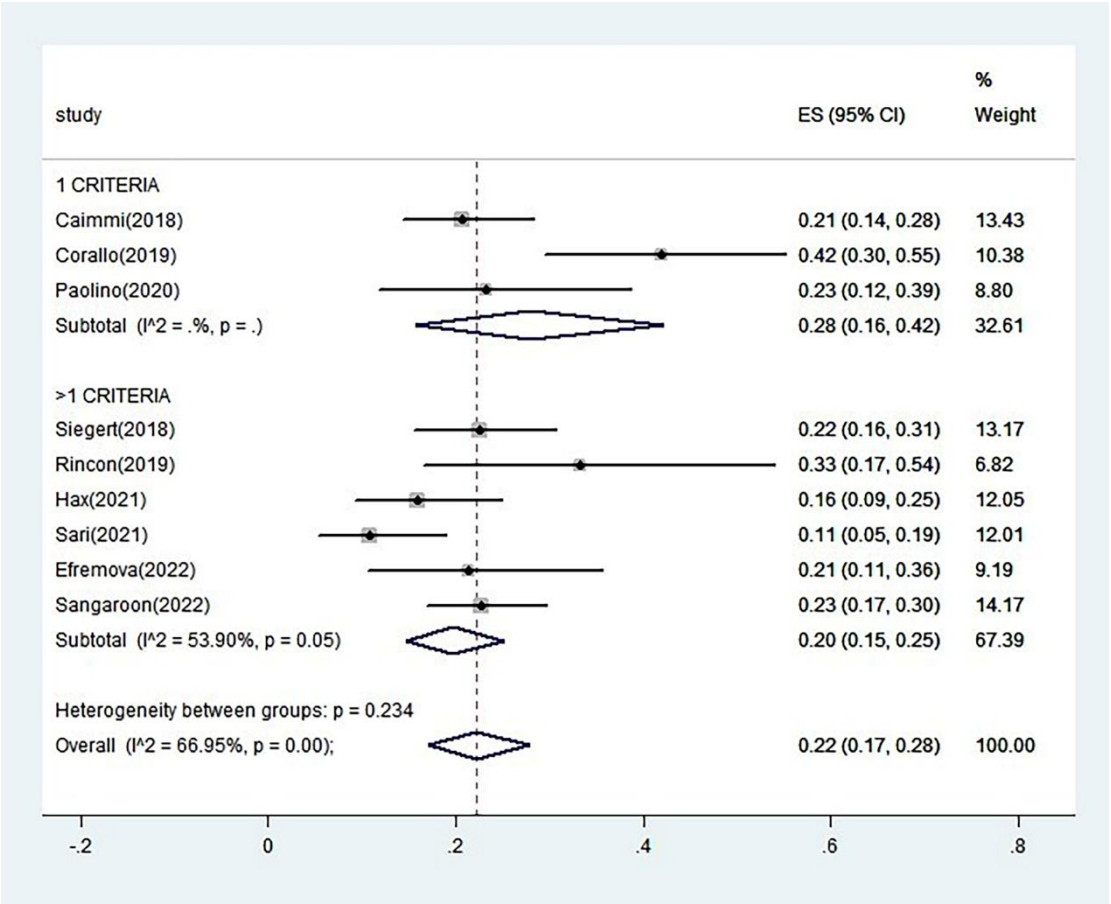
Table S8 Newcastle-Ottawa Scale for Cohort study

Study	Selection				Comparability	Outcome			Total Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Paolino (2020)	0	1	1	0	1	1	0	0	4

Table S9 Meta-regression analyses of sarcopenia prevalence

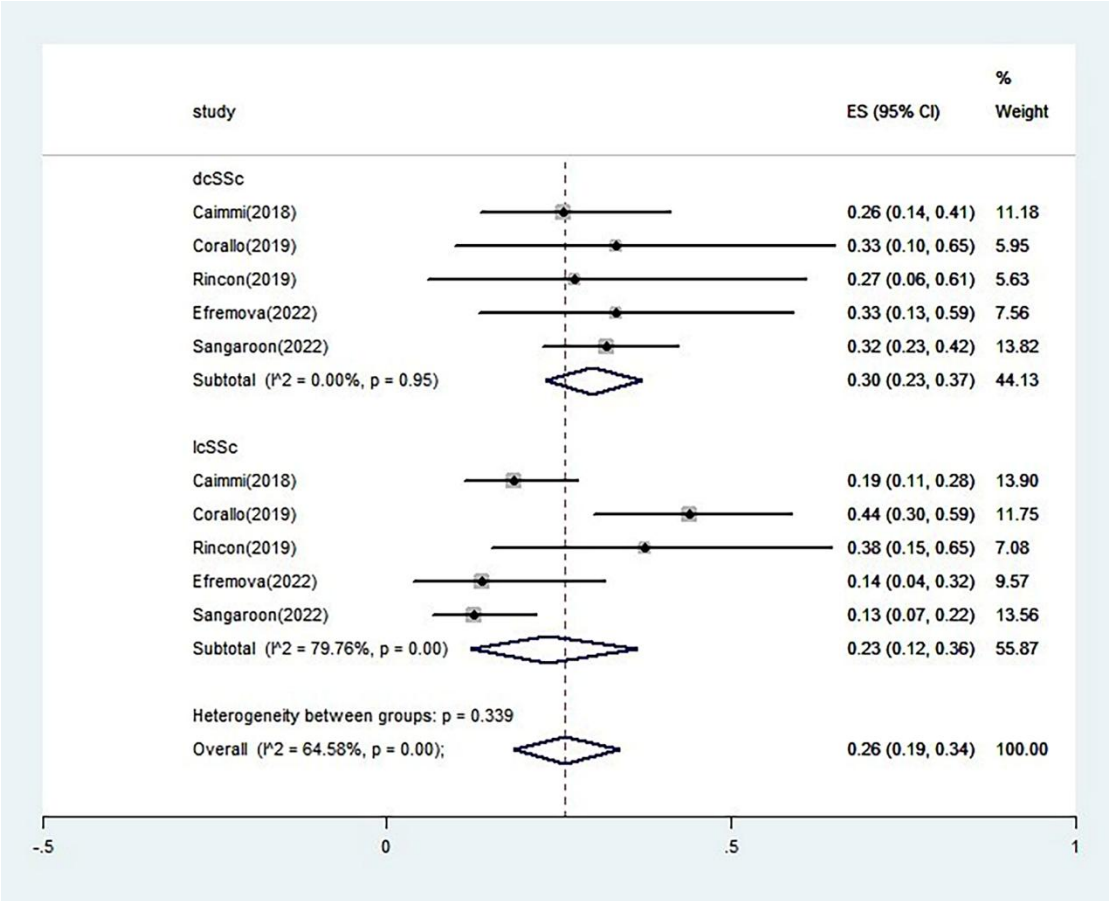
Variables	Coefficient	SE	P value	CI-Lower	CI-Upper
Sample size	-0.0022	0.0026	0.424	-0.0083	0.0039
Average age	0.0210	0.0319	0.532	-0.0545	0.0965
Proportion of female	-1.0603	1.3233	0.449	-4.1893	2.0687
Duration of SSc	-0.0606	0.0488	0.255	-0.1760	0.0549

Figure S1 Prevalence of sarcopenia by criteria



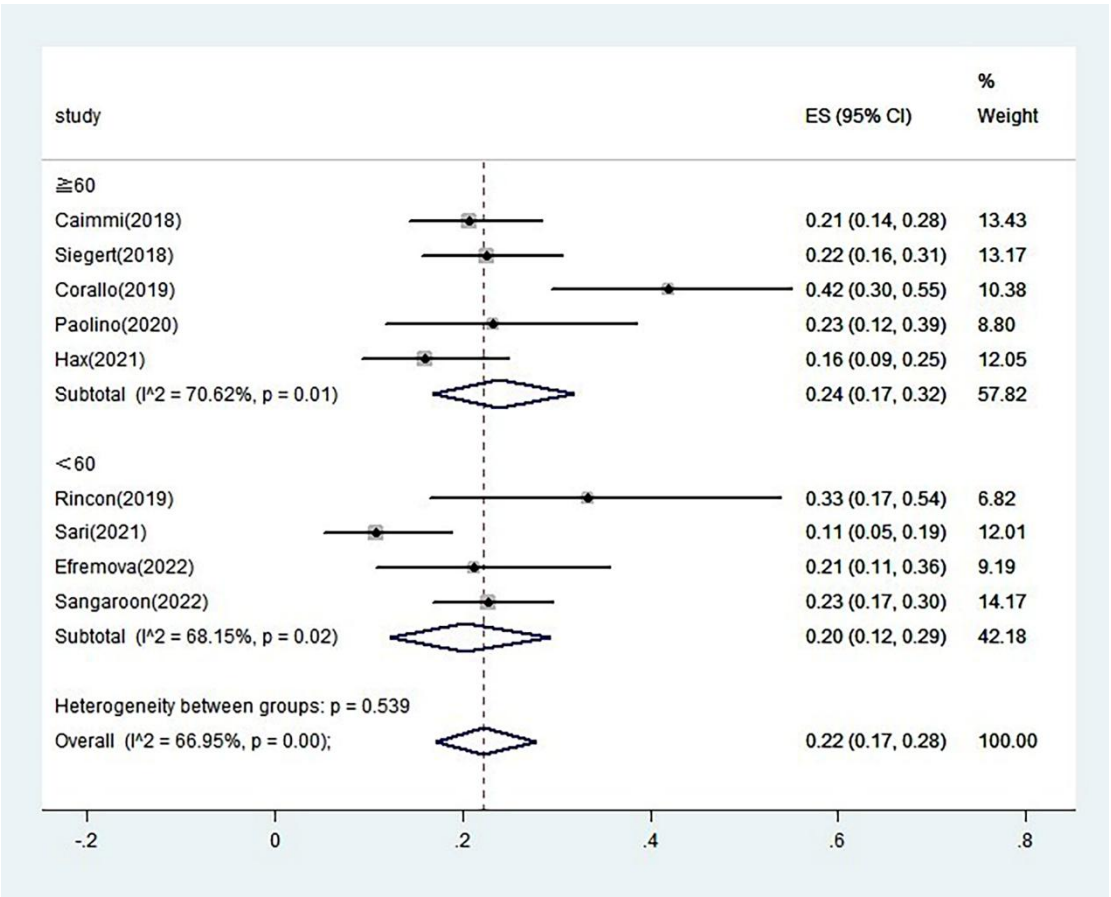
ES = effect size (prevalence); I^2 = I^2 heterogeneity statistic. A random effects model was used for analysis, and there was no significant difference between subgroups (P = 0.234).

Figure S2 Prevalence of sarcopenia by disease subtype



ES = effect size (prevalence); I^2 = I^2 heterogeneity statistic. The random effects model was used for the analysis, and there was no significant difference between the subgroups (P = 0.339).

Figure S3 Prevalence of sarcopenia by mean age



ES = effect size (prevalence); I^2 = I^2 heterogeneity statistic. The random effects model was used for the analysis, and there was no significant difference between the subgroups (P = 0.539).

Figure S4 Sensitivity analysis

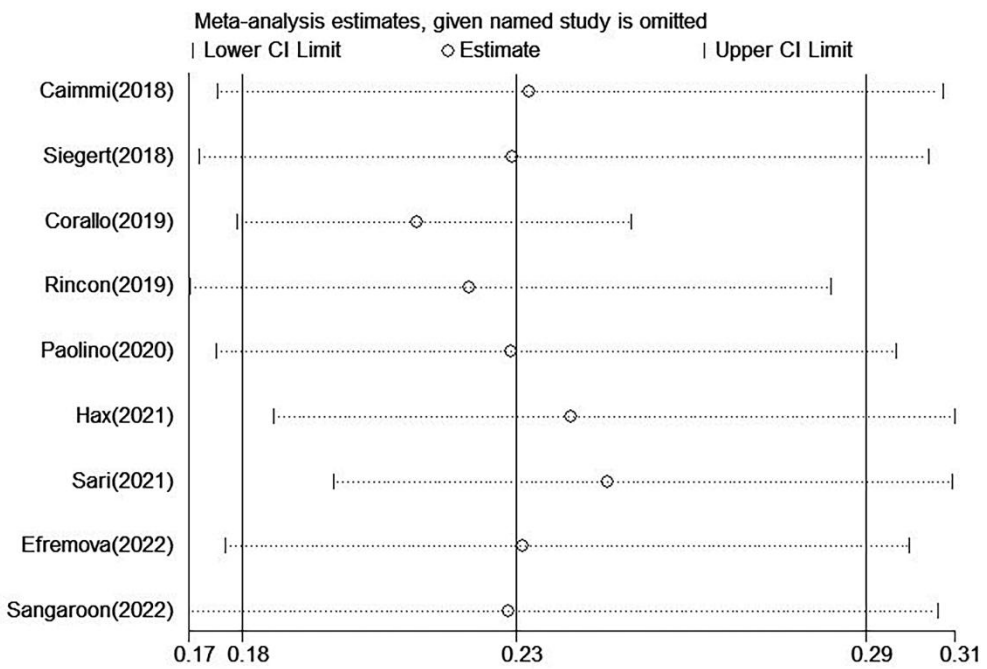
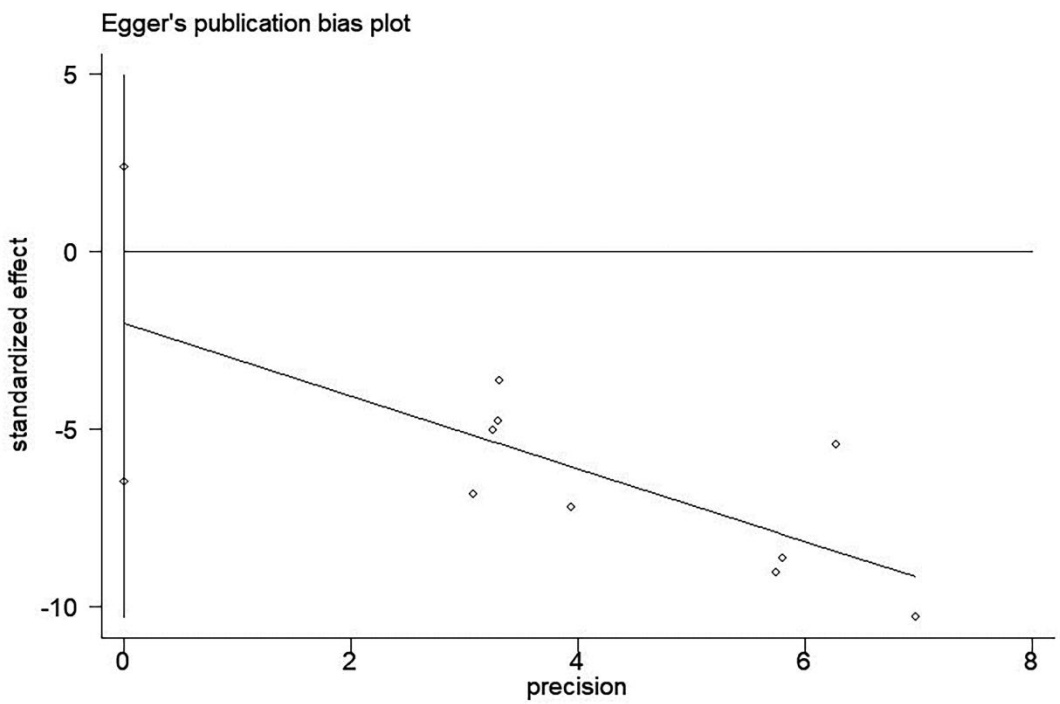


Figure S5 Egger's test for publication bias



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg. 1, lines 1-2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 5, lines 1-11
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 5, lines 13-15
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg. 6, lines 7-18
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg. 5, lines 18-22; Pg. 6, lines 1-5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S1-4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 7, lines 7-12
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg. 7, lines 12-19
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 6, lines 20-22; Pg. 7 lines 1-3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Table S6 and Figure 3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 7, lines 21-22; Pg. 8 lines 1-6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg. 8, lines 12-16
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Figure 2-3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg. 7, lines 17-19
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg. 8, lines

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			10-12
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg. 8, lines 8-16
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg. 8, lines 21-22; Pg. 9 lines 7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg. 9, lines 10-11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg. 9, lines 12-13
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	None
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1, Table S5
Study characteristics	17	Cite each included study and present its characteristics.	Table S6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S7-8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-3, Figure S1-3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Figure 2-3, Figure S1-3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg. 11, lines 3-20
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figure S1-3, Table S9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg. 13, lines 6-7, Figure S4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg. 13, lines 6-7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	None
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg. 14,

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			lines 19-22; Pg. 15, lines 1-22; Pg. 16 lines 1-9
	23b	Discuss any limitations of the evidence included in the review.	Pg. 15, lines 6-7
	23c	Discuss any limitations of the review processes used.	Pg. 17, lines 9-20
	23d	Discuss implications of the results for practice, policy, and future research.	Pg. 16, lines 11-22; Pg. 17 line 1
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg. 5, lines 18-20
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg. 5, lines 18-20
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 18, lines 11-20
Competing interests	26	Declare any competing interests of review authors.	Page 18, lines 21-22
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Table S6, Figure 2-3, Figure S1-3

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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