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Prevalence of systemic sclerosis and atherosclerosis: A systemic review and meta-analysis

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Abstract

Systemic sclerosis (SSc) and atherosclerosis-related diseases are among the most diagnosed diseases persisting globally. In agreement with earlier publications, we wanted to determine the prevalence of SSc and atherosclerosis. Thorough systematic searches of published studies across various countries in Embase, Medline, Web of Science, Scopus, and PubMed were performed to update our systemic review from January 1990 to December 2020. The author/s, year of publication, sampling size, Mortality, Study design, the prevalence of a particular Sex in that study, mean age, follow up years, limited cutaneous systemic sclerosis (LcSSc) patients, disease duration, body mass index, the prevalence for various symptoms of SSc and NOS of the selected study were explored in this study. The search yielded 1191 articles among which 81 articles were finally encompassed in this study. Among these selected 81 articles, 63 were related to Atherosclerosis among which 29 and 34 articles were prospective and retrospective studies respectively. The studies related to atherosclerosis involved a total of 43, 60,282 participants with their average age of mortality as 54.68 patients per 1000 individuals among the prevalent persons of the disease. However, 18 articles were related to Systemic Sclerosis involving 5821 patients with mean age 53.79 years. This study revealed that the SSc and atherosclerosis symptoms correlate with each other and SSc increases the prevalence of atherosclerosis. SSc patients are at higher risk of having atherosclerotic diseases especially cardiovascular diseases and on the diagnosis of SSc in the patients. As a result, preventative actions for atherosclerotic disorders must be adopted.

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Introduction

Systemic sclerosis (SSc), commonly known as scleroderma, is distinguished by Vasculopathy, extensive fibrosis of the skin and visceral organs, microangiopathy, and immunological disorders. It is a complex multi-systemic chronic inflammatory autoimmune disease of unknown etiology. SSc is estimated to impact 20 per million persons (Nikpour *et al.*, 2010) and is defined by three hallmarks: a vascular disease with pathognomonic microvascular involvement, skin and visceral organ fibrosis, and systemic inflammation with circulating autoantibodies and pro-inflammatory cytokines (Panopoulos *et al.,* 2013; Dumoitier *et al.,* 2014;). Despite evidence of better longevity, systemic sclerosis has the highest mortality rate of any rheumatic condition, especially in people with widespread cutaneous systemic sclerosis (Nihtyanova *et al.*, 2010; Tyndall *et al.*, 2010). For the patient, systemic sclerosis is coupled with a high level of uncertainty about the result and the emergence of potentially fatal or life-altering symptoms. Because systemic sclerosis is a rare disease with a significant unmet medical need, it is classified as an orphan disease (Denton, 2015; Khanna *et al.*, 2015; Chung *et al.,* 2015). If a patient's diagnosis is delayed, it adds to their suffering. Symptoms of inflammatory skin illness, puffy and swollen fingers, musculoskeletal inflammation, and constitutional indications such as weariness have been reported in some patients (Bellando-Randone *et al.,* 2012). Organ-based symptoms of the disease, such as lung fibrosis, pulmonary arterial hypertension, renal failure (typically with accelerated phase hypertension and a thrombotic microangiopathy clinical picture), or gastrointestinal problems, have been found in some patients.

Microvasculopathy is well-recognized in SSc and is clinically mirrored by the Raynaud phenomenon which is one of the earliest features of SSc. Endothelial breakdown, mononuclear cell infiltration of the vascular wall, blatant obliterative lesions, and gradual capillary loss are all pathologic alterations. Chronic inflammation, circulating autoantibodies, and proinflammatory cytokines all have a role in the etiology of pulmonary arterial hypertension, scleroderma renal crisis, and digital ulcers in SSc patients (Kurmann *et al.*, 2019). Endothelial dysfunction is one of the first steps in the pathophysiology of SSc, and it can lead to vasculopathy, which can lead to atherosclerosis (Ali *et al.*, 2015).

The heart is one of the principal organs affected by SSc, and clinically obvious cardiac involvement is linked to a bad prognosis, with up to 70% mortality recorded after 5 years (Ferri *et al.,* 2002; Ashida *et al*, 2009). Approximately 25% of all SSc-related deaths are due to cardiac reasons (Hachulla *et al.,* 2009; Tyndall *et al.,* 2010). Recently a population-based cohort showed that SSc patients had increased incidence rates of myocardial infarct (MI) and stroke (Heidenreich *et al.*, 2011). Khurma *et al.*2008 found a high rate of detectable coronary artery calcification in SSc patients who did not have any subcutaneous calcinosis.Myocardial involvement is common in SSc, and when sensitive tools are used, it has been estimated to occur in up to 100% of SSc patients (Allanore *et al.,* 2008; Meune *et al.,* 2010). All of the cardiac tunics, including the endocardium, myocardium, and pericardium, could be affected. Pericardial effusion, auricular and ventricular arrhythmias, conduction system anomalies, valvular impairment, myocardial ischemia, hypertrophy, and myocardial dysfunction with/without heart failure are all possible outcomes.

Raynaud's phenomenon, skin thickening, and internal organ fibrosis characterize the clinical presentation of SSc. Although the cause of SSc is uncertain, autoimmune inflammation, fibrosis, and vasculopathy may play a role (Elhai *et al.*, 2015; Denton and Khanna, 2017). When compared to healthy controls, SSc patients have lower peripheral vascular reactivity and endothelial dysfunction (Frech, *et al.,* 2015). According to a meta-analysis, persons with SSc have a greater risk of coronary artery disease (Ungprasert *et al.*, 2014). Patients with rheumatic illnesses (Ungprasert *et al.*, 2014) such as systemic lupus erythematosus and SSc (Solomon *et al.*, 2003; Hesselvig *et al.*, 2016) have an elevated fracture risk (incidence 9.50 percent). Furthermore, patients with SSc and a spinal fracture have a greater 1-year mortality risk than healthy people (13 Vs 3 percent). Previous research has highlighted the

severity of bone loss in SSc patients, with low BMD rates ranging from 27 to 53.3 percent (Hesselvig *et al.*, 2016). According to WHO, Systemic sclerosis is one of the major deaths causing disease of the present time in the world. The organ related adverse effects of systemic sclerosis is shown in Table 1.

Table 1. Organ system, clinical manifestation and prophylactic treatment of systemic sclerosis.

Organ system	Clinical manifestation	Examples of treatments
Skin and musculoskeletal	Scleroderma Inflammatory arthritis	Immunosuppressive therapy e.g., cyclophosphamide (up to 2mg/kg per day), methotrexate (15–25mg/week), and mycophenolate mofetil (up to 3g/day)
Respiratory	Pulmonary arterial hypertension	Endothelin-receptor antagonists Prostacyclin analogs Phosphodiesterase type 5 (PDE5) inhibitors Soluble guanylate cyclase agonists
	Interstitial lung disease	Immunosuppressive therapy (e.g., cyclophosphamide and mycophenolate mofetil
Peripheral vascular	Raynaud's phenomenon and digital ulcers	Calcium-channel blockers PDE5 inhibitors Angiotensin II-receptor blockers Endothelin-receptor antagonists Prostacyclin analogues (e.g., intravenous iloprost)
Cardiovascular	Heart failure	Appropriate drug therapies used in heart failure (e.g., ACE inhibitors and diuretics)
	Inflammatory cardiac disease	Immunosuppressive therapy (e.g., steroid and/or cyclophosphamide)
Gastrointestinal	Gastro-oesophageal reflux disease	Proton-pump inhibitors
Renal	Scleroderma renal crisis	ACE inhibitors

Atherosclerosis (from the Greek arterios, which means artery, and sclerosis, which means hardening), also known as Arteriosclerotic Vascular Disease or ASVD, is the most common form of cardiovascular disease and the world's largest cause of death (WHO, 2011). The mechanisms promoting atherosclerosis in connective tissue illnesses are uncertain, however chronic inflammation (Rho *et al.,* 2009) altered lipid profiles and function (McMahon *et al.*, 2006; O'Neill *et al.,* 2010) autoantibodies (Piper *et al.,* 2007), and endothelial dysfunction (Hansson, 2005) are thought to play a role. Atherosclerosis is a condition characterized by inflammation and malfunction of the lining of the affected blood vessels, as well as the accumulation of cholesterol, lipids, and cellular debris. Atherosclerosis is a specific type of arteriosclerosis, but the terms are sometimes used interchangeably. Atherosclerosis is more common in older adults; however, it can begin in adolescence. Inside the artery, streaks of white blood cells will appear on the artery wall. Signs depend on which artery is narrowed or blocked. The various stages of the onset of atherosclerosis are shown in Fig. 1.

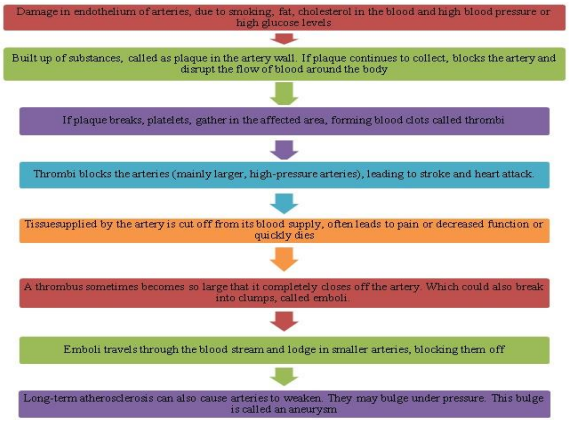

Fig. 1. The flow chart given below depicts the cause of Atherosclerosis and various stages of atherosclerosis.

The main process of cardiovascular disease is atherosclerosis which starts at an early age of a patient without any major symptom in the initial stages. Symptoms get worse after their progression into the advanced stages (McGill *et al.*, 2002; Hong, 2010). The growing burden of atherosclerotic diseases on the healthcare systems indicates an urgent need for research and its preventive measure implementations. The organ-related signs and symptoms of atherosclerosis are shown in Table 2.

Table 2. Atherosclerosis Signs and Symptoms.

SN	Organ related	Symptoms
1	Coronary Arteries	Coronary heart disease (CHD) angina and heart attack. Arrhythmia, an unusual heartbeat Coronary microvascular disease MVD (angina, shortness of breath), Sleep problems, Fatigue (tiredness), and lack of energy Pain or pressure in your upper body, including your chest, arms, neck, or jaw (angina). Shortness of breath. Chest pain, vomiting, extreme anxiety, coughing, faintness.
2	Carotid arteries	Numbness or weakness in your arms or legs Trouble speaking or understanding speech Drooping facial muscles Paralysis Sudden and severe headache Trouble seeing in one or both eyes Sudden weakness, Difficulty in breathing Dizziness, Loss of balance or coordination Unexplained falls Loss of consciousness
3	Peripheral arteries	Leg pain when walking Numbness In severe cases, death and gangrene can occur Increases the risk of a stroke or heart attack.
4	Renal arteries	Chronic kidney disease High blood pressure Kidney failure Loss of appetite, Swelling of the hands and feet, Difficulty concentrating, tiredness, Changes in how you urinate, nausea (feeling sick to the stomach), Itchiness or numbness Trouble concentrating

The studies linking systemic sclerosis with atherosclerosis were involved for this comprehensive review focusing that atherosclerosis exacerbates in patients with systemic sclerosis. This study also attempted to summarize all previous findings in order to serve as a foundation for future research.

Materials and methods

Search and selection Strategy of the Articles

PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-analysis) guidelines (Moher *et al*., 2009) were used for the systemic review of Systemic sclerosis and Atherosclerosis. An assessment of literature from 1st January, 1990 to the last week of December 2021 was comprehensively and systematically searched. Articles on atherosclerosis and systemic sclerosis from throughout the world, spanning the previous three decades, were chosen. The literature search was limited to the English language without geographic restrictions in online databases namely Embase, Medline, Web of Science, Scopus, and PubMed using various combinations of words related to 'Systemic Scleroderma' or 'Systemic sclerosis' or 'Autoimmune diseases' or 'Cardiovascular disease' or Systemic lupus erythematosus or Vasculopathy etc. and Arteriosclerotic Vascular Disease or ASVD or atherosclerosis or Coronary heart disease (CHD) or Coronary microvascular disease (CMD)or Stroke or Plaque, etc. The potentially relevant articles from the reference lists were hand-searched to locate additional studies.The studies reporting data related to atherosclerosis and systemic sclerosis were included in this study. The likely overestimation in the healthcare facility and hospital-based studies were excluded. The multiple publications based on larger sample size, single study, recent one as well as the study with comprehensive results were included.

Data extraction

All the relevant information related to authors, Year of publication, Study design, Sample size, Sampling method, Mean Age Group, Gender with its Prevalence, disease symptoms, mean follow-up years, Mortality, NOS scale, etcwere included in the review article. For studies where censoring age groups were reported, we imputed the midpoint of age groups in thestudies for further analysis. The year of publication was considered for the analysis and year of investigation was excluded as the same was not reported for many studies.

Results

The initial search involved 1191 articles of which 366 were found to be duplicates, 825 records were screened out of which 289 were irreverent records and were excluded from the studies. 536 records were screened on the basis of Title/s or Abstracts. The thorough reading of these studies resulted in 362 articles with no comparison groups, 32 studies with irrelevant dataand 64 articles with non-availability of specific data which was needed for the inclusion in our study.

Hence, 458 articles were also excluded on the basis of these reasons resulting in the involvement of 78 articles for our study. However, 3 articles were also hand-selected from the reference searches and were added to our study. 81 articles were finally included in this study using mostly higher Newcastle-Ottawa scores for higher study quality (Newcastle-Ottawa Scale (NOS), 2013).Among these selected 81 articles 63 were related to Atherosclerosis and 18 articles were related to Systemic Sclerosis. PRISMA study chart showing the study selection process is illustrated in Fig. 2.

Systemic sclerosis

18 studies (1995 to 2019) were includedfor the present study including 5821 patients with 53.79 years as the mean age for all studied cases. The author name, Year of publication, Sample size (number of patients/cases), patients with limited cutaneous systemic sclerosis (LcSSc), duration of disease, male or female number diagnosed with the disease, BMI, SSc symptoms and their prevalence, New Castle-Ottawa Scorewere reported in this studies (Table 3).

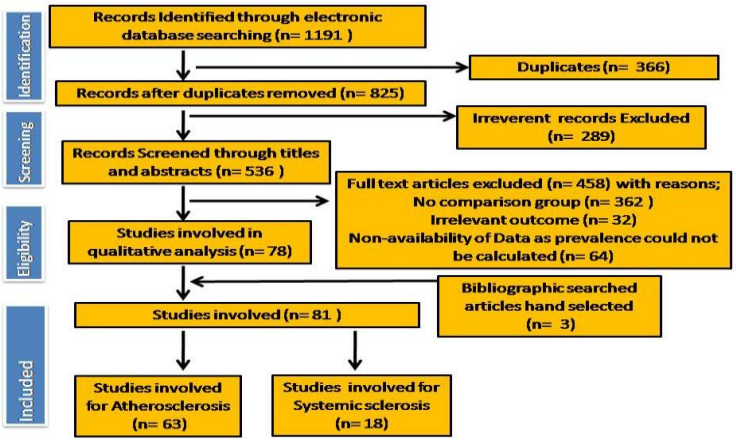

Fig. 2. PRISMA Flow Chart of the study selection process.

Table 3. Prevalence of SSc with respect to various parameters.

References	SSC (n)	Age, years mean ± D/ median, range	LcSScn(%)	Disease duration, mean±SD years	Male/Femalen(%)	SSC's symptoms	BMI,kg/m² (mean ±SD)	Prevalence (%)	NOS
Abu-Shakra and Lee, 1995	37	47.1	135 (57)	3.8	F 196 (83)	Lung involved in pulmonary hypertension	NA	91 (38)	7
Abu-Shakra and Lee,1995	37	47.1	135 (57)	3.8	F 196 (83)	Heart involvement	NA	21 (9)	7
Youssef *et al.*, 1995	31	23–81	31(100)	>5	F 31 (100)	CAD (Diabetes)	NA	1(3%)	5
Youssef *et al.*, 1995	31	23–81	31(100)	>5	F 31 (100)	CAD (Hypertension)	NA	7(23%)	5
Youssef *et al.*, 1995	31	23–81	31(100)	>5	F 31(100)	CAD (Smoking)	NA	4(13%)	5
Jacobsen *et al.*, 1998	344	55.0	226 (66)	8.6	F 278 (81)	Digital pitting scars or ulcers	NA	214 (62)	8
Jacobsen *et al.*, 1998	344	55.0	226 (66)	8.6	F 278 (81)	Lung involved in pulmonary hypertension	NA	88 (26)	8
Geirsson *et al.*, 2001	100	47.2	66 (66)	4.9	F 67 (67)	Digital pitting scars or ulcers	NA	12 (12)	7
Geirsson *et al.* 2001	100	47.2	66 (66)	4.9	F 67 (67)	Heart involvement	NA	32 (32)	7
Scussel Lonzetti *et al.*, 2002	309	49.0	60 (84)	8.6	F 66 (86)	Digital pitting scars or ulcers	NA	79 (26)	7
Scussel Lonzetti *et al.*, 2002	309	49.0	60 (84)	8.6	F 66 (86)	Lung involved in pulmonary hypertension	NA	34 (11)	7
Scussel Lonzetti *et al.*, 2002	309	49.0	60 (84)	8.6	F 66 (86)	Heart involvement	NA	28 (9)	7
Ferri *et al.*, 2002	1012	50.5	567 (56)	5.1	F 897 (89)	Digital pitting scars or ulcers	NA	486 (48)	7
Ferri *et al.*, 2002	1012	50.5	567 (56)	5.1	F 897 (89)	Lung involved in pulmonary hypertension	NA	607 (60)	7

References	SSC (n)	Age, years mean ± D/ median, range	LcSScn(%)	Disease duration, mean±SD years	Male/Femalen(%)	SSC's symptoms	BMI,kg/m² (mean ±SD)	Prevalence (%)	NOS
Ferri *et al.*, 2002	1012	50.5	567 (56)	5.1	F 897 (89)	Heart involvement	NA	304 (30)	7
Simeón *et al.*, 2003	79	48.8	57 (72)	4.5	F 68 (86)	Lung involved in pulmonary hypertension	NA	35 (44)	6
Simeón *et al.*, 2003	79	48.8	57 (72)	4.5	F 68 (86)	Heart involvement	NA	15 (19)	6
Tarek *et al.*, 2006	14	52±12	13 (68)	NA	F 18 (95)	CAD (Diabetes)	NA	1 (5)	6
Tarek *et al.*, 2006	14	52±12	13 (68)	NA	F 18 (95)	CAD (Hypertension)	NA	2 (11)	6
Tarek *et al.*, 2006	14	52±12	13 (68)	NA	F 18 (95)	CAD (Hyperlipidemia)	NA	5 (26)	6
Arias Nuñez *et al.* 2008	78	59.8	55 (70.5)	8.3	F 62 (79.5)	Digital pitting scars or ulcers	NA	32 (41)	8
Arias Nuñez *et al.* 2008	78	59.8	55 (70.5)	8.3	F 62 (79.5)	Lung involved in pulmonary hypertension	NA	35 (45)	8
Arias Nuñez *et al.* 2008	78	59.8	55 (70.5)	8.3	F 62 (79.5)	Heart involvement	NA	48 (61)	8
Khurma *et al.*, 2008	17	53±10	10 (59)	6.5	F 14 (82)	CAD (Hypertension)	26±5	3 (18%)	7
Khurma *et al.*, 2008	17	53±10	10 (59)	6.5	F 14 (82)	CAD (Smoking)	26±5	1(6%)	7
Mok *et al.*, 2009	19	48±7	5 (36)	NA	F 14 (100)	CAD (Diabetes)	NA	0	6
Mok *et al.*, 2009	19	48±7	5 (36)	NA	F 14 (100)	CAD (Hypertension)	NA	3 (21)	6
Mok *et al.*, 2009	19	48±7	5 (36)	NA	F 14 (100)	CAD (Hyperlipidemia)	NA	0	6
Mok *et al.*, 2009	19	48±7	5 (36)	NA	F 14 (100)	CAD (Smoking)	NA	0	6
Komocsi *et al.*, 2010	120	55±13	81 (68)	NA	F 106 (88)	CAD (Diabetes)	25	3 (3)	7
Komocsi *et al.*, 2010	120	55±13	81 (68)	NA	F 106 (88)	CAD (Hypertension)	25	52 (43)	7
Komocsi *et al.*, 2010	120	55±13	81 (68)	NA	F 106 (88)	CAD (Hyperlipidemia)	25	8 (7)	7
Mok *et al.*, 2011	53	53±13	41 (77)	9	F 50 (94)	CAD (Diabetes)	21±4	4 (8)	8
Mok *et al.*, 2011	53	53±13	41 (77)	9	F 50 (94)	CAD (Hypertension)	21±4	11 (13)	8
Mok *et al.*, 2011	53	53±13	41 (77)	9	F 50 (94)	CAD (Hyperlipidemia)	21±4	1 (2)	8
Mok *et al.*, 2011	53	53±13	41 (77)	9	F 50 (94)	CAD (Smoking)	21±4	6 (11)	8
Ngian *et al.*, 2012	850	59±12	575 (68)	NA	F 735 (87)	CAD (Diabetes)	26±5	37 (4)	8
Ngian *et al.*, 2012	850	59±12	575 (68)	NA	F 735 (87)	CAD (Hypertension)	26±5	336 (40)	8
Ngian *et al.*, 2012	850	59±12	575 (68)	NA	F 735 (87)	CAD (Hyperlipidemia)	26±5	187 (33)	8
Ngian *et al.*, 2012	850	59±12	575 (68)	NA	F 735 (87)	CAD (Smoking)	26±5	93 (11)	8
Man *et al.*, 2012	865	59±14	NA	NA	F 742 (86)	CAD (Diabetes)	NA	45 (5)	8
Man *et al.*, 2012	865	59±14	NA	NA	F 742 (86)	CAD (Hypertension)	NA	204 (24)	8
Man *et al.*, 2012	865	59±14	NA	NA	F 742 (86)	CAD (Hyperlipidemia)	NA	121 (14)	8
Man *et al.*, 2012	865	59±14	NA	NA	F 742 (86)	CAD (Smoking)	NA	161 (19)	8
Nordin *et al.*, 2013	111	61±12	78 (87)	NA	F 81 (90)	CAD (Diabetes)	22±4	7 (6)	6
Nordin *et al.*, 2013	111	61±12	78 (87)	NA	F 81 (90)	CAD (Hypertension)	22±4	33 (30)	6
Nordin *et al.*, 201	111	61±12	78 (87)	NA	F 81 (90)	CAD (Smoking)	22±4	12 (11)	6
Chu *et al.*, 2013	1344	51±14	NA	NA	F 1017 (76)	CAD (Diabetes)	NA	163 (12)	7
Chu *et al.*, 2013	1344	51±14	NA	NA	F 1017 (76)	CAD (Hypertension)	NA	312 (23)	7
Chu *et al.*, 2013	1344	51±14	NA	NA	F 1017 (76)	CAD (Hyperlipidemia)	NA	263 (20)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Diabetes mellitus	24.2±3.6	23 (5.6)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Dyslipidemia	24.2±3.6	72 (17.7)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Arterial hypertension	24.2±3.6	131 (32.1)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Coronary event	24.2±3.6	11 (2.7)	7

References	SSC (n)	Age, years mean ± D/ median, range	LcSScn(%)	Disease duration, mean±SD years	Male/Femalen(%)	SSC's symptoms	BMI,kg/m² (mean ±SD)	Prevalence (%)	NOS
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Stroke	24.2±3.6	8 (1.9)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Ischemic stroke	24.2±3.6	5 (1.2)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Hemorrhagic stroke	24.2±3.6	3 (0.7)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Neoplasia	24.2±3.6	17 (4.2)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Chronic obstructive pulmonary disease	24.2±3.6	21 (5.2)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Osteoporosis	24.2±3.6	98 (24.0)	7
Panopoulos *et al.*, 2018	408	58.4 ± 13.5	NA	10.1 ± 7.8	F 364 (89%)	Depression	24.2±3.6	90 (22.1)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Limited cutaneous	26.5±5.9	63 (81)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Diffuse cutaneous	26.5±5.9	11 (14)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Sine scleroderma	26.5±5.9	2 (3)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Telangiectasias	26.5±5.9	39 (50)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Calcinosis	26.5±5.9	18/75 (24)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Interstitial lung disease	26.5±5.9	7 (9)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Pulmonary arterial hypertension	26.5±5.9	7 (9)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Inflammatory arthritis	26.5±5.9	36/74 (49)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Myositis	26.5±5.9	11/75 (15)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Scleroderma renal crisis	26.5±5.9	6/73 (8)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Gastroesophageal reflux disease	26.5±5.9	58/76 (76)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Gastrointestinal dysmotility	26.5±5.9	38/75 (51)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Chronic intestinal pseudo-obstruction	26.5±5.9	6/75 (8)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Gastric antral vascular ectasia	26.5±5.9	5/74 (7)	7
Kurmann *et al.*, 2019	78	56.1±15.7	NA	11.2±8.7	F 71 (91)	Limited cutaneous	26.5±5.9	63 (81)	7

BMI, body mass index; LcSSc, limited cutaneous systemic sclerosis; NA, not applicable; NOS, Newcastle-Ottawa Scale; SSc, systemic sclerosis.

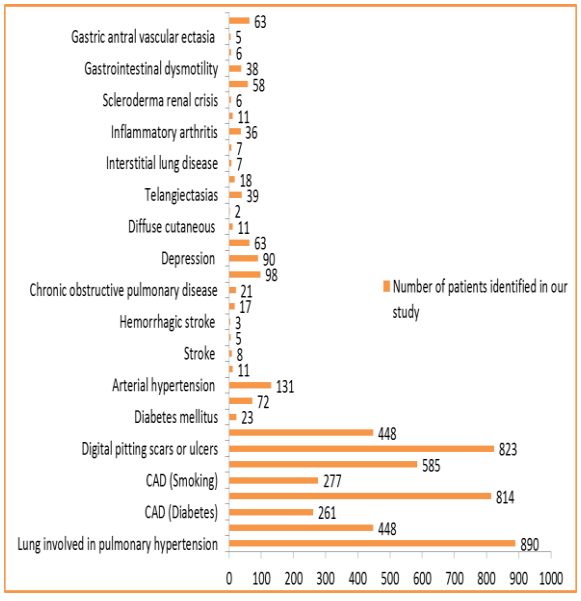

Fig. 3. Number of patients identified in our study for a particular symptom of SSc.

The percentage of prevalence for a particular symptom of SSc in these selected 18 studies is shown in Fig. 3.

Atherosclerosis

The 63 studies (1990 to 2020) related to atherosclerosis included a total of 43,60,282 cases. The 29 articles were Prospective studies while as 34 articles were related to retrospective studies.

The average age of the appearance of the atherosclerotic symptoms was found to be at an age of 67.51years with an average mortality of 54.68 patients per 1000 individuals among the prevalent persons of the disease.

The average follow-up for all the studies involved was 4.84 years **(**Table 4).

Table 4. Prevalence of atherosclerotic symptoms with respect to various parameters.

First Author name	Study setting/ country	Study design	Publication Year	Number of Cases/ patients	Sex (%)	Mean age	Atherosclerosis symptoms	Mean follow up years	Mortality [events /1000 patients]
Mckenna	USA	P	1991	744	M-46.1	66.2	PAD	3.28	67
Dormandy	UK	P	1991	1969	M-79.8	63.2	IC/ PAD	1	43.2
Criqui	USA	P	1992	475	M-45.7	66	APAD	10	56.1
Dawson	Netherlands	R	1993	376	M-83.5	63.9 ±11.5	CAD	5.9	23.9
McDermott	USA	R	1994	422	M-53.8	67.6	*	4.3	121.2
Karacagil	Sweden	R	1995	267	M-67.9	68.5 ±12	*	3	13.7
Leng	Scotland	R	1996	1498	M-51.4	67.4	Symp PAD	5	37.7
Kalman	Canada	P	1997	358	M-68	68 ±10	CAD	5	45.9
Luther	Finland	R	1997	188	M-53.2	72.5	*	5	29.3
Sikkink	Netherlands	R	1997	154	M-66.2	63	ABI	5	57.1
Brevetti	Italy	P	1998	110	M-88.2	63.6	IC	2	17.9
Jager	Netherlands	P	1999	631	M-48.7	64.5	ABI	5	50.6
Akbari	USA	P	2000	962	M-61.9	68.4	CAD	5	41.9
Kobayashi	Japan	R	2000	137	M-91.2	69	IC	4.17	82.3
Muluk	USA	R	2001	2777	M-100	64.7	IC/PAD	3.92	125.3
Vickrey	USA	R	2001	10846	M-53.7	67.3	Stroke, MI, &PAD	1.26	*
Pasqualini	Italy	P	2001	297	M-73.7	70.4	PAD	4	85.9
Jonsson	Sweden	R	2002	240	M-57.1	69.2	PAD	12	69.5
Murabito	USA	P	2003	674	M-37.5	80.8	ABI	4	62
Fiotti	Italy	P	2003	669	M-80.7	64	IC	13	64
Hooi	Netherland	P	2004	3634	M-46.9	59.1	PAD	7.2	46.7
Resnik	USA	P	2004	3989	M-60.1	56.1	ABI	8.3	53.8
Lee	UK	P	2004	1507	*	54-74	APAD	12	40.5
Leibson	USA	P	2004	335	M-63.6	61.2 ±5.3	CAD	23	74.5
Caro	USA	R	2005	16440	M-54.9	67.3	MI/ Stroke/PAD	5.9	82.4
Faglia	Italy	R	2006	564	M-64.9	70.1	CLI	3.4	90.2
Feringa	Netherlands	R	2006	2420	M-72	67	PAD	8	55.1
O'Hare	USA	R	2006	5682	M-42.4	73	ABI	11.1	94.2
Steg	France	R	2007	8581	M-63.8	69	PAD	1	37.6
Sutton-Tyrrell	USA	P	2008	2682	M-46.8	73.6	ABI	6.7	47.1
Sprengers	Netherlands	P	2009	800	M-69	59.5	PAD	4.7	*
Vaartjes	Netherlands	R	2009	4158	M-61.1	66.4	MI/ Stroke/PAD	3.78	78.2
Surinach	Spain	P	2009	763	*	*	CVD	1.67	61
Souminen	Finland	R	2009	1974	M-58.4	69.7	PAD	3.25	92.5
Taute	Germany	R	2009	109	M-80.7	60.8	IC	8.67	29.6
Abularrage	USA	R	2010	920	M- 64.3	71.2	CAD	2.9	44
Li[	China	R	2010	3732	M-52.5	61.9	PAD	3.14	68.8
Cheng	China	P	2000	665	M-60.3	71.1 ±11.1	CAD	2.3	42
Jude	UK	R	2001	136	M-59.6	64.7 ±10.8	CAD	4.5	81.7
Wolfle	Germany	R	2003	211	M-65.4	69	*	1	5.1
Missouris	UK	P	2004	110	M-60	70.8±10	CAD	6.1	54.7
Garg	USA	P	2006	460	M-59.4	71.9 ±8.4	CAD	4.8	24
Collins	USA	R	2007	796	M-99	64.7 ±9.9	*	1.4	40.6
Dick	Switzerland	P	2007	400	M-57.7	75.5 ±10.9	*	1	26.5
Malmstedt	Sweden	P	2008	1840	M-53.1	76.2±9.5	CAD	2.2	34.4
Diehm	Germany	R	2009	6821	M-42	73	APAD	5	41.7
Goodney	Lebanon	P	2010	2036	M-67	73	CAD	1	7
Pasqualini	Italy	P	2012	654	M-45.7	74.8	ABI	1.6	215.2
Abola	Philippines	R	2012	7996	M-71.1	65.4	CVD	3	68.2
Suzuki	Japan	R	2013	884	M-69.2	71.4±10.2	CAD	1.5	42
Chu	Taiwan	P	2013	1344	F-75.7	50.6	Acute MI	5.2	*

First Author name	Study setting/ country	Study design	Publication Year	Number of Cases/ patients	Sex (%)	Mean age	Atherosclerosis symptoms	Mean follow up years	Mortality [events /1000 patients]
Chiang	Taiwan	R	2013	1238	F-76	49.4	Stroke	4.7	*
Man	UK	R	2013	865	F-85.8	58.7	Stroke	5.2	*
Golledge	Australia	P	2014	1177	M-74.1	71	CAD	1.7	10.5
Mueller	Austria	R	2014	487	M-69.8	70	PAD	5	19.3
Miura	Japan	R	2014	2930	M-78.7	71.5 ±8.9	CAD	2.7	7.7
Mueller	Austria	P	2014	884	M-69.2	69.8	CAD	5	18.9
Vrsalovic	Croatia	R	2016	319	M-66.5	71	CAD	2	68
Avina-Zubieta	British Columbia and Canada	P	2016	1223	F-83.2	56.1	Stroke, MI, CVD	5	*
Hesselvig	Danish Population	P	2018	1962	F-80	49.2	CVD	*	*
Ying	USA	R	2019	4545	F-17	60.9	Stroke	5.1	*
Butt	Danish administrative registries	R	2019	2778	F-76	55	MI, Stroke, PVD	*	*
Kim	South Korea	R	2019	4,235,437	M-47.3	64.07	ASCVD	2	*

CAD= Coronary Artery Disease; CVD =cardiovascular disease, MI=myocardial infarction;PVD=peripheral vascular disease; APAD= Asymptomatic peripheral Artery disease; P=prospective study, RC=retrospective;ABI = ankle brachial index; CLI = critical limb ischemia; IC =intermittent claudication; PAD =peripheral arterial disease M=Males; F=Females; *= Not Available/ Not reported

Discussion

Systemic sclerosis (SSc) is marked by calcification, vasculopathy, and endothelial wall injury, all of them may raise the chances for atherosclerosis and heart disease. During the last few decades, the death rate due to cardiovascular disease in systemic sclerosis (SSc) patients has substantially increased, whether this is because of accelerated atherosclerosis (Dimitroulas *et al.*, 1997).Women are at a much higher risk of developing SSc than men ranging from 3:1 to 14:1 and the average age at diagnosis is in the fifth life decade (Gabrielli *et al.,* 2009) however there is reduced cardiovascular risk in women and has been conferred to female hormone estrogen which has protective role in lipid homeostasis and endothelial functioning(Burke *et al.,* 2001; Kardys *et al.,* 2007; Sangiorgi *et al.*, 2013). The significant risk factors like smoking, diabetes and hypertension are predominantly found in men and are hence prone to atherosclerosis (Song *et al.*, 2020). Cen *et al.*, 2020 has confirmed the association between SSc and atherosclerotic cardiovascular disease (CVD) for the Peripheral Vascular Disease (PVD), stroke and myocardial infarction (MI) with symptoms of atherosclerotic lesions and has also concluded that SSc is highly associated with increased risk of these cardiovascular diseases. SSc patients had a higher prevalence of coronary atherosclerosis, peripheral vascular disease, and cerebrovascular calcification etc in comparison to the healthy controls (Table 3) (Au *et al.,* 2011). The significant increase in the mortality by 20-30% in SSc patients during last few decades has been due to CVD and cerebrovascular diseases (Nussinovitch, and Shoenfeld, 2011). Frerix *et al.,* 2014 has examined 90 SSc and 100 Systemic lupus erythematosus (SLE) patients by duplex sonography, among which 59 SSc patients were detected, 84 with carotid artery plaques and 90 with femoral artery plaques and has clearly reported that most of the SSc's patients' atherosclerosis and its associated symptoms are very common, and are on a rise among the human population and should be taken seriously. Sciarra *et al.,* 2020 has reported that plaque was higher in patients with SSc increasing intima-media thickness of common carotid artery (CCAIMT) and FMD (flow mediated dilation) than in safe controls. According to Australian Scleroderma Cohort Study (ASCS), individuals with SSc appeared 3.2 times more susceptible to coronary heart disease than the general population in risk to atherosclerosis (Hu *et al.*, 2018). The mortality rate in SSc patients has been assessed through a meta-analysis of cohort studies confirming

the most common cause of death as heart disease (29%), followed by lung involvement, among 732 fatalities (Elhai *et al.,* 2012). The study of prevalence of atherosclerotic cardiovascular disease (ASCVD) of different age groups has been retrospectively studied in South Korea for the years 2014 and 2015 and it was found that females are slightly more specific for ASCVD than males (98.25: 101.11/ 1000 individuals), ASCVD prevalence and incidence increased at age irrespective of disease type *i.e.,* higher the age, higher the risk of having ASCVD; the disease prevalence in old age people specifically in women is more than the rest of the population **(**Kim *et al.*, 2019). Similar studies in Chinese population were compared with the European population's and it has been reported that approximately one third of Chinese adults had carotid plaques and the minimum thickness of carotid atherosclerosis similar to that of Europeans, although in some parts of China it was much more severe however, plaques were 50% greater in smokers than in non-smokers (34% versus 23%), and more than 2% higher in individuals with SBP (Systolic Blood Pressure) of ≥160mmHg than SBP< 120mmHg (39% versus 19%) in the CKB (China Kadoorie Biobank study), after adjustments for aging, gender and area (Clarke *et al.,* 2017). Song *et al.,* 2018 has estimated that advanced age increased the prevalence of carotid plaque (CP) and carotid atherosclerosis (CAS) in rural population of china with hypertension, diabetes and smoking as risk factors for CAS, and males having higher prevalence consistently than females across all age groups. Rodríguez-Saldaña *et al.,* 2014 resoluted the prevalence and degree of atherosclerosis lesions by autopsying five arteries associated with arterial territories (namely circle of Willis, coronary, carotid, renal, and aorta) in Mexican population of age groups of 0 to 90 years including males and females and reported that 36% of lesions were observed in age group of below 15 years and 67% in age group of 16-35 years however, histopathological studies confirmed that 97.8% had atherosclerotic lesions in at least one arterial territories arteries; 92.2% had lesions in at least two or more arterial territories arteries; all the five territories were involved in 48.6% men and 39.7% women.

The increased events of atherosclerosis in systemic sclerotic patients are shown in Table 5.

Table 5. Increased events/symptoms of atherosclerosis in SSc's patients.

Parameter of Atherosclerosis	% age of occurrence in SSc patients	% age of occurrence in Non-SSc patients	Reference (s)
Medium-vessel coronary atherosclerosis	48	43	D'Angelo *et al.,* 1969; Au, *et al.,* 2011
Atherosclerotic lesions of the small coronary arteries or arterioles	17	2	D'Angelo *et al.,* 1969; Au, *et al.,* 2011
Coronary artery disease	39	23	Youssef *et al*, 1995; Au, *et al.,* 2011
Coronary atherosclerosis	56.2	18.8	Khurma *et al.,* 2008; Au, *et al.,* 2011
Intracerebral calcification	32.4	9.5	Heron, *et al.,* 1999; Au, *et al.,* 2011
Peripheral vascular disease	58	10	Youssef *et al*, 1995; Au, *et al.,* 2011

Conclusion

The present review study was aimed to investigate the risk prevalence, association, and correlation in the symptoms between systemic sclerosis and atherosclerosis. It was found that the symptoms of SSc are clearly linked to the cardiovascular diseases of Atherosclerosis.

This study also tried to sum up all previous studies in this review article to form the base for future studies. Furthermore, it was concluded that the patients with SSc are at a higher risk of atherosclerotic diseases especially CVD and preventive measures should be taken for the CVD also at the time of SSc diagnosis.

Declaration of interest

The authors declare no conflicts of interest

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