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EDITED BY
Katarzyna Romanowska-Próchnicka,
National Institute of Geriatrics, Rheumatology and Rehabilitation, Poland

REVIEWED BY
Saeed Mohammadi,
Golestan University of Medical Sciences, Iran
Sandeep Krishna Agarwal,
Baylor College of Medicine, United States

*CORRESPONDENCE
Arduino A. Mangoni
arduino.mangoni@flinders.edu.au

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Circulating cell adhesion molecules in systemic sclerosis: a systematic review and meta-analysis

Arduino A. Mangoni[1,2]* and Angelo Zinellu[3]

[1]Discipline of Clinical Pharmacology, College of Medicine and Public Health, Flinders University, Adelaide, SA, Adelaide, Australia, [2]Department of Clinical Pharmacology, Flinders Medical Centre, Southern Adelaide Local Health Network, Adelaide, SA, Adelaide, Australia, [3]Department of Biomedical Sciences, University of Sassari, Sassari, Italy

Introduction: Patients with systemic sclerosis (SSc) have an increased risk of endothelial dysfunction, atherosclerosis, and cardiovascular events compared to the general population. Therefore, the availability of robust circulating biomarkers of endothelial dysfunction and atherogenesis may facilitate early recognition and management of cardiovascular risk in SSc. We sought to address this issue by conducting a systematic review and meta-analysis of studies investigating various types of circulating cell adhesion molecules involved in endothelial dysfunction and atherogenesis (i.e., immunoglobulin-like vascular cell, VCAM-1, intercellular, ICAM-1, platelet endothelial cell, PECAM-1, neural cell, NCAM, Down syndrome cell, DSCAM, and endothelial cell-selective, ESAM, adhesion molecules, E-, L-, and P-selectin, integrins, and cadherins) in SSc patients and healthy controls.

Methods: We searched PubMed, Scopus, and Web of Science from inception to 1 May 2024. Risk of bias and certainty of evidence were assessed using validated tools.

Results: In 43 eligible studies, compared to controls, patients with SSc had significantly higher plasma or serum concentrations of ICAM-1 (standard mean difference, SMD=1.16, 95% CI 0.88 to 1.44, p<0.001; moderate certainty), VCAM-1 (SMD=1.09, 95% CI 0.72 to 1.46, p<0.001; moderate certainty), PECAM-1 (SMD=1.65, 95% CI 0.33 to 2.98, p=0.014; very low certainty), E-selectin (SMD=1.17, 95% CI 0.72 to 1.62, p<0.001; moderate certainty), and P-selectin (SMD=1.10, 95% CI 0.31 to 1.90, p=0.007; low certainty). There were no significant between-group differences in L-selectin concentrations (SMD=-0.35, 95% CI -1.03 to 0.32, p=0.31; very low certainty), whereas minimal/no evidence was available for cadherins, NCAM, DSCAM, ESAM, or integrins. Overall, no significant associations were observed between the effect size and various patient and study characteristics in meta-regression and subgroup analyses.

Discussion: The results of this systematic review and meta-analysis suggest that specific circulating cell adhesion molecules, i.e., ICAM-1, VCAM-1, PECAM-1, E-selectin, and P-selectin, can be helpful as biomarkers of endothelial dysfunction and atherogenesis in the assessment of cardiovascular risk in SSc patients.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42024549710.

KEYWORDS

cell adhesion molecules, immunoglobulin-like cell adhesion molecules, selectins, integrins, cadherins, systemic sclerosis, biomarkers, endothelial activation

Introduction

Systemic sclerosis (SSc), an autoimmune condition primarily affecting women, is characterized by vascular dysfunction and progressive fibrosis of the skin and internal organs (1, 2). The global incidence of SSc ranges between 8-56 new cases per million persons per year and the prevalence varies between 38-341 cases per million persons (3). The mortality in SSc patients is three- to four-fold higher than the general population due to cardiorespiratory complications, renal and gastrointestinal disease, cancer, and infections (4, 5). Increasing evidence also suggests that atherosclerosis is a critical additional component of the pathophysiology of SSc. This has led to a shift in the focus of basic and clinical research studies which have convincingly reported several pro-atherosclerotic arterial abnormalities, e.g., endothelial dysfunction, increased intima-media thickness and arterial stiffness, in SSc (6–10). Such alterations are similar to those observed in rheumatoid arthritis, another autoimmune condition associated with atherosclerosis and cardiovascular disease (11, 12). Epidemiological studies have also reported an increased risk of atherosclerotic cardiovascular events in SSc, particularly myocardial infarction and peripheral vascular disease (13, 14). In these studies, the prevalence and/or severity of hypertension, diabetes, and dyslipidemia in SSc patients was similar to that in control groups (9, 13). This suggests that conventional risk factors only partially account for the increased risk of atherosclerosis and cardiovascular disease in SSc. Therefore, a focus of current research is the identification of alternative, more robust biomarkers of atherosclerosis allowing early risk stratification and preventive treatment.

Functional and structural alterations of the endothelium, associated with the impaired synthesis of the critical endogenous messenger nitric oxide, represent the initial step in the pathogenesis of atherosclerosis (15). At a cellular and molecular level, these alterations involve the adhesion of leukocytes and lymphocytes to the endothelium (endothelial activation) and their consequent migration to the tunica intima, where they initiate a sequence of events leading to the formation of the atherosclerotic plaque (16, 17). The process of cellular adhesion to the endothelium is mediated by several molecules, e.g., the immunoglobulin-like vascular cell adhesion molecule-1 (VCAM-1), the intercellular vascular adhesion molecule-1 (ICAM-1), the platelet endothelial cell adhesion molecule-1 (PECAM-1), the neural cell adhesion molecule (NCAM), the Down syndrome cell adhesion molecule (DSCAM), and the endothelial cell-selective adhesion molecule (ESAM) (18–21). VCAM-1 is expressed in endothelial cells and macrophages and binds to integrin $\alpha_4\beta_1$ (22, 23). ICAM-1 is upregulated during inflammation and binds to the leukocyte specific β_2 integrins (24, 25). PECAM-1 is expressed in leukocytes, platelets, and endothelial cells, and exerts its effects through the translocation of integrin $\alpha_6\beta_1$ (26). NCAM is expressed in the brain, skeletal muscle, and hematopoietic system. In addition to regulating cell adhesion, it modulates brain and kidney development and plays a pathophysiological role in cancer, schizophrenia, and other neurodegenerative disorders (27). DSCAM is primarily expressed in the brain and regulates neural development (28). ESAM is expressed mainly in endothelial cells and is critical in modulating angiogenesis, endothelial integrity, leukocyte adhesion and transmigration (29).

The immunoglobulin-like cell adhesion molecules can be measured in plasma or serum (21, 27, 28, 30, 31). Their concentrations, particularly VCAM-1, ICAM-1, and ESAM, have been shown to be associated with endothelial dysfunction, vascular damage, and increased risk of atherosclerotic cardiovascular disease (32–38). Other molecules facilitating cell adhesion to the endothelium include selectins, integrins, and cadherins (39, 40). The selectins include P-selectin, expressed in platelets and endothelial cells, L-selectin, expressed in leukocytes, and E-selectin, expressed in endothelial cells (41–43). L-selectin mediates lymphocyte rolling, whereas P-selectin and E-selectin influence the rolling of monocytes, neutrophils, and lymphocytes (44, 45). Similar to the immunoglobulin-like cell adhesion molecules, selectins, integrins, and cadherins can be measured in plasma or serum, and their concentrations have also been shown to be associated with an increased risk of atherosclerosis and cardiovascular disease (46–52).

To evaluate the possible role of cell adhesion molecules as biomarkers of endothelial activation, dysfunction, and atherosclerosis in SSc, we conducted a systematic review and meta-analysis of studies investigating their plasma or serum

concentrations in SSc patients and healthy controls. Where possible, we investigated possible associations between the effect size of the between-group differences in cell adhesion molecules and pre-defined study and patient characteristics.

Materials and methods

Search strategy and study selection

We searched PubMed, Web of Science, and Scopus from inception to 21 July 2024 for relevant articles using the following terms: "systemic sclerosis" OR "scleroderma" AND "soluble cell adhesion molecules" OR "intercellular adhesion molecule" OR "ICAM" OR "sICAM" OR "ICAM" OR "vascular cell adhesion molecule" OR "VCAM" OR "sVCAM" OR "VCAM" OR "platelet endothelial cell adhesion molecule" OR "PECAM" OR "sPECAM" OR "PECAM" OR "Selectin" or "P-selectin" OR "sP-selectin" OR "L-selectin" OR "sL-selectin" OR "E-selectin" OR "sE-selectin" OR "ESAM" OR "sESAM" OR "endothelial cell-selective adhesion molecule" OR "NCAM" OR "sNCAM" OR "neural cell adhesion molecules" OR "DSCAM" OR "sDSCAM" OR "Down syndrome cell adhesion molecule" OR "integrins" OR "cadherin".

Each abstract was screened by two independent investigators and reviewed as full text if considered relevant. Any disagreement between the investigators throughout the screening process was resolved by a third investigator. The inclusion criteria were: (a) the measurement of soluble ICAM-1, VCAM-1, PECAM-1, ESAM, NCAM, DSCAM, E-selectin, L-selectin, P-selectin, integrins, and cadherins in plasma or serum; (b) the comparison between SSc patients and healthy controls in original case-control research studies; (c) the inclusion of patients aged ≥18 years; and (d) the availability of the full text of the publication in English language. The exclusion criteria were: (a) the investigation of other autoimmune or autoinflammatory conditions; (b) case reports and review articles; and (c) the inclusion of children and/or adolescents. References of reviewed articles were also searched to identify additional studies.

Two investigators independently extracted the following data from each article: year of publication, first author, study country and continent, sample size, age, male to female ratio, SSc type (diffuse or localized), disease duration, concentrations of individual cell adhesion molecules, and biological matrix assessed (serum or plasma). The data were then manually transferred to separate custom extraction forms created using Microsoft Excel. Any discrepancy between the extraction forms was resolved by a third investigator.

The risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for analytical studies (53). The certainty of evidence was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system (54). The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Supplementary Table 1) (55). The protocol was registered in an international repository (PROSPERO registration number, CRD42024549710).

Statistical analysis

Standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated to generate forest plots and assess the differences in the concentrations of individual cell adhesion molecules between SSc patients and healthy controls. A p-value <0.05 was considered statistically significant. If required, data were extracted from graphs using the Graph Data Extractor software (San Diego, CA, USA). Means and standard deviations were calculated from medians and interquartile ranges or full ranges according to published methods (56). The heterogeneity of SMD across studies was evaluated using the Q-statistic (significance level at $p<0.10$) and classified as low (I^2 ≤25%), moderate (25%< I^2 <75%), or high (I^2 ≥75%) (57, 58). Sensitivity analysis and assessment of publication bias were conducted according to established methods (59–62).

Univariate meta-regression and subgroup analyses were conducted to investigate associations between the effect size and the following parameters: year of publication, study continent, number of participants, age, male to female ratio, SSc type (diffuse or localized), mean disease duration, and biological matrix assessed (serum or plasma). Statistical analyses were performed using Stata 14 (Stata Corp., College Station, TX, USA).

Results

Study selection

The flow chart of study selection is illustrated in Figure 1. After initially identifying 1,542 articles, 1,486 were excluded because they were either irrelevant or presented duplicate data. A full-text review of the remaining 56 articles led to the exclusion of one study because of duplicate data, two studies because of missing information, four studies because their design was not case-control, and six studies because they included patients under 18 years old. Therefore, 43 studies were included in the analysis (Table 1) (63–105). The risk of bias was low or moderate in all studies except one which was assessed as having high risk (84) (Supplementary Table 2). The initial level of the certainty of evidence was considered low because of the case-control design of the selected studies (level 2).

ICAM-1

Seventeen studies, including 18 group comparisons, reported ICAM-1 concentrations in 962 SSc patients (mean age 53 years, 85% females) and 645 healthy controls (mean age 45 years, 65% females) (64–67, 69, 71, 76, 77, 83, 84, 92, 94, 95, 97, 101, 103, 104) (Table 1). Ten studies were conducted in Europe (65–67, 71, 76, 83, 92, 94, 101, 103) and the remaining seven in other geographical areas (64, 69, 77, 84, 95, 97, 104). Measurements were conducted in serum in 14 studies (65–67, 69, 71, 77, 83, 92, 94, 95, 97, 101, 103, 104), plasma in two (76, 84), and both plasma and serum in the remaining one (64). Ten studies reported disease duration, ranging between 1.7 and 14.6 years (65, 67, 69, 77, 83, 92, 94, 95, 97, 104)

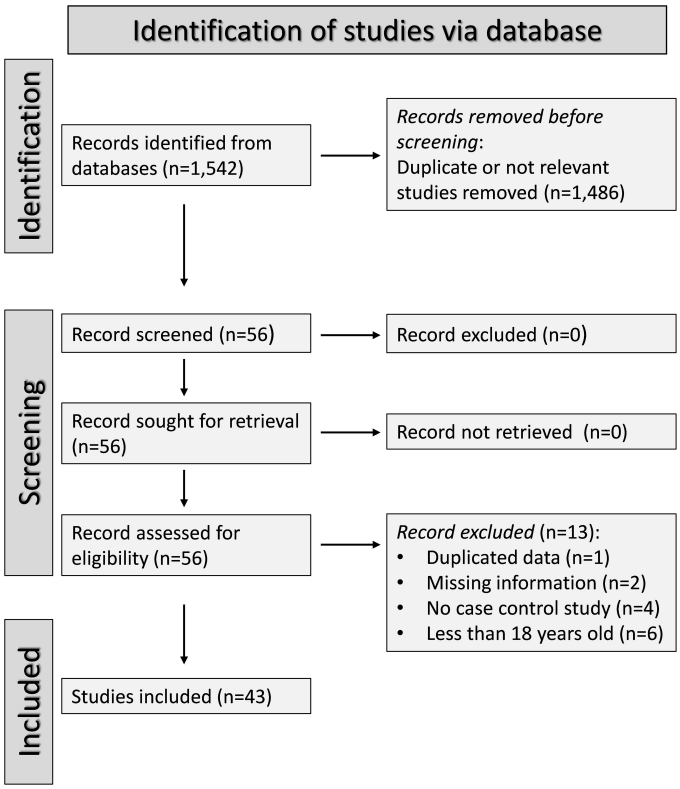

FIGURE 1
PRISMA 2020 flow diagram.

TABLE 1 Main characteristics and results of the studies included in the meta-analysis.

	Healthy controls					Patients with systemic sclerosis				
Study	n	Age (Years)	M/F	ICAM-1 VCAM-1 PECAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)	n	Age (Years)	M/F	ICAM VCAM PECAM-1 ELAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)
Carson et al., 1993, USA (63)	71	44.3	36/35	NR NR NR	1.2 ± 0.2 NR NR NR	69	47.8	16/53	NR NR NR	2.08 ± 0.5 NR NR NR
Sfikakis et al., 1993, USA (64)	22	31	13/9	373 ± 127 NR NR	NR NR NR NR	37	46	6/31	587 ± 207 NR NR	NR NR NR NR
Kiener et al., 1994, Austria (65)	82	47	38/44	312 ± 78 NR NR	NR NR NR NR	33	53	7/26	449 ± 135 NR NR	NR NR NR NR
Blann et al., 1995, UK (66)	80	45	39/41	319 ± 107 746 ± 265 NR	58 ± 20 NR NR NR	37	43	11/26	447 ± 212 1090 ± 649 NR	131 ± 83 NR NR NR

(Continued)

TABLE 1 Continued

	Healthy controls					Patients with systemic sclerosis				
Study	n	Age (Years)	M/F	ICAM-1 VCAM-1 PECAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)	n	Age (Years)	M/F	ICAM VCAM PECAM-1 ELAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)
Gruschwitz et al., 1995, Germany (67)	36	NR	NR	150 ± 18 497 ± 43 NR	48 ± 19 NR 262 ± 85 NR	12	50.7	3/9	168 ± 26 652 ± 178 NR	46 ± 10 NR 258 ± 82 NR
Blann et al., 1996, UK (68)	42	48	21/21	NR NR NR	NR 1244 ± 269 NR NR	18	46	6/12	NR NR NR	NR 1190 ± 334 NR NR
Ihn et al., 1997, Japan (69)	20	NR	NR	192 ± 49 NR NR	NR NR NR NR	88	50.3	9/79	317 ± 170 NR NR	NR NR NR NR
Ihn et al., 1998, Japan (70)	20	matched	NR	NR 506.8 ± 126.3 NR	53.5 ± 14.6 NR NR NR	80	50	8/72	NR 786.6 ± 297.6 NR	83.7 ± 30.7 NR NR NR
Majewski et al., 1999, Poland (71)	25	NR	NR	207 ± 63 NR NR	NR NR NR NR	36	52.7	8/28	375 ± 123 NR NR	NR NR NR NR
Sfikakis et al., 1999, Greece (72)	40	matched	matched	NR NR NR	NR NR 245 ± 97 NR	25	49	6/19	NR NR NR	NR NR 332 ± 167 NR
Andersen et al., 2002, Sweden (73)	24	57.7	matched	NR 593 ± 121 NR	47.4 ± 12.8 NR NR NR	24	57.9	4/20	NR 768 ± 241 NR	60.3 ± 23.7 NR NR NR
Macko et al., 2002, USA (74)	22	matched	3/19	NR NR NR	37.8 ± 14.5 NR NR NR	45	51.5	3/42	NR NR NR	67.7 ± 50.3 NR NR NR
Blann et al., 2003, France (75)	38	54	5/33	NR NR NR	NR NR 44.7 ± 19.4 NR	67	54	6/61	NR NR NR	NR NR 144 ± 114 NR
Cerinic et al., 2003, Italy (76)	16	matched	matched	211 ± 48 472 ± 66 NR	25.7 ± 12.4 NR NR NR	29	45.3	2/27	353 ± 113 711 ± 247 NR	46 ± 17.8 NR NR NR
Zamzam et al., 2003, Egypt (77)	10	42	2/8	101.8 ± 13.67 NR NR	NR NR NR NR	20	48.0	5/15	163.75 ± 56.93 NR NR	NR NR NR NR
Allanore et al., 2004, France (78)	20	51	3/17	NR 482 ± 64 NR	NR NR NR NR	40	57	7/33	NR 705 ± 156 NR	NR NR NR NR

(Continued)

TABLE 1 Continued

	Healthy controls					Patients with systemic sclerosis				
Study	n	Age (Years)	M/F	ICAM-1 VCAM-1 PECAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)	n	Age (Years)	M/F	ICAM VCAM PECAM-1 ELAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)
Ates et al., 2004, Turkey (79)	16	50.2	4/12	NR NR NR	24.9 ± 12.9 672 ± 140 292 ± 199 NR	30	47.8	3/27	NR NR NR	44.9 ± 22.3 552 ± 224 246 ± 163 NR
Kuryliszyn-Moskal et al., 2004, Poland (80)	30	matched	matched	NR 528.6 ± 172.9 NR	34.7 ± 12.1 NR NR NR	31	55.2	0/31	NR 682.6 ± 172.8 NR	47.3 ± 13.4 NR NR NR
Dovio et al., 2008, Italy (81)	60	55.5	12/48	NR 664 ± 80 NR	NR NR NR NR	60	54.8	12/48	NR 1032 ± 197 NR	NR NR NR NR
Hettema et al., 2008, The Netherlands (82)	32	50.9	3/29	NR 291 ± 88 NR	NR NR NR NR	49	55.4	8/41	NR 243 ± 94 NR	NR NR NR NR
Iannone et al., 2008, Italy (83)	25	46.7	NR	588 ± 48 261 ± 9 41 ± 2	NR NR 132 ± 12 NR	35	51.4	NR	3077 ± 903 301 ± 12 47.8 ± 3.4	NR NR 363 ± 58 NR
Nomura et al., 2009, Japan (84)	30	43	11/19	343 ± 30 492 ± 59 NR	42.3 ± 9.1 NR 112 ± 25 NR	42	48.4	7/35	335 ± 226 781 ± 73 NR	64.2 ± 11.2 NR 184 ± 25 NR
Minier et al., 2010, Hungary (85)	30	NR	NR	NR NR NR	31.6 ± 15 NR NR NR	131	55.9	12/119	NR NR NR	35.4 ± 15.4 NR NR NR
Olewicz-Gawlik et al., 2010, Poland (86)	30	47.1	2/28	NR NR NR	39.5 ± 20.8 NR 46.2 ± 20.7 NR	30	52.9	3/27	NR NR NR	50.2 ± 21.9 NR 132.8 ± 107.1 NR
Alzawawy et al., 2011, Egypt (87)	10	matched	3/7	NR 1214.33 ± 324.29 NR	NR NR NR NR	15	32.1	2/13	NR 1931.15 ± 593.52 NR	NR NR NR NR
Riccieri et al., 2011, Italy (88)	16	matched	matched	NR NR 12.4 ± 4.8	NR NR NR NR	65	53.9	2/63	NR NR 38.1 ± 28.7	NR NR NR NR
Dunne et al., 2012, Canada (89)	30	55.9	matched	NR NR NR	NR 906 ± 40 NR NR	30	55.3	6/24	NR NR NR	NR 885 ± 71 NR NR
Aydoğdu et al., 2013, Turkey (90)	20	49.3	1/19	NR NR NR	NR NR NR 2.73 ± 6.0	40	48.3	2/38	NR NR NR NR	NR NR NR 3.75 ± 5.8

(Continued)

TABLE 1 Continued

	Healthy controls					Patients with systemic sclerosis				
Study	n	Age (Years)	M/F	ICAM-1 VCAM-1 PECAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)	n	Age (Years)	M/F	ICAM VCAM PECAM-1 ELAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)
Iversen et al., 2013, Denmark (91)	49	46	6/43	NR NR NR	27.4 ± 1.8 NR 34.13 NR	121	57	19/102	NR NR NR	41.9 ± 2 NR 43.2 ± 14.7 NR
Cossu et al. (a) 2016, Italy (92)	43	NR	NR	349.17 ± 222.75 619.95 ± 207.18 NR	22.6 ± 9 NR NR NR	95	57.4	NR	478.01 ± 318.65 583.07 ± 228.62 NR	25.1 ± 9.9 NR NR NR
Cossu et al. (b) 2016, Italy (92)	43	NR	NR	349.17 ± 222.75 619.95 ± 207.18 NR	22.6 ± 9 NR NR NR	86	59	NR	593.13 ± 405.34 669.65 ± 243.72 NR	28.4 ± 10.7 NR NR NR
Yalçınkaya et al., 2016, Turkey (93)	20	NR	NR	NR 3231 ± 1,435 NR	205 ± 78 NR 364 ± 137 NR	72	44.9	6/66	NR 3945 ± 1754 NR	269 ± 106 NR 287 ± 86 NR
Delle Sedie et al., 2018, Italy (94)	31	53.5	6/25	21.57 ± 5.07 11.05 ± 3.84 NR	NR NR NR NR	41	54	1/40	31.33 ± 16.00 14.84 ± 6.28 NR	NR NR NR NR
Thakkar et al., 2018, Australia (95)	34	51.2	NR	201.8 ± 57.2 1125.6 ± 273.4 NR	NR NR NR NR	64	52.6	6/58	297.4 ± 134 1432.7 ± 427.4 NR	NR NR NR NR
Wodok-Wieczorek et al., 2018, Poland (96)	41	46.3	13/28	NR NR NR	25.3 ± 12.9 NR NR NR	42	49	7/35	NR NR NR	43.62 ± 21.7 NR NR NR
Hegazy et al., 2019, Egypt (97)	60	41.58	20/40	158.49 ± 43.31 NR NR	NR NR NR NR	30	47.31	7/23	437.62 ± 175.52 NR NR	NR NR NR NR
Pacholczak-Madej et al., 2020, Poland (98)	36	56.3	11/25	NR 818 ± 160 NR	NR NR NR NR	42	59.2	7/35	NR 858 ± 256 NR	NR NR NR NR
Al-Omary Obadeh et al., 2021, Ukraine (99)	35	39.5	13/22	NR 339 ± 184 NR	NR NR NR NR	78	43.2	27/51	NR 685 ± 454 NR	NR NR NR NR
Kuszmiersz et al., 2021, Poland (100)	56	50	9/48	NR 816 ± 61 NR	NR NR NR NR	67	57	16/51	NR 852 ± 76 NR	NR NR NR NR
Stern et al., 2021, UK (101)	12	34	NR	14287 ± 6055 22427 ± 14297 NR	NR NR NR NR	40	57	NR	25449 ± 11316 23291 ± 11645 NR	NR NR NR NR

(Continued)

TABLE 1 Continued

	Healthy controls					Patients with systemic sclerosis				
Study	n	Age (Years)	M/F	ICAM-1 VCAM-1 PECAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)	n	Age (Years)	M/F	ICAM VCAM PECAM-1 ELAM-1 (Mean ± SD)	E-Selectin L-Selectin P-Selectin VE-Cadherin (Mean ± SD)
Brezovec et al., 2022, Slovenia (102)	36	55	5/31	NR NR NR	NR 1128 ± 99 NR NR	38	57	7/31	NR NR NR	NR 1190 ± 334 NR NR
Colic et al., 2022, Serbia (103)	46	51.3	5/41	24.3 ± 4.6 30.8 ± 8.8 NR	4.1 ± 1.7 NR NR NR	58	54.3	7/51	29.5 ± 7.8 37.3 ± 11.3 NR	5.2 ± 1.4 NR NR NR
Jee et al., 2023, Australia (104)	30	36.8	5/25	370 ± 172 0.93 ± 0.23 NR	24.1 ± 10.4 NR NR NR	179	57.9	31/148	657 ± 324 1.27 ± 0.62 NR	38.4 ± 18 NR NR NR
Corrado et al., 2024, Italy (105)	37	57.86	4/33	NR 391.27 ± 102.54 NR	NR NR NR NR	57	58.91	5/52	NR 738.15 ± 123 NR	NR NR NR NR

ELAM-1, Endothelial leucocyte adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; M/F, male to female ratio; NR, not reported; PECAM-1, Platelet/endothelial cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

and ten whether the disease was diffuse or localized (64, 65, 69, 71, 76, 92, 94, 95, 101, 103).

The risk of bias was considered low or moderate in all studies except one, which was assessed as having high risk (84) (Supplementary Table 2).

Pooled analyses showed that ICAM-1 concentrations were significantly higher in SSc patients than controls (SMD=1.16, 95% CI 0.88 to 1.44, p<0.001; I^2 = 82.4%, p<0.001; Figure 2). Sensitivity analysis showed stability of the results with pooled SMD values ranging between 1.04 and 0.84; Supplementary Figure 1).

There was significant publication bias (Begg's test, p=0.002; Egger's test, p=0.003). The "trim-and-fill" method was consequently used to address and correct this bias (62). This method operates under the assumption that the results of some studies, often those with null or negative findings, might be missing, leading to an asymmetric distribution in the funnel plot. Consequently, it estimates the number of such missing studies and adds them to the funnel plot to create a symmetrical distribution. This adjustment helps in evaluating the impact of publication bias on the overall results. The meta-analysis is then recalculated to include these additional studies. In this case, the "trim-and-fill" method identified seven missing studies to be added to the left side of the funnel plot to ensure symmetry (Supplementary Figure 2). This adjustment led to an attenuation of the resulting SMD however the effect size remained significant (SMD=0.76, 95% CI 0.44 to 0.90, p<0.001). This suggests that while there was evidence of publication bias, the overall effect size of ICAM-1 concentrations remained robust.

Univariate meta-regression analysis did not show any significant associations between the effect size and age (t=-0.26, p=0.82), male to female ratio (t=0.25, p=0.81), year of publication (t=-0.33, p=075), sample size (t=-1.30, p=0.21), and SSc duration (t=0.05, p=0.96). In sub-group analyses, there were non-significant differences (p=0.92) in pooled SMD between studies conducted in Europe (SMD=1.17, 95% CI 0.80 to 0.55, p<0.001; I^2 = 83.6%, p<0.001) and other geographical areas (SMD=1.15, 95% CI 0.68 to 1.62, p<0.001; I2 = 82.8%, p<0.001). There were non-significant differences (p=0.72) in pooled SMD between studies measuring serum (SMD=1.19, 95% CI 0.87 to 1.51, p<0.001; I^2 = 84.5%, p<0.001) and plasma (SMD=0.97, 95% CI 0.04 to 1.91, p=0.041; I^2 = 80.2%, p=0.025). Similarly, there were non-significant differences (p=0.70) in pooled SMD between studies with a diffuse/localized disease patient ratio <1 (SMD=1.30, 95% CI 0.81 to 1.78, p<0.001; I^2 = 82.8%, p<0.001) and >1 (SMD=1.14, 95% CI 0.78 to 1.50, p<0.001; I^2 = 36.0%, p=0.21), with a reduced between-study variance in the >1 subgroup.

The overall level of certainty was upgraded to moderate (level 3) after considering the low-moderate risk of bias in most studies (no change), the high but partially explainable heterogeneity (no change), the lack of indirectness (no change), the large effect size (SMD=1.16; upgrade one level) (106), and the presence of publication bias which was addressed with the "trim-and-fill" method (no change).

VCAM-1

Twenty-three studies, including 24 group comparisons, reported VCAM-1 concentrations in 1,413 SSc patients (mean age

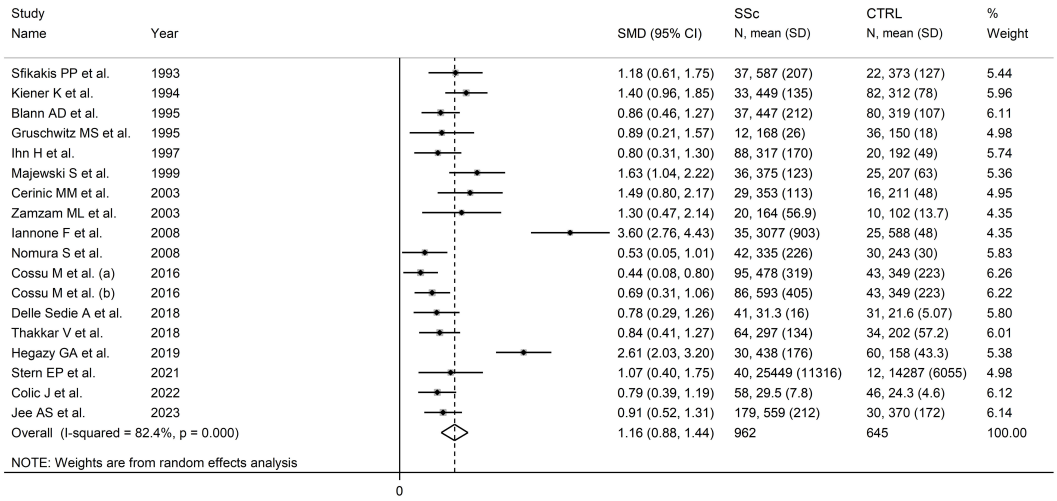

FIGURE 2
Forest plot of studies investigating ICAM-1 concentrations in SSc patients and controls.

54 years, 84% females) and 806 healthy controls (mean age 49 years, 75% females) (66, 67, 70, 73, 76, 78, 80–84, 87, 92–95, 98–101, 103–105) (Table 1). Seventeen were conducted in Europe (66, 67, 73, 76, 78, 80–83, 92, 94, 98–101, 103, 105) and the remaining six in other geographical areas (70, 84, 87, 93, 95, 104). Measurements were conducted in serum in 18 studies (66, 67, 70, 78, 80–83, 87, 92–95, 98, 101, 103–105) and plasma in five (73, 76, 84, 99, 100). Disease duration, reported in 15 studies, ranged between 2.6 and 14.6 years (66, 70, 78, 80, 81, 83, 87, 92–95, 98, 100, 104, 105). Fourteen studies reported whether SSc was localized or diffuse (70, 73, 76, 80, 87, 92–95, 98, 100, 101, 103, 105).

The risk of bias was considered low or moderate in all studies except one, which was assessed as having high risk (84) (Supplementary Table 2).

Pooled analyses showed that VCAM-1 concentrations were significantly higher in SSc than controls (SMD=1.09, 95% CI 0.72 to 1.46, p<0.001; I^2 = 92.7%, p<0.001; Figure 3). The results were stable in sensitivity analysis, with pooled SMD values ranging between 0.96 and 1.16 (Supplementary Figure 3).

There was significant publication bias (Begg's test, p<0.001; Egger's test, p=0.001). The "trim-and-fill" method identified seven missing studies to be added to the left side of the funnel plot to ensure symmetry (Supplementary Figure 4). The resulting SMD was attenuated but remained significant (SMD=0.51, 95% CI 0.08 to 0.94, p=0.021)

No significant associations were found between the effect size and age (t=-0.96, p=0.35), male to female ratio (t=-1.59, p=0.13), publication year (t=-1.07, p=0.30), sample size (t=-1.13, p=0.27), or

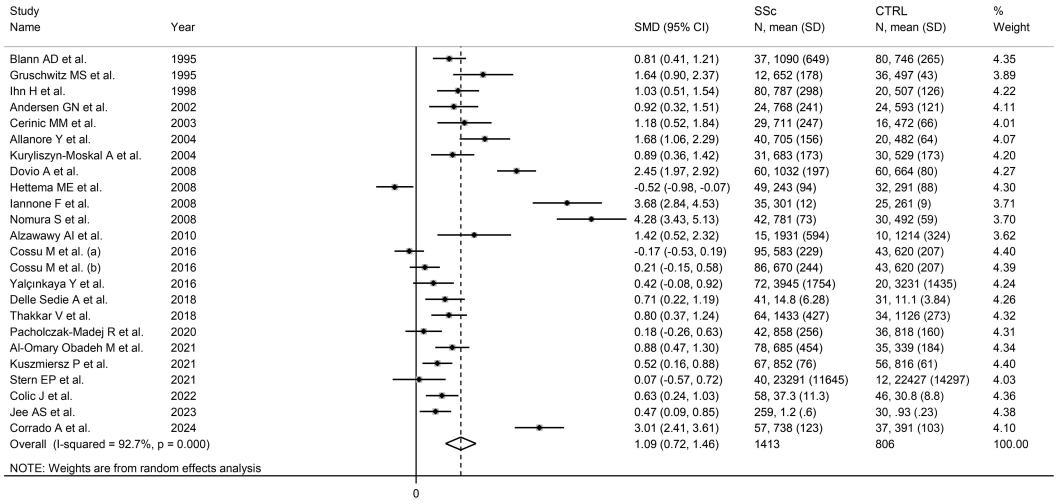

FIGURE 3
Forest plot of studies investigating VCAM-1 concentrations in SSc patients and controls.

SSc duration (t=1.29, p=0.22) in univariate meta-regression analysis. In sub-group analysis, there were non-significant differences (p=0.55) in pooled SMD between studies conducted in Europe (SMD=1.01, 95% CI 0.58 to 1.44, p<0.001; I^2 = 93.0%, p<0.001) and other geographical areas (SMD=1.34, 95% CI 0.52 to 2.17, p=0.001; I^2 = 92.9%, p<0.001). Non-significant differences (p=0.40) in pooled SMD were also observed between studies measuring serum (SMD=0.99, 95% CI 0.57 to 1.40, p<0.001; I^2 = 92.7%, p<0.001) and plasma (SMD=1.50, 95% CI 0.55 to 2.45, p=0.002; I^2 = 93.8%, p<0.001). Similarly, non-significant differences (p=0.56) in pooled SMD were observed between studies with a diffuse/localized disease patient ratio <1 (SMD=0.92, 95% CI 0.43 to 1.41, p<0.001; I^2 = 88.4%, p<0.001) and >1 (SMD=0.62, 95% CI 0.27 to 0.97, p=0.001; I^2 = 59.0%, p=0.045), with lower between-study variance in the >1 subgroup.

The overall level of certainty was upgraded to moderate (level 3) after considering the low-moderate risk of bias in most studies (no change), the high but partially explainable heterogeneity (no change), the lack of indirectness (no change), the large effect size (SMD=1.09; upgrade one level) (106), and the presence of publication bias which was addressed with the "trim-and-fill" method (no change).

PECAM-1

Two European studies reported PECAM-1 concentrations in 100 SSc patients and 41 healthy controls (83, 88) (Table 1). Measurements were conducted in serum in one study (83) and plasma in the other (88). The risk of bias was low in one study (83) and moderate in the other (88) (Supplementary Table 2).

Pooled analyses showed that PECAM-1 concentrations were significantly higher in SSc patients compared to controls (SMD=1.65, 95% CI 0.33 to 2.98, p=0.014; I^2 = 89.0%, p=0.003; Figure 4). Assessment of the risk of bias, meta-regression, and subgroup analyses could not be performed because of the small number of studies. The overall level of evidence was downgraded to very low (level 1) because of the high and unexplained heterogeneity and the lack of assessment of publication bias.

E-selectin

Eighteen studies, including 19 group comparators, assessed E-selectin concentrations in 1,293 SSc patients (mean age 54 years, 86% females) and 677 healthy controls (mean age 48 years, 70% females) (63, 66, 67, 70, 73, 74, 76, 79, 80, 84–86, 91–93, 96, 103, 104) (Table 1). Eleven studies were conducted in Europe (66, 67, 73, 76, 80, 85, 86, 91, 92, 96, 103) and seven in other continents (63, 70, 74, 79, 84, 93, 104). Thirteen studies investigated serum (63, 66, 67, 70, 79, 80, 85, 86, 92, 93, 96, 103, 104) and five plasma (73, 74, 76, 84, 91). Disease duration, reported in 12 studies, ranged between 2.6 and 13.6 years (67, 70, 73, 74, 79, 80, 85, 86, 91–93, 104). Disease type (diffuse or localized) was reported in ten studies (70, 73, 74, 76, 80, 86, 91–93, 103).

The risk of bias was considered low or moderate in all studies, except one which was assessed as having high risk (84) (Supplementary Table 2).

Pooled analysis showed that SSc patients had significantly higher E-selectin concentrations when compared to controls (SMD=1.17, 95% CI 0.72 to 1.62, p<0.001; I^2 = 94.0%, p<0.001; Figure 5). Sensitivity analysis showed that the pooled SMD values remained stable, ranging between 0.86 and 1.24 (Supplementary Figure 5), although one study, by Iversen et al, significantly influenced the effect size (91). This study also had a distortive effect on the funnel plot (Supplementary Figure 6). Its removal led to an attenuation of the effect size, which, however, remained significant (SMD=0.86, 95% CI 0.62 to 1.10, p<0.001), with lower between-study variance (I^2 = 77.9, p<0.001).

No publication bias was observed after removing the study by Iversen et al. (91) (Begg's test, p=0.26; Egger's test, p=0.53). The "trim-and-fill" did not identify any missing studies to be added to the funnel plot to ensure symmetry (Supplementary Figure 7).

Meta-regression analysis did not show any significant associations between the effect size and age (t=0.86, p=0.41), male to female ratio (t=0.70, p=0.50), year of publication (t=0.17, p=0.87), sample size (t=0.96, p=0.35), or SSc duration (t=1.15, p=0.27). In sub-group analysis, there were non-significant differences (p=0.91) in pooled SMD between studies conducted in Europe (SMD=1.21, 95% CI 0.53 to 1.89, p<0.001; I^2 = 95.9%,

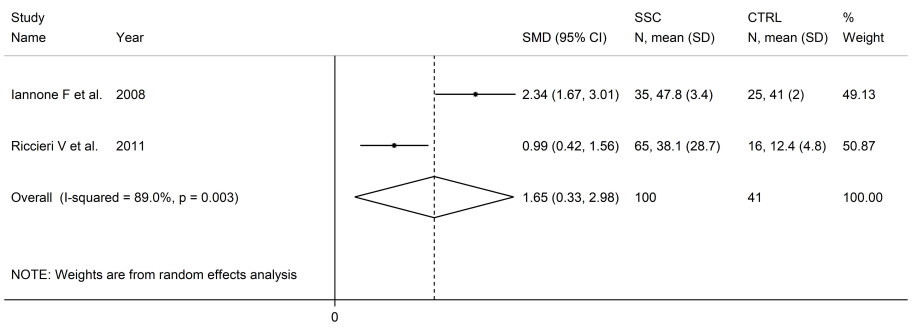

FIGURE 4
Forest plot of studies investigating PECAM-1 concentrations in SSc patients and controls.

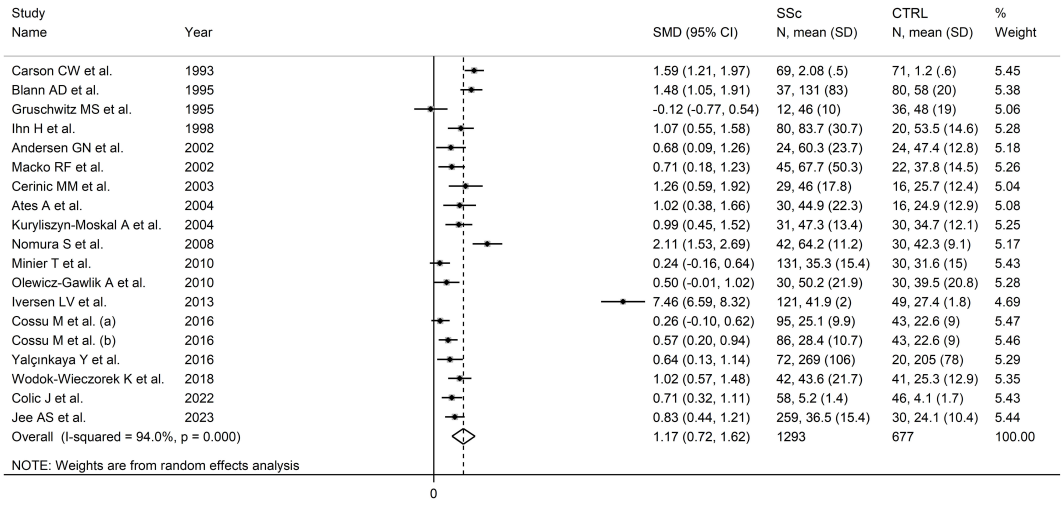

FIGURE 5
Forest plot of studies investigating E-selectin concentrations in SSc patients and controls.

p<0.001) and other continents (SMD=1.13, 95% CI 0.75 to 1.51, p<0.001; I^2 = 76%, p=0.003), with a lower between-study variance in the non-European subgroup. By contrast, a significant difference (p=0.044) in pooled SMD was observed between studies investigating serum (SMD=0.78, 95% CI 0.53 to 1.03, p<0.001; I^2 = 76.7%, p<0.001) and plasma (SMD=2.42, 95% CI 0.45 to 4.39, p=0.016; I^2 = 94.1%, p<0.001), with a lower heterogeneity in the serum subgroup. Finally, non-significant differences (p=0.52) in pooled SMD were observed between studies with a diffuse/localized disease patient ratio <1 (SMD=1.73, 95% CI 0.53 to 2.93, p=0.005; I^2 = 97.3%, p<0.001) and >1 (SMD=0.73, 95% CI 0.40 to 1.07, p<0.001; I^2 = 21.9%, p=0.28), with reduced between-study variance in the >1 subgroup.

The overall level of certainty was upgraded to moderate (level 3) after considering the low-moderate risk of bias in most studies (no change), the high but partially explainable heterogeneity (no change), the lack of indirectness (no change), the large effect size (SMD=1.17; upgrade one level) (106), and the absence of publication bias (no change).

L-selectin

Five studies assessed L-selectin concentrations in 141 SSc patients (mean age 52 years, 80% females) and 164 healthy controls (mean age 51 years, 68% females) (68, 72, 79, 89, 102) (Table 1). Four studies were conducted in Europe (68, 72, 89, 102) and one in Asia (79). Measurements were conducted in serum except one study which investigated plasma (89).

All studies had a low or moderate risk of bias (Supplementary Table 2).

Pooled analyses showed that L-selectin concentrations were non-significantly different between SSc patients and controls (SMD=-0.35, 95% CI -1.03 to 0.32, p=0.31; I^2 = 87.4%, p<0.001; Figure 6).

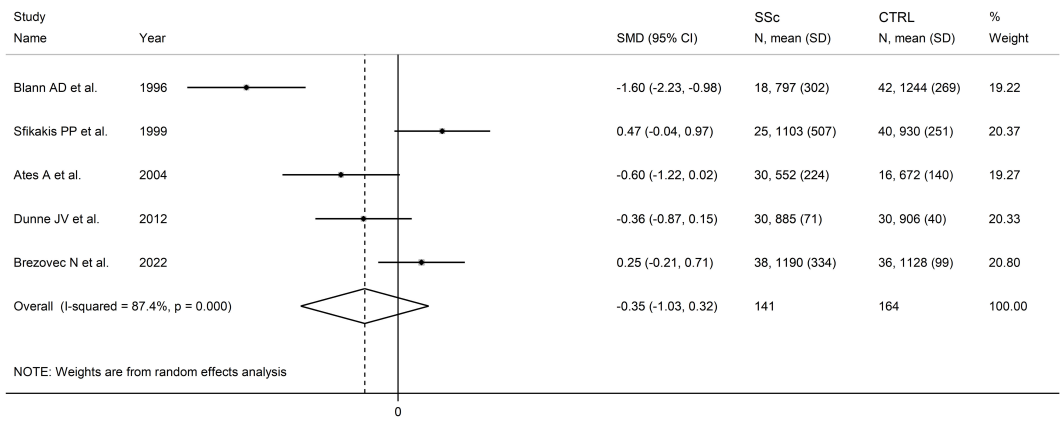

FIGURE 6
Forest plot of studies investigating L-selectin concentrations in SSc patients and controls.

The pooled SMD values were stable in sensitivity analysis, ranging between -0.56 and -0.29 (Supplementary Figure 8).

Assessment of publication bias, meta-regression and sub-group and analysis could not be performed because of the small number of studies.

The overall level of evidence was downgraded to very low (level 1) because of the high and unexplained heterogeneity and the lack of assessment of publication bias.

P-selectin

Nine studies assessed P-selectin concentrations in 434 SSc patients (mean age 52 years, 87% females) and 284 healthy controls (mean age 48 years, 82% females) (67, 72, 75, 79, 83, 84, 86, 91, 93) (Table 1). Six studies were conducted in Europe (67, 72, 75, 83, 86, 91) and three in Asia (79, 84, 93). Measurement was performed in serum in six studies (67, 72, 79, 83, 86, 93) and plasma in the remaining three (75, 84, 91).

The risk of bias was considered low or moderate in all studies except one which was assessed as having high risk (84) (Supplementary Table 2).

Pooled analyses showed that SSc patients had significantly higher P-selectin concentrations when compared to controls (SMD=1.10, 95% CI 0.31 to 1.90, p=0.007; I^2 = 95.0%, p<0.001; Figure 7). The results were stable in sensitivity analysis, with pooled SMD values ranging between 0.66 and 1.34 (Supplementary Figure 9).

Assessment of publication bias meta-regression analysis could not be conducted given the relatively small number of studies. In sub-group analysis, the pooled SMD was significantly higher in studies conducted in Europe (SMD=1.33, 95% CI 0.52 to 2.13, p=0.001; I^2 = 93.1%, p<0.001) but not in other continents (SMD=0.61, 95% CI -1.53 to 2.74, p=0.58; I^2 = 97.4%, p<0.001). The pooled SMD was also significantly higher in studies assessing plasma (SMD=1.51, 95% CI 0.44 to 2.58, p=0.006; I^2 = 93.9%, p<0.001) but not serum (SMD=0.91, 95% CI -0.25 to 2.07, p=0.13; I^2 = 95.5%, p<0.001). Finally, the pooled SMD was significantly higher in studies with diffuse/localized disease patient ratio >1 (SMD=0.86, 95% CI 0.47 to 1.25, p<0.001; I^2 = 51.5%, p=0.151) but not <1 (SMD=0.34, 95% CI -0.79 to 1.47, p=0.56; I^2 = 92.9%, p<0.001), with lower heterogeneity in the >1 subgroup.

The overall level of certainty remained low (level 2) after considering the low-moderate risk of bias in most studies (no change), the high but partially explainable heterogeneity (no change), the lack of indirectness (no change), the large effect size (SMD=1.10; upgrade one level) (106), and the lack of assessment of publication bias (downgrade one level).

Cadherins

One study with a low risk of bias (Supplementary Table 2) conducted in Turkey assessed vascular endothelium (VE)-cadherin in serum in 20 SSc patients and 40 healthy controls. Significantly higher VE-cadherin concentrations were observed in SSc patients (3.75 ± 5.8 vs 2.73 ± 6.0 pg/mL, p=0.016) (90) (Table 1).

NCAM, DSCAM, ESAM, and integrins

No studies investigating these cell adhesion molecules in SSc and healthy controls were identified.

Discussion

The results of this systematic review and meta-analysis have highlighted the presence of significant elevations in the concentrations of specific cell adhesion molecules, markers of endothelial activation, dysfunction, and atherogenesis, in patients with SSc. Such elevations were particularly evident in studies investigating ICAM-1, VCAM-1, PECAM-1, E-selectin, and P-selectin. The results were stable in sensitivity analysis, and the effect size of the observed between-group differences was generally

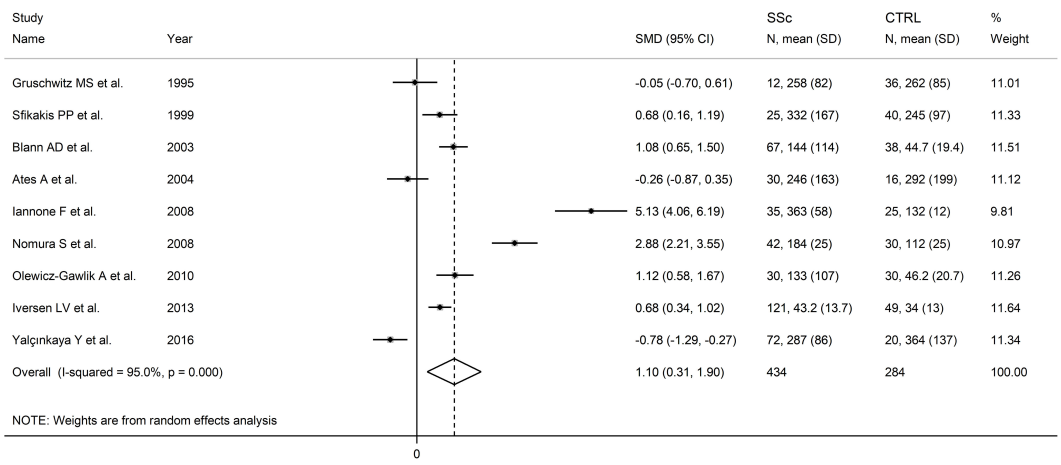

FIGURE 7
Forest plot of studies investigating P-selectin concentrations in SSc patients and controls.

not associated with individual study and patient characteristics. In particular, the lack of significant associations with SSc duration supports the proposition that elevations in cell adhesion molecules are already present in SSc patients with early disease, further supporting their potential clinical utility in assessing atherosclerotic burden. By contrast, no between-group differences were observed with L-selectin and minimal/no evidence was available for NCAM, DSCAM, ESAM, cadherins, and integrins.

Epidemiological studies have highlighted the increased risk of atherosclerotic cardiovascular events in SSc. The largest, conducted in Denmark, used data from administrative sources between 1995 and 2015 to identify patients with SSc and age- and sex-matched controls in a 1:5 ratio (14). Over a follow-up period of 8.9 years, SSc patients (n=2778) had a significantly increased risk of myocardial infarction (hazard ratio, HR=2.08, 95% CI 1.65 to 2.64), ischemic stroke (HR=1.28, 95% CI 1.04 to 1.58), and peripheral vascular disease (HR=5.73, 95% CI 4.63 to 7.09). These associations were maintained, except for ischemic stroke (HR=1.13, 95% CI 0.90 to 1.42), after adjusting for co-morbidities and medications. Our analyses suggest that measuring specific cell adhesion molecules might be helpful in evaluating atherosclerotic burden, stratifying cardiovascular risk, and facilitating the initiation of preventive strategies in SSc patients. Pending further research, assessing cell adhesion molecules may be particularly useful to demonstrate early endothelial dysfunction in absence of overt clinical evidence of vascular damage and atherosclerosis. However, an important issue to be addressed in further studies is whether such alterations in cell adhesion molecules might reflect endothelial dysfunction not only in the microcirculation, a vascular territory primarily affected in SSc (107, 108), but also in middle-size and large arteries, typically affected by the atherosclerotic process (7, 109–111).

Several studies have reported significant alterations in surrogate markers of endothelial function and arterial stiffness and an increased atherosclerotic burden in SSc (6–10). Endothelial cell injury, the main promoter of these alterations, stimulates adhesion and transmigration of leukocytes and monocytes into the tunica media of the arterial wall, initiating a sequence of events leading to the formation of the atherosclerotic plaque (8). A number of factors have been proposed as triggers of endothelial cell injury in SSc, including viruses (e.g., cytomegalovirus and Epstein Barr virus) (112, 113), cytotoxic CD4+ and CD8+ T-cells (114), autoantibodies against endothelial cells (115), and oxidative stress (116). However, further research is warranted to determine their role *in vivo*.

The capacity to restore endothelial function in SSc pharmacologically has been reported with dihydropyridine calcium channel blockers, statins, nitrate, endothelin-1 receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase activators, prostacyclins, and cyclophosphamide (8),. Notably, dihydropyridine calcium channel blockers (117), statins (118, 119), endothelin-1 receptor antagonists (120), phosphodiesterase-5 inhibitors (121), soluble guanylate cyclase activators (122), and prostacyclins (123) have also been shown to downregulate several cell adhesion molecules *in vitro* and *in vivo*. Furthermore, systematic reviews and meta-analyses on the effects of statins on cell adhesion molecules in other patient populations have shown an effect size (SMD) on VCAM-1 and ICAM-1 between -0.28 and -0.75 and on E-, L-, and P-selectin between -0.39 and -0.73 (118, 119). The magnitude of these effects suggests that statins may be effective in reducing the circulating concentrations of cell adhesion molecules in SSc. Regardless, further research should investigate whether the measurement of cell adhesion molecules in SSc patients receiving these therapies may reflect a state of improved endothelial function and reduced atherosclerotic burden.

Strengths of our study include the comprehensive assessment of a wide range of cell adhesion molecules, the robust evaluation of the certainty of evidence for each cell adhesion molecule investigated, the evaluation of specific study and patient characteristics associated with the effect size by means of meta-regression and subgroup analysis, and the generalizability of our findings to different geographical areas although most studies were conducted in European countries. One important limitation is represented by the generally high heterogeneity observed which, however, could be partially explained for some cell adhesion molecules (ICAM-1 and VCAM-1: diffuse/localized disease patient ratio; E-selectin: study continent, biological matrix assessed, and diffuse/localized disease patient ratio; P-selectin: diffuse/localized disease patient ratio).

In conclusion, our study has shown significant elevations of specific cell adhesion molecules, i.e., ICAM-1, VCAM-1, PECAM-1, E-selectin, and P-selectin in SSc, which reflects a state of endothelial activation, dysfunction, and atherogenesis in this patient group. Pending the results of further prospective studies in patients with subclinical and overt atherosclerosis, which also investigate the microcirculation and the effect of specific therapies, cell adhesion molecules may assist in cardiovascular risk stratification in SSc.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

AM: Data curation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. AZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1438302/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Sensitivity analysis of the association between ICAM-1 concentrations and SSc.

SUPPLEMENTARY FIGURE 2
Funnel plot of studies investigating the association between ICAM-1 concentrations and SSc after "trimming-and-filling". Dummy studies and genuine studies are represented by enclosed circles and free circles, respectively.

SUPPLEMENTARY FIGURE 3
Sensitivity analysis of the association between VCAM-1 concentrations and SSc.

SUPPLEMENTARY FIGURE 4
Funnel plot of studies investigating the association between VCAM-1 concentrations and SSc after "trimming-and-filling". Dummy studies and genuine studies are represented by enclosed circles and free circles, respectively.

SUPPLEMENTARY FIGURE 5
Sensitivity analysis of the association between E-selectin concentrations and SSc.

SUPPLEMENTARY FIGURE 6
Funnel plot of studies investigating the association between E-selectin concentrations and SSc.

SUPPLEMENTARY FIGURE 7
Funnel plot of studies investigating the association between E-selectin concentrations and SSc after "trimming-and-filling". Dummy studies and genuine studies are represented by enclosed circles and free circles, respectively.

SUPPLEMENTARY FIGURE 8
Sensitivity analysis of the association between L-selectin concentrations and SSc.

SUPPLEMENTARY FIGURE 9
Sensitivity analysis of the association between P-selectin concentrations and SSc.

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