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Title: Utility of Coronary Calcium Scoring (CCS) in Connective Tissue Disorders (CTDs) for the Evaluation of Subclinical Coronary Atherosclerosis – A Systematic Review

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The authors have no conflicts of interests and have not received any benefits or funding to conduct this project. There has been no financial support or competing interest for this project.

Ethics approval was waived as this is a systematic review without patient identifiers. Patient consent was waived as this is a systematic review without patient identifiers.

Abstract:

Objectives: To assess the current state of knowledge for the utility of coronary calcium scoring (CCS) in connective tissue disorders (CTDs) as it relates to the presence/quantification of coronary atherosclerosis.

Methods: Following PRISMA guidelines, a literature search via PubMed, Embase, Scopus, Web of Science Core Collection, CINAHL, and Cochrane Database of Systematic Review retrieved 1019 studies (since database inception – May 7, 2018) from which 121 manuscripts were eligible for review. Inclusion criteria consisted of studies that investigated CCS in adults with respective CTDs. Studies were excluded if a complete manuscript was not written in English, or was a case report.

Results: 31 studies were included (27 with healthy age/gender matched control group for comparison and 4 without). CTDs analyzed in articles with control group: 11 rheumatoid arthritis (RA), 14 systemic lupus erythematosus (SLE), 4 systemic sclerosis (SSc), 1 idiopathic inflammatory myopathies (IIM), 1 Takayasu arteritis, and 1 psoriasis. 9 out of 11 RA studies, 12 out of 14 SLE studies, and 2 out of 4 SSc studies showed statistically significant increased CCS when compared to control group. CTDs analyzed in studies without control group: 2 Kawasaki disease, 1 juvenile idiopathic arthritis (JIA), and 1 antiphospholipid syndrome (APS) article which demonstrated increased coronary arterial calcium (CAC) burden, however, without statistically significant data.

Conclusions: CTDs, especially SLE and RA, are associated with higher CCS compared to control group, indicating increased risk of coronary atherosclerosis. . Our search did not elicit sufficient publications or statistically significant results in many other connective tissue disorders.

Introduction

The association between atherosclerosis and inflammation has been well established (1). Atherosclerosis has been attributed to oxidative injury to the endothelial walls from inflammatory cells (2,3). Most connective tissue disorders (CTDs) are known chronic inflammatory disorders, of which some have been associated with cardiovascular disease (CVD). This CVD association has been mostly shown in systemic lupus erythematosus (SLE)

and rheumatoid arthritis (RA). One study demonstrated that the risk of cardiovascular disease in those with SLE was reported to be more than two times compared to their control group (4). Another study that investigated the risk of CVD in a multitude of inflammatory disorders found the highest risk in those with RA and other connective tissue disorders (5). The pathophysiologic mechanisms of why this occurs in diseases such as RA and SLE is still not fully understood, though inflammation seems to play a central role. Given the established association of atherosclerosis with inflammation, all connective tissue disorders should be investigated for their possible contributions for CVD.

Traditional cardiovascular risk factors such as age, race, systolic blood pressure, cholesterol, diabetes, smoking, and others have been previously validated for their increased risk of cardiovascular disease, and have been used to predict the risk of future cardiovascular events (6). A growing number of studies suggest that inflammatory and autoimmune disorders have both a higher burden of atherosclerosis and a higher number of cardiovascular hard events (4, 5). Furthermore, there is a disproportionate rate of CVD seen in the younger population with CTDs who lack traditional cardiovascular risk factors which accrue with age (7). This could be explained by the ebb and flow of systemic inflammation which has been well described as an underlying mechanism of atherosclerotic plaque (1). The traditional CVD risk stratification model might underestimate the true cardiovascular risks in CTDs, and new risk calculation models are needed.

Currently, there is no cardiac risk stratification model that includes pro-inflammatory CTDs as a risk factor for CVD. Coronary event risk calculators such as the American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease (ASCVD) risk calculator (6) do not include CTDs as a contributor to cardiovascular events.

The impact of CTDs on one's cardiovascular health is an important relationship to understand to be able to aid in its prevention. Surrogate markers for CVD such as coronary calcium score (CCS) have been shown to be an effective tool to predict increased risk of coronary heart disease events (8), such as myocardial infarction. The utility of CCS in identifying the cardiovascular risk in patients with CTDs has not been studied over the spectrum of CTDs (such as vasculitis, myositis, and mixed connective tissue disorders).

The purpose of this systematic review is to evaluate the coronary atherosclerotic disease risk of all connective tissue disorders by computed tomography (CT) scan with coronary arterial calcification (CAC) or coronary calcium score.

Methods

Protocol and registration

This descriptive systematic review was registered with PROSPERO (registration number CRD42019128607) and was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (9).

Search strategy

A structured search of published studies relating to coronary artery calcium scoring and connective tissue diseases was conducted in Medline via PubMed, Embase, Scopus, Web of Science Core Collection, CINAHL, and Cochrane Database of Systematic Review from database inception through May 7, 2018.

Search strategies were customized for each database and included appropriate controlled vocabulary terms and keywords related to coronary artery calcification and connective tissue disorders. Full details of the strategies for each database are available (Appendix 1). The reference lists of all included studies were hand searched to identify any additional relevant publications.

The Medical Subject Headings (MeSH) used to identify coronary artery calcification were the terms that were used to illustrate the connective tissue disorders and CT scan findings in the search concept (Table 1).

Eligibility criteria

Inclusion criteria consisted of studies that illustrated the CCS/CAC of the respective CTD in adults. Studies were excluded if they were a case report, not written in English, or were an abstract article without a full manuscript to evaluate. Each manuscript was evaluated to look for coronary arterial calcium detected from chest computed tomography scan in each respective connective tissue disorder (Figure 1).

Study selection, data extraction, and data items

Two reviewers evaluated the data and studies independently. 1907 abstracts were initially obtained from our search, which was reduced to 1019 after duplicates were removed. The 1,019 abstracts were analyzed for relevancy which resulted in 898 abstracts being excluded due to title and/or abstract that did not evaluate CCS/CAC of CTDs. 121 full manuscripts remained which were analyzed for mean, median, and/or prevalence/incidence of CCS/CAC in each respective CTD as either a primary outcome of the study, or as a secondary outcome. CCS/CAC was measured by CT scan of the chest without intravascular contrast and interpreted by a reviewer for CCS or CAC incidence/prevalence. All CT image modalities, including multidetector row computed tomography (MDCT) or electron beam tomography (EBT) were included. The units used to describe

the CCS was described by Agatston et al (10) and are reported in this review as Agatston units. Studies were also investigated for variables such as age, gender, ethnicity, and cardiovascular risk factors such as hypertension, diabetes, smoking, and hyperlipidemia.

This search strategy resulted in 33 studies that were eligible for full manuscript review (Figure 1). 27 studies compared the CCS/CAC of the respective CTD to a control group, and 6 studies did not have a control group for comparison. Of these 6 studies, 2 were excluded (1 RA, 1 SLE) due to the sufficient number of higher quality RA and SLE studies which had a control group for comparison. The remaining 4 studies (2 Kawasaki disease, 1 juvenile idiopathic arthritis [JIA], and 1 antiphospholipid syndrome [APS]) were included in this review despite the absence of a control group for comparison due to the lack of better-quality studies that investigated this association. This resulted in a total of 31 articles that were evaluated in this systematic review. Of these, the quantity and type of CTDs analyzed with a control group for comparison were: 11 rheumatoid arthritis (RA), 14 systemic lupus erythematosus (SLE), 4 systemic sclerosis (SSc), 1 idiopathic inflammatory myopathies (IIM), 1 Takayasu arteritis, and 1 psoriasis. The quantity and type of CTDs analyzed without a control group for comparison were: 2 Kawasaki, 1 JIA, and 1 APS.

Risk of bias in individual studies

The quality of articles included in this review were assessed using the Newcastle-Ottawa Scale (NOS) (11) assessment scale for cohort studies and the Agency for Healthcare Research and Quality (AHRQ) (12) criteria for cross-sectional studies. The Newcastle–Ottawa Scale assigns a maximum of 9 points to each study. The assessment scale analyzes three broad perspectives of each study: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies (11). When a study receives more than the median number of stars, it is considered to be of good quality (or low risk of bias); otherwise, it was deemed to be of low quality (or high risk of bias). All NOS assessments for cohort studies in this review had a score > 4 indicating good quality (Appendix 2). The individual assessments using AHRQ did not have a score value but did assess important study qualities through a series of investigational questions to assess for possible bias. The AHRQ assessment of the included cross-sectional studies subjectively demonstrated that they are also of good or fair quality (Appendix 3).

Results:

CCS/CAC of CTDs compared to healthy matched control group (Table 2)

Connective Tissue Diseases Summary

11 rheumatoid arthritis, 14 systemic lupus erythematosus, 4 systemic sclerosis, 1 idiopathic inflammatory myopathy, 1 Takayasu arteritis, and 1 psoriasis article were analyzed. Not all studies investigated CCS in the respective CTD as a primary outcome yet were able to be included as they met inclusion/exclusion criteria. Some studies investigated the CCS/CAC of multiple CTDs compared to a control group. MDCT or EBT was used in these studies to detect CAC/CCS. Some articles (16, 18, 30) used participants from the Multi-Ethnic Study of Atherosclerosis (MESA) (40) study, which evaluated CAC in different ages, sex, ethnicities, and cardiovascular risk factors to match for their control group. Table 2 outlines details of each study, including the type of CTD, CCS/CAC findings, statistical significance, and sample size. Descriptive characteristics of each article are outlined in Appendix 4.

Rheumatoid Arthritis (RA)

9 out of 11 (82%) RA articles showed a statistically significant increase in CAC prevalence and/or CCS in RA patients compared to control group. Among the 9 articles, 3 of them (14, 15, 17) analyzed the CCS and CAC prevalence in early RA (<5 and <6 years disease duration) and late RA (>10-year duration). All of these studies found that the CAC prevalence and CCS were higher in the late RA group. One article (20) only analyzed female patients and control group. Two articles (16, 19) did not demonstrate increased CAC in RA, however, neither of these studies demonstrated statistical significance. One article (16) illustrated that both prevalence and progression of CAC were similar between the RA and control group, and the other (19) demonstrated that the median CAC was not increased in RA patients when compared to control group (in a small sample size of 37 patients).

Systemic Lupus Erythematosus (SLE)

12 out of 14 (86%) studies demonstrated with statistical significance that CCS, CAC incidence/prevalence, and/or CAC burden was increased in SLE when compared to control group. Three articles (28, 29, 30) only analyzed female patients and controls. One study (31) only analyzed male patients and controls. Two out of the fourteen studies did not comment on disease duration at time of CAC/CCS. The median or mean disease duration of the other twelve studies were at least >5 years duration. Of the 2 studies that did not demonstrate statistical significance, one study (29) showed that the SLE group had higher prevalence of CAC and higher rates of CAC progression when compared to control group. The other study (19) showed that the median CAC was not increased in SLE patients, but had a small sample size of 33 SLE patients.

Systemic Sclerosis (SSc)

2 out of 4 studies (50%) showed statistically significant increased CCS or CAC incidence/prevalence compared to control group, though one study (35) had a very small population size (17 patients for each group). The other two studies (19, 37) did not demonstrate statistical significance and illustrated that CAC/CCS was not increased in SSc when compared to control group. The mean or median disease duration in all studies was at least 6 years.

Idiopathic Inflammatory Myopathy (IIM) also known as (Dermatomyositis [DM]/Polymyositis [PM])

One article (38) was reviewed which did show slight increase in the median CCS for IIM when compared to control group (not statistically significant; p=0.27). The mean disease duration was 9 years. The IIM group had more patients with CCS score ≥ 400 (20%) compared to control group (4%) (p=0.04). However, multivariate analysis demonstrated that the confounding factors associated with this were age and smoking, and there was no significant association found between the number of patients with higher CCS and IIM.

Takayasu Arteritis

One article (33) was reviewed which illustrated increased CAC incidence in Takayasu arteritis when compared to control group, however, this data was not statistically significant. The mean disease duration was 9.5 years. This same study did show that the incidence of CAC was greater in SLE than in Takayasu arteritis (with statistical significance).

Psoriasis

One article (39) was reviewed which showed that those with psoriasis had slightly higher CCS than control group, however, this was not statistically significant. The mean disease duration was 16 years. The psoriasis and control group populations had similar prevalence of CAC.

CCS/CAC of CTDs without a control group for comparison (Table 3)

Connective Tissue Diseases Summary

The following articles were included in this study due to the lack of better-quality studies to evaluate CAC/CCS in these respective connective tissue disorders compared to a control group. These consisted of one antiphospholipid syndrome (APS) article (43) which analyzed serologically positive APS antibodies from a previous study (45) of patients that had CCS/CAC calculated, two Kawasaki articles (41, 42) which did not have a control group for comparison, and one JIA article (44) which did not have a control group for comparison. Table 3 illustrates the

details of each study, including the type of CTD, CCS/CAC findings, statistical significance, and sample size. MDCT or EBT was used in these studies to detect CAC/CCS. The results demonstrate a higher CAC burden in people with these diseases than would be expected in their respective age groups, however, there is no control group for comparison, and data was not statistically significant. Descriptive characteristics of each article are outlined in Appendix 4.

Kawasaki Arteritis

Two articles (41, 42) were reviewed which demonstrated that CAC was increased in most patients with Kawasaki who developed a coronary aneurysm, though this data was not statistically significant. The median disease duration was at least 14.8 and 19.7 years. The median ages at the time of CT scan were 20 and 19.7 years in each study, respectively. There was no control group for comparison in either study. Both studies demonstrated that all of the participants without coronary dilation or aneurysm had no coronary arterial calcium detected.

Antiphospholipid Syndrome (APS)

One article (43) was analyzed from a pool of patients of the CARDIA study (Coronary Artery Risk Development in Young Adults) (45) which consisted of young adults aged 18-30 years old enrolled in the study in 1985. CAC was measured at 15 and 20 years. This study demonstrated that CAC was more prevalent in these patients with serum positivity for APS than would be expected for their age group. Antiphospholipid antibodies (IgG and IgA anti-β2-GPI antibodies) were associated with CAC > 0 at year 15 after adjustment for traditional cardiovascular factors, gender, and race. Anti-β2-GPI antibodies (more so anti-β2-GPI IgG) were associated with CAC > 0 at year 20, but the relationship was not as strong as that for CAC at year 15.

Juvenile Idiopathic Arthritis (JIA)

One article (44) discovered that 26% of patients were found to have CAC (not statistically significant), demonstrating an increased CAC burden than would be expected at this young age. The mean disease duration was 29.2 years, with a median age group of 38 years at the time of CT scan with CAC calculation.

Discussion

The goal of this study was to evaluate the cardiovascular risk of connective tissue diseases as measured by coronary arterial calcium prevalence/incidence or coronary calcium score. Overall, the articles that compared their respective CTD to a control group effectively matched to age and gender, and had mostly similar cardiovascular risk factors. Unfortunately, there were not an adequate amount of publications meeting this study's

inclusion/exclusion criteria that evaluated CAC/CCS in connective tissue disorders besides SLE and RA. Therefore, this systematic review was unable to definitively assess the cardiovascular risk through means of CCS/CAC in the other connective tissue disorders, though the suspicion for cardiovascular disease is still high based on all of the studies evaluated. Nevertheless, this systematic review did confirm that there is a strong association of coronary artery calcification, and thus, coronary atherosclerosis in RA and SLE. All of the studies with statistical significance included in this systematic review that compared the RA and SLE patient population to a control group demonstrated increased CAC/CCS in the RA and SLE groups. Given these findings, CCS has shown to be an effective modality in the evaluation of coronary atherosclerosis in these two CTDs. It is important for future studies to address if the strict control of other risk factors of CAD such as hypertension, smoking, and hyperlipidemia, in addition to the control of disease activity itself, can assist in preventing future cardiovascular events in this patient population.

Systemic sclerosis had conflicting data on its cardiovascular risk, with half of the studies demonstrating increased CAC/CCS compared to control group. However, the two out of four studies with data of statistical significance did demonstrate increased CAC burden in the SSc group. In addition, one systematic review which investigated the incidence of CAD from autopsy findings, CAC, and coronary angiographic findings demonstrated that SSc is associated with increased incidence of CAD (46). These findings are more supportive of an increased cardiovascular burden from SSc, though additional studies with larger patient population sizes are needed to confirm this.

One IIM study did show that patients with IIM had a higher number of individuals with CCS ≥400 than the healthy control group, however that was found to be attributed to confounding risk factors of tobacco smoking and patient age, and not IIM. More studies are needed to investigate this correlation. The Takayasu arteritis and psoriasis studies also demonstrated increased CAC (though not statistically significant), however, more studies are needed with a larger patient population size for reliable assessment.

Overall, the analysis of articles without a control group for comparison demonstrated higher CAC/CCS in the Kawasaki, APS, and JIA population than would be expected for their younger patient population (not statistically significant), but additional studies are needed for direct comparison to a control group, as well as larger sample sizes. Kawasaki disease is unique in that there is a direct coronary artery injury in the pediatric population complicated by post traumatic effects such as coronary aneurysm. These studies were consistent in finding that those with coronary aneurysms did have increased CAC, though the data was not statistically significant. The JIA study also demonstrated increased CAC prevalence than would be expected in its young patient population. The APS study showed a CAC burden greater than zero in those with serum positivity for antiphospholipid antibodies which is not expected to be found in a young population of age 18-30 years old, however, a control group would be helpful in validating these findings.

Limitations

This systematic review has several limitations. First, this is a descriptive review and lacks statistical analysis to summarize the results of these studies and assist in eliminating some bias. The authors believe that publication bias could be present but cannot be assessed in this review due to the different expected magnitude of effect and different publication bias across these connective tissue disorders.

Another limitation of this study is the few number of articles that studied CCS in CTDs besides SLE and RA, which prevents proving or disproving the hypothesis that CCS/CAC is higher in all CTDs when compared to healthy control groups. Third, this review included many cross-sectional observation studies which could not evaluate the temporal relationship of each respective CTD and coronary arterial calcification.

Conclusion

From the evidence of articles evaluated, this systematic review demonstrates that some CTDs (RA and SLE) have higher CCS and/or CAC incidence or prevalence compared to normal controls, and thus, may be an independent risk factor of coronary atherosclerosis, while the SSc data is still ambiguous. For SLE and RA, we suggest this risk from studies that demonstrated this association with statistical significance, though the quality of the articles evaluated (cross sectional and cohort studies) must be considered. Based on the current published data regarding other CTDs, increased coronary atherosclerosis also seems likely, however better-quality studies are needed to prove this association. This review also identified that aside from Takayasu arteritis and Kawasaki disease, there is currently no published data in the spectrum of vasculitides, which have been associated with high inflammatory burden. It is unclear if MDCT or EBT-measured CCS is a reliable and generalizable tool to assess subclinical atherosclerosis across the spectrum of CTDs, however we ascertain that it can be useful for cardiovascular risk assessment in patients with SLE and RA, with consideration of its disadvantages including radiation exposure and cost.

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The 4 Domains of Connective Tissue Disorders
1. Rheumatoid Arthritis
2. Seronegative spondyloarthropathies
a. Ankylosing Spondylitis
b. Reactive Arthritis
c. Enteropathic Arthropathy OR Spondylitis Associated with Inflammatory Bowel Disease
d. Psoriatic Arthritis
e. Undifferentiated Spondyloarthropathy
3. Connective Tissue Diseases
a. Systemic Sclerosis
b. Primary Sjogren's Syndrome
c. Systemic Lupus Erythematosus
d. Antiphospholipid Syndrome
e. Relapsing Polychondritis
f. Idiopathic inflammatory myopathies: Polymyositis, Dermatomyositis, Anti-synthetase Syndrome, Inclusion-body Myositis, Necrotizing Autoimmune Myopathy
g. Mixed Connective Tissue Disorder
h. Undifferentiated Connective Tissue Disease
4. Vasculitis:
a. Large vessel vasculitis:
i. Takayasu Arteritis
ii. Giant Cell Arteritis

Author, Year, & Reference	CTD / Sample size	Mean, median, or incidence/prevalence of CAC or CCS results (Agatston units)	Statistical significance
Abdel-Khalek (2011) (13)	RA - 60 Control - 20	RA Mean CCS: 126 ± 115.23 Control Mean CCS: 4.7 ± 4.03	p < 0.001
Asanuma (2007) (14)	Early RA - 90 Established RA - 67 Control - 87	Early RA (< 6 years) Median CCS: 0 (0-47) Established RA (> 10 years) Median CCS: 63 (0-368) Control Median CCS: 0 (0-18)	p < 0.001
Avalos (2007) (15)	Early RA - 57 Late RA - 60 Control - 65	Early RA (< 6 years) – Median CCS 0 (0–33.8) Late RA (> 10 years) – Median CCS 65.5 (0–400.5) Controls – Median CCS 0 (0–16.4)	p < 0.001
Chung (2013) (16)	RA - 155 Control – 835*	Median CCS RA - 3.1 (0-135.1) Median CCS control - 6.4 (0-119.6)	NS
Chung (2005) (17)	Early RA - 70 Established RA - 71 Control - 86	Early RA (< 5 years) - median CCS 0 (0-42.6), CAC in 42.9% Established RA (> 10 years) - median CCS 40.2 (0-358), CAC in 60.6% Control - median CCS 0 (0-19.2), CAC in 38.4%	p = 0.001
Giles (2009) (18)	RA - 195 Control - 1,073*	RA mean CCS: 175 ± 31 Control mean CCS: 122 ± 13	p = 0.002
Kakuta (2016) (19)	RA - 37 SSc - 24 SLE - 33 Control - 74	Median CCS RA – 0 (0-136) Median CCS SSc – 0 (0-111) Median CCS SLE – 0 (0-138) Median CCS Control – 30 (0-225)	NS
Kao (2008) (20)	SLE - 105	Prevalence of CAC:	p = 0.02

b. Medium vessel vasculitis:
i. Polyarteritis Nodosa
ii. Kawasaki Disease
c. Small vessel vasculitis
i. Microscopic Polyangiitis
ii. Granulomatosis with Polyangiitis
iii. Eosinophilic Granulomatosis with Polyangiitis
d. Variable vessel vasculitis
i. Behcet's Disease
ii. Cogan's Syndrome
e. Immune complex small vessel vasculitis
i. Anti-glomerular Basement Membrane (anti-GBM) Disease
ii. Cryoglobulinemic Vasculitis
iii. IgA Vasculitis (Henoch-Schonlein)
iv. Hypocomplementemic Urticarial Vasculitis (anti-C1q vasculitis)

Table 1. Search terms for connective tissue disorders

Author, Year, & Reference	CTD / Sample Size	Mean, median, or incidence/prevalence of CAC or CCS results (Agatston units)	Statistical significance
Kahn (2012) (41)	RA – 105 Kawasaki – 70 Control – 105 No control group	SLE - 47.6%, RA - 47.6%, Control - 35.2% No coronary dilation (44/70) - none had CAC Transient dilation (12/70) - 1/11 patients had CAC With coronary aneurysm (14/70) – all patients had CAC and the highest CAC burden	NS
Paccou (2014) (21)	RA - 75 Control - 75	RA CAC prevalence - 65.3% Control CAC prevalence - 49.3%	p = 0.04
Wang (2009) (22)	RA - 85 Kawasaki – 116 Control - 85 No control group	RA Mean CCS - 62.8 ± 197.0 No coronary dilation (100/160) - 0 CAC Control Mean CCS - 11.3 ± 38.5 Transient/persistent dilation (33/160) – 1 out of 33 patients had CAC Aneurysm (9/33) – all had CAC and the highest CAC burden	p = 0.002 NS
Kahn et al. (2017) (42)	RA - 85 SLE - 69 APS – 2,203* Control - 106 No control group	RA and SLE Mean CCS - 42.2 ± 154.3 APS: CAC was prevalent in 9.5% of young adults (age 18-30) with APS antibodies. Control Mean CCS - 1.4 ± 13.0	NS p < 0.01
Majka et al. (2013) (43)	SLE - 65 Control - 69	SLE Mean CCS: 68.9 ± 244.2 Control Mean CCS: 8.8 ± 41.8	p = 0.002
Yiu (2012) (23)	JIA – 84 No control group	22 of 84 JIA patients (26%) had a CCS above 0	NS
Asanuma (2003) (24)	SLE - 93 Control – 65	SLE CAC incidence and Mean CCS - 19.4% and 39 ± 200 16 patients had CCS 1-10 6 patients had CCS > 10 Control CAC incidence and Mean CCS - 6.2% and 4 ± 30	p = 0.02
Aalie et al. (2014) (44)	SLE - 113 Control - 80	SLE Mean CCS - 43.4 ± 189.8 Control Mean CCS - 3.8 ± 27.9	p = 0.002
Chung (2006) (25)	SLE - 30 Control - 30	SLE Mean CCS: 42 ± 111.09 Control Mean CCS: 0, no CAC was detected	p = 0.04
Chung (2008) (26)	SLE - 80 Control – 241*	Age 45-54 CAC prevalence: SLE - 58%. Control - 22/125 (36%) Age 55-64 CAC prevalence: SLE - 57%. Control - 42/116 (36%)	Age 45-54: p < 0.001 Age 55-64: NS
Heshmat (2015) (27)	SLE - 149 Control - 124	CAC was more prevalent in SLE patients and had significantly higher progression	NS
Kiani (2015) (28)	SLE - 60 Control - 60	SLE Mean CCS - 59.2 ± 20.3 Control Mean CCS - 2.6 ± 1.85	p < 0.001
Lertratanakul (2014) (29)	SLE - 95 Control - 100	SLE - CAC incidence 18% Control - CAC incidence 7%	p = 0.03
Othman (2013) (30)	SLE - 139 Control - 100	SLE - CAC incidence 7.2% Control - CAC incidence 1%	p = 0.02
Romero-Diaz (2018) (31)	Takayasu - 47 SLE - 43 Control - 70	Takayasu CAC incidence: 11% SLE CAC incidence: 21% Control CAC incidence: 3%	Takayasu: NS SLE: p = 0.010
Romero-Diaz (2012) (32)	SLE - 50 Control - 50	SLE CAC prevalence - 42% Control CAC prevalence - 8%	p < 0.01
Seyahi (2013) (33)	SSc - 17 Control - 17	SSc Mean CCS - 126.6 ± 251.0 Control Mean CCS - 14.7 ± 52.2	p = 0.003
Yiu (2009) (34)	SSc - 53 Control - 106	SSc - 56.5% had CCS > 101 Control - 29.4% had CCS > 101	p = 0.01
Khurma (2008) (35)	SSc - 41 Control – 123	SSc median CAC – 0 (0-133.5) Control median CAC – 0 (0-454.1)	NS
Mok (2011) (36)	IIM - 76 Control – 48	IIM: Median CCS 18 (0 - >400) Control: Median CCS 5 (0 - >400)	NS
Seung-Geun (2013) (37)	Psoriasis - 40 Control - 42	Psoriasis Mean CCS - 9.9 ± 35.2 Control Mean CCS - 2.8 ± 12.0	NS
Diederichsen (2015) (38)			
Seremet (2014) (39)			

Table 2. Descriptive summary of CCS/CAC of CTDs with control group for comparison; CAC = coronary artery calcium; CCS = coronary calcium score; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; IIM = idiopathic inflammatory myopathy; NS = not significant; * = sample patients from (40) Multi-Ethnic Study of Atherosclerosis [MESA] Study

Table 3. Descriptive summary of CCS/CAC of CTDs without control group for comparison; CAC = coronary artery calcium; CCS = coronary calcium score; APS = antiphospholipid syndrome; JIA = juvenile idiopathic arthritis; NS = not significant; * = sample patients from (45) Coronary Artery Risk Development In Young Adults (CARDIA) study

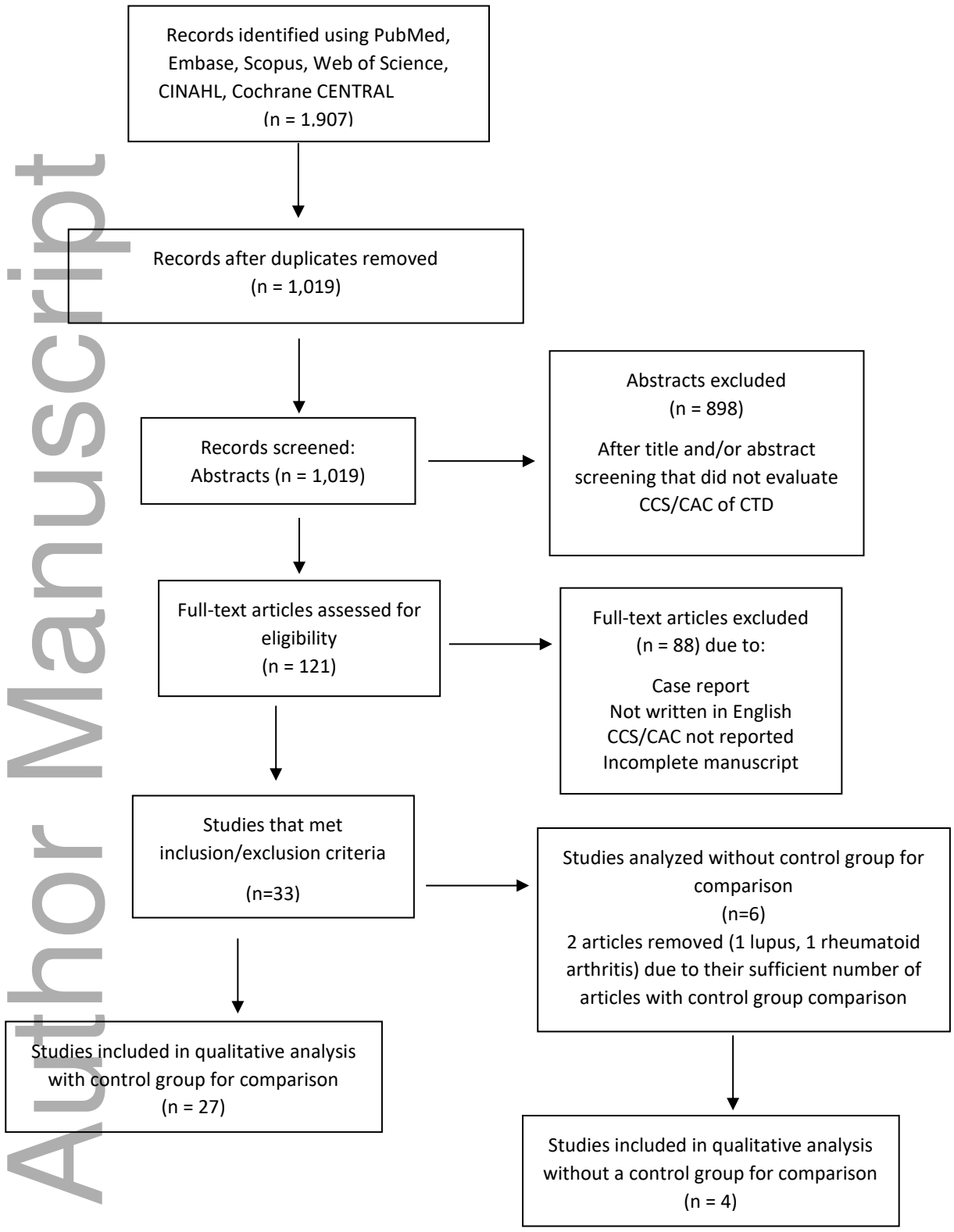

Figure 1. Flow Diagram - Search design