PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association Between Systemic Sclerosis and Peripheral Arterial Disease: A Nationwide Observation Retrospective Claim Records Cohort Study In Taiwan
AUTHORS	Hsieh, Ming-Chia; Chen, Hsin-Hung; Chou, Tzu-Yi; Su, Ta-Wei; Lin, Cheng-Li; Kao, Chia-Hung

VERSION 1 – REVIEW

REVIEWER	Theodoros Dimitroulas Hippokratio Hospital, Thessaloniki, Greece
REVIEW RETURNED	06-Feb-2021

GENERAL COMMENTS	This is a nationwide study discussing the relationship between SSc and PAD concluding that large vessels disease in lower limps is common in SSc patients. Despite the large number of subjects studied, the study has several weaknesses which preclude publication. The main limitation of the study is the lack of validated method for the diagnosis of PVD. The study design is too weak and the diagnosis from “claim records” for the main parameter assessed in the study is not acceptable. At least it should somehow be mentioned in the title. The presence of PAD is well-described and the study does not add something new regarding the true impact of macrovascular disease in SSc The authors do not adequately address how microvascular disease – the cornerstone of SSc vascular derangement – may be related with large vessels involvement and vice versa. Discussion: “PAD leads to skin ulcers especially in lower extremity” I strongly disagree as digital ulceration is the result of obliterative microvessels disease coupled with abnormal vasoconstriction and not the consequence of PAD. Subsequently the authors seem to ignore basic components of SSc pathogenesis. For example the vasculopathy in SSc is primarily due to involvement of microcirculation with manifestations such as Raynauds, PAH which is not highlighted in the Introduction. Given that journals’ audience extends beyond rheumatologists, the clarification of micro- and macro-vascular involvement is essential. Similarly the sentence: “The arteries other than those supplying blood to the heart or brain become narrow in patients with SSc…” does not provide the rationale of the study

REVIEWER	Muriel Elhai Paris Descartes Unviersity Interuniversity Medical Library Medicine and Dentistry section
REVIEW RETURNED	12-Feb-2021

GENERAL COMMENTS	This is an interesting cohort study about association of peripheral arterial disease in SSc. The study is well designed,respects STROBE recommandations and demonstrates an association between PAD and SSc. Minor comments in the introduction: - SSc can be of diffuse or limited form according to extent fo skin fibrosis, please correct - The data referring at survival are not correct, please refer to new cohorts or data (for example see Sobanski et al.

REVIEWER	Nathalie Conrad Medical Sciences Division
REVIEW RETURNED	14-May-2021

GENERAL COMMENTS	Summary The authors present an analysis of the association between SSC and incident PAD. A major strength of this study is its population-based design. Limitations include its relatively small size and inability to adjust for key cardiovascular risk factors. Analyses appear to have been performed meticulously and are well described. Findings from this study are important and are likely to have clinical implications. Major Comments Raynaud's syndrome appears to be part of SSc diagnostic criteria and PAD clinical definition (in particular ICD code 443 "Other peripheral vascular diseases" includes Raynaud's syndrome). Authors should please address this point and explain how this impacts their analyses and findings. The authors specify how index date was defined for the SSc cohort (date of SSc diagnosis), but should also explain how they defined index date for the matched cohort (which do not have an SSc diagnosis). Authors should also please clarify how patients were matched on "age" (I assume they mean birthyear or age at index?) and "year of SSc diagnosis" (perhaps they mean index date?). In the discussion section, authors discuss possible explanations for the observed association between SSc and PAD. Shared risk factors (for eg. smoking, a major risk factor for Raynaud's and PAD) would also deserve to be addressed and discussed. The manuscript is generally well written but would in my view benefit from a brief English proof-reading. Minor Comments Table 1 – follow-up time also refers to t-test and should be marked as such. Table 2 – as per methods, aHR also includes sex. Authors should please clarify the enrollment period (abstract states up to 2010 and methods up to 2011). In strength and limitations, the meaning of "2. All insurance claims should be scrutinized by medical reimbursement specialists and peer review" is unclear to me. The discussion is somewhat repetitive and could, in my opinion be shortened. The last paragraph, "summary" could be made clearer with a focus on results from the present study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:

This is a nationwide study discussing the relationship between SSc and PAD concluding that large vessels disease in lower limps is common in SSc patients. Despite the large number of subjects studied, the study has several weaknesses which preclude publication.

The main limitation of the study is the lack of validated method for the diagnosis of PVD. The study design is too weak and the diagnosis from “claim records” for the main parameter assessed in the study is not acceptable. At least it should somehow be mentioned in the title.

Reply: Thank you for your comments. It is true that due to the lab data restriction in Taiwan we could not use the real world data such as ABI exam for analysis. We will add Claim Records in Taiwan for the title

The presence of PAD is well-described and the study does not add something new regarding the true impact of macrovascular disease in SSc

Reply: Thank you for your comments. We will add on the new data for the macrovascular disease in SSc with reference 41

utt SA, Jeppesen JL, Torp-Pedersen C, Sam F, Gislason GH, Jacobsen S, Andersson C. Cardiovascular Manifestations of Systemic Sclerosis: A Danish Nationwide Cohort Study. J Am Heart Assoc. 2019 Sep 3;8(17):e013405. doi: 10.1161/JAHA.119.013405. Epub 2019 Aug 24. PMID: 31446827; PMCID: PMC6755829.

The authors do not adequately address how microvascular disease – the cornerstone of SSc vascular derangement – may be related with large vessels involvement and vice versa.

Reply: Thank you for your comment and we will add on the sentence to our article.

Discussion: “PAD leads to skin ulcers especially in lower extremity” I strongly disagree as digital ulceration is the result of obliterative microvessels disease coupled with abnormal vasoconstriction and not the consequence of PAD.

Reply: Thank you for your comment. We delete the sentence.

Subsequently the authors seem to ignore basic components of SSc pathogenesis. For example the vasculopathy in SSc is primarily due to involvement of microcirculation with manifestations such as Raynauds, PAH which is not highlighted in the Introduction. Given that journals’ audience extends beyond rheumatologists, the clarification of micro- and macro-vascular involvement is essential.

Reply: Thank for your comment. We mentioned the pulmonary arterial hypertension from the reference 1 in the introduction. We would add your example to our article.

Similarly the sentence: “The arteries other than those supplying blood to the heart or brain become narrow in patients with SSc…” does not provide the rationale of the study
Reply: Thank you for your comment. We would delete the sentence

Reviewer: 2
Comments to the Author:
This is an interesting cohort study about association of peripheral arterial disease in SSc. The study is well designed, respects STROBE recommandations and demonstrates an association between PAD and SSc.
Minor comments in the introduction:
- SSc can be of diffuse or limited form according to extent for skin fibrosis, please correct

Reply: Thank you for your comment and we will correct it in the introduction.

- The data referring at survival are not correct, please refer to new cohorts or data (for example see Sobanski et al.
Reply: thank you for your comment . We write the article again with reference 2 and 3

2. Sobanski V, Giovannelli J, Allanore Y, Riemekasten G, Airò P, Vettori S, Cozzi F, Distler O, Matucci-Cerinic M, Denton C, Launay D, Hachulla E; EUSTAR Collaborators. Phenotypes Determined by Cluster Analysis and Their Survival in the Prospective European Scleroderma Trials and Research Cohort of Patients With Systemic Sclerosis. Arthritis Rheumatol. 2019 Sep;71(9):1553-1570. doi: 10.1002/art.40906. Epub 2019 Aug 12. PMID: 30969034; PMCID: PMC6771590.

3. Sobanski V, Launay D, Hachulla E, Humbert M. Current Approaches to the Treatment of Systemic-Sclerosis-Associated Pulmonary Arterial Hypertension (SSc-PAH). Curr Rheumatol Rep. 2016 Feb;18(2):10. doi: 10.1007/s11926-015-0560-x. PMID: 26841964.

Reviewer: 3
Comments to the Author:
Summary
The authors present an analysis of the association between SSC and incident PAD. A major strength of this study is its population-based design. Limitations include its relatively small size and inability to

adjust for key cardiovascular risk factors. Analyses appear to have been performed meticulously and are well described. Findings from this study are important and are likely to have clinical implications.

Major Comments

Raynaud's syndrome appears to be part of SSc diagnostic criteria and PAD clinical definition (in particular ICD code 443 "Other peripheral vascular diseases" includes Raynaud's syndrome). Authors should please address this point and explain how this impacts their analyses and findings.

Reply: Thank you for your comment and we use ICD code 443 for another analysis and it also confirmed the result.

Table. The overall Incidence of peripheral arterial disease (per 1,000 person-years), estimated hazard ratios and subhazard ratios in PD patients with systemic sclerosis compared to those without Systemic sclerosis

	Systemic sclerosis	
Variables	No(N=4424)	Yes(N=1106)
Person-years	24611	4052
Event, n	58	237
Rate	2.36	58.5
Crude HR (95% CI)	1(Reference)	22.3(16.7, 29.8)
Adjusted HR (95% CI)[a]	1(Reference)	22.8(17.1, 30.5)

Adjusted HR† : multivariable analysis including age, gender, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, stroke, and asthma

*p<0.01, **p<0.001

The authors specify how index date was defined for the SSc cohort (date of SSc diagnosis), but should also explain how they defined index date for the matched cohort (which do not have an SSc diagnosis). Authors should also please clarify how patients were matched on "age" (I assume they mean birthyear or age at index?) and "year of SSc diagnosis" (perhaps they mean index date?).

Reply: Thank you for your comment. The index date for non-SSc subjects was randomly appointed a month and day with the same index year of the matched SSc cases. Yes, the age was calculated as (index date-birthyear)/365.

In the discussion section, authors discuss possible explanations for the observed association between

SSc and PAD. Shared risk factors (for eg. smoking, a major risk factor for Raynaud's and PAD) would also deserve to be addressed and discussed.
The manuscript is generally well written but would in my view benefit from a brief English proof-reading.
Reply: Thank you for your comment. We will add the discussion of risk factor of smoking.

Minor Comments
Table 1 – follow-up time also refers to t-test and should be marked as such.

Reply: Thank you for your comment and we modify it.

Table 2 – as per methods, aHR also includes sex.

Reply: Thank you for your comment and we complete it.

Authors should please clarify the enrollment period (abstract states up to 2010 and methods up to 2011).

Reply: Thank you for your comment and we correct it.

In strength and limitations, the meaning of "2. All insurance claims should be scrutinized by medical reimbursement specialists and peer review" is unclear to me.
The discussion is somewhat repetitive and could, in my opinion be shortened. The last paragraph, "summary" could be made clearer with a focus on results from the present study.
Reply: Thank you for your comments and we will re write it

VERSION 2 – REVIEW

REVIEWER	Theodoros Dimitroulas Hippokratio Hospital, Thessaloniki, Greece
REVIEW RETURNED	27-Jun-2021

GENERAL COMMENTS	The authors have adequately addressed a number of comments, however the interrelation between micro- and macrovascular involvement should be discussed more extensively including pathogenetic mechanisms (Curr Pharm Des. 2014;20(4):536-44, Autoimmunity Reviews17(3), pp. 201-214) and biomarkers such as ADMA (Inflammation. 2015 Feb;38(1):218-23) Introduction: I think that a couple of sentences "introducing" atherosclerosis and its impact on SSc prior the discussion about PAD would improve reading and provide a better rationale for the study (Rheumatol Int. 2017 Jan;37(1):85-95, . Clin Rheumatol 2021 Mar 6. doi: 10.1007/s10067-021-05672-0). In this regard a reference to SSc patients dying due to

	atherosclerosis is essential (Ann Rheum Dis. 2017 Nov;76(11):1897-190). As long as the authors state the role of comorbidities in the development of PAD a recent review discussing this issue (Rheumatol Int. 2019 Sep;39(9):1507-1517) could be cited and discussed.

REVIEWER	Nathalie Conrad Medical Sciences Division
REVIEW RETURNED	08-Jul-2021

GENERAL COMMENTS

Association Between Systemic Sclerosis and Peripheral Arterial Disease: A Nationwide Observation Retrospective Cohort Study
Summary
The authors present an analysis of the association between SSC and incident PAD. A major strength of this study is its population-based design. Limitations include its relatively small size and inability to adjust for key cardiovascular risk factors. Analyses appear to have been performed meticulously and are well described. Findings from this study are important and are likely to have clinical implications. Authors have revised their manuscript following a first set of reviews. I have added my thoughts to the revisions in blue below.

Major Comments
Raynaud's syndrome appears to be part of SSc diagnostic criteria and PAD clinical definition (in particular ICD code 443 "Other peripheral vascular diseases" includes Raynaud's syndrome). Authors should please address this point and explain how this impacts their analyses and findings.

Reply: Thank you for your comment and we use ICD code 443 for another analysis and it also confirmed the result.

Reply from R3: I am very sorry but I do not understand the authors' response. Do they mean that they have performed sensitivity analyses excluding Raynaud's syndrome from the PAD definition and found similar results? If so, that is ok, but authors should please clearly explain their approach in methods and results (or the appendix).

Table. The overall Incidence of peripheral arterial disease (per 1,000 person-years), estimated hazard ratios and subhazard ratios in PD patients with systemic sclerosis compared to those without Systemic sclerosis

	Systemic sclerosis	
Variables	No(N=4424)	Yes(N=1106)
Person-years	24611	4052
Event, n	58	237
Rate	2.36	58.5

	Crude HR (95% CI)	1(Reference)	22.3(16.7, 29.8)
	Adjusted HR (95% CI)[a]	1(Reference)	22.8(17.1, 30.5)
	Adjusted HR† : multivariable analysis including age, gender, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, stroke, and asthma *p<0.01, **p<0.001 The authors specify how index date was defined for the SSc cohort (date of SSc diagnosis), but should also explain how they defined index date for the matched cohort (which do not have an SSc diagnosis). Authors should also please clarify how patients were matched on "age" (I assume they mean birthyear or age at index?) and "year of SSc diagnosis" (perhaps they mean index date?). Reply: Thank you for your comment. The index date for non-SSc subjects was randomly appointed a month and day with the same index year of the matched SSc cases. Yes, the age was calculated as (index date-birthyear)/365. Reply from R3: Please could the author clearly describe this in their methods section. The manuscript is generally well written but would in my view benefit from a brief English proof-reading. Reply from R3: This last point has not been addressed. Perhaps the editors can help here. NEW comment: the strengths and limitations section have been rewritten following another reviewer's comment, but the new version is very difficult to comprehend. (#2 – what is 'Eastern Country' and how do patterns differ?; #3 is, in my view, difficult to comprehend) I assume this is mainly a matter of English language and perhaps editors can help here. Minor Comments The discussion is somewhat repetitive and could, in my opinion be shortened. The last paragraph, "summary" could be made clearer with a focus on results from the present study. Reply: Thank you for your comments and we will re write it Reply from R3: I cannot see any changes to the aforementioned section.		

VERSION 2 – AUTHOR RESPONSE

Reviewer:1

The authors have adequately addressed a number of comments, however the interrelation between micro- and macrovascular involvement should be discussed more extensively including pathogenetic mechanisms (Curr Pharm Des. 2014;20(4):536-44, Autoimmunity Reviews17(3), pp. 201-214) and biomarkers such as ADMA (Inflammation. 2015 Feb;38(1):218-23)
Reply: Thank you for your suggestions and we will add on it for our articles

Introduction: I think that a couple of sentences “introducing” atherosclerosis and its impact on SSc prior the discussion about PAD would improve reading and provide a better rationale for the study (Rheumatol Int. 2017 Jan;37(1):85-95, . Clin Rheumatol 2021 Mar 6. doi: 10.1007/s10067-021-05672-0).

In this regard a reference to SSc patients dying due to atherosclerosis is essential (Ann Rheum Dis. 2017 Nov;76(11):1897-190).

Reply: Thank you for your suggestions and we will add on it for our articles

As long as the authors state the role of comorbidities in the development of PAD a recent review discussing this issue (Rheumatol Int. 2019 Sep;39(9):1507-1517) could be cited and discussed.

Reply: Thank you for your suggestions and we will add on it for our articles

Reviewer:3

Major Comments

Raynaud’s syndrome appears to be part of SSc diagnostic criteria and PAD clinical definition (in particular ICD code 443 “Other peripheral vascular diseases” includes Raynaud’s syndrome). Authors should please address this point and explain how this impacts their analyses and findings.

Reply: Thank you for your comment and we use ICD code 443 for another analysis and it also confirmed the result.

Reply from R3: I am very sorry but I do not understand the authors’ response. Do they mean that they have performed sensitivity analyses excluding Raynaud’s syndrome from the PAD definition and found similar results? If so, that is ok, but authors should please clearly explain their approach in methods and results (or the appendix).

Reply: We re-created a systemic sclerosis and comparison cohort established an PAD using ICD-9 code 443 as new outcome, which was well matched by age, sex, index year. The overall incidence of PAD was 61% higher in the systemic sclerosis cohort than the control cohort (61.0 vs. 2.66 per 1000 person-years) with an adjusted HR of 22.8 (95% CI=17.0-30.7).

Table. The overall Incidence of peripheral arterial disease (per 1,000 person-years), estimated hazard ratios in patients with systemic sclerosis compared to those without Systemic sclerosis

	Systemic sclerosis	
Variables	No(N=4396)	Yes(N=1099)
Person-years	24802	4212
Event, n	66	257
Rate	2.66	61.0
Crude HR (95% CI)	1(Reference)	20.7(15.8, 27.1)***
Adjusted HR (95% CI)[a]	1(Reference)	22.8(17.0, 30.7)***

Adjusted HR† : multivariable analysis including age, gender, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, stroke, and asthma

*p<0.01, **p<0.001

The authors specify how index date was defined for the SSc cohort (date of SSc diagnosis), but should also explain how they defined index date for the matched cohort (which do not have an SSc diagnosis). Authors should also please clarify how patients were matched on “age” (I assume they mean birthyear or age at index?) and “year of SSc diagnosis” (perhaps they mean index date?).

Reply: Thank you for your comment. The index date for non-SSc subjects was randomly appointed a month and day with the same index year of the matched SSc cases. Yes, the age was calculated as (index date-birthyear)/365.

Reply from R3: Please could the author clearly describe this in their methods section.

The manuscript is generally well written but would in my view benefit from a brief English proofreading.

Reply from R3: This last point has not been addressed. Perhaps the editors can help here.

NEW comment: the strengths and limitations section have been rewritten following another reviewer’s comment, but the new version is very difficult to comprehend. (#2 – what is ‘Eastern Country’ and how do patterns differ?; #3 is, in my view, difficult to comprehend) I assume this is mainly a matter of English language and perhaps editors can help here.

Reply: We changed it to other Asia country.

Minor Comments

The discussion is somewhat repetitive and could, in my opinion be shortened. The last paragraph, "summary" could be made clearer with a focus on results from the present study.

Reply: Thank you for your comments and we will re write it.

Reply from R3: I cannot see any changes to the aforementioned section.

Reply: Thank you for your comment and we modified the summary again.

VERSION 3 – REVIEW

REVIEWER	Nathalie Conrad Medical Sciences Division
REVIEW RETURNED	30-Aug-2021

GENERAL COMMENTS	Authors have addressed most of reviewers' comments, yet one major aspect remains unclear. Raynaud's syndrome is part of both SSc and PAD clinical definitions (in particular ICD code 443 "Other peripheral vascular diseases" includes Raynaud's syndrome). This creates an obvious overlap between the clinical definitions of the two diseases and might explain part of the observed association (since anyone with Raynaud's syndrome will be diagnosed with SSc and PAD). Could authors please perform sensitivity analyses excluding Raynaud's syndrome from the PAD definition and explain how this impacted their results?

VERSION 3 – AUTHOR RESPONSE

Reviewer: 3

Comments to the Author:

Authors have addressed most of reviewers' comments, yet one major aspect remains unclear. Raynaud's syndrome is part of both SSc and PAD clinical definitions (in particular ICD code 443 "Other peripheral vascular diseases" includes Raynaud's syndrome). This creates an obvious overlap between the clinical definitions of the two diseases and might explain part of the observed association (since anyone with Raynaud's syndrome will be diagnosed with SSc and PAD).
Could authors please perform sensitivity analyses excluding Raynaud's syndrome from the PAD definition and explain how this impacted their results?

Reply: Thank you for your comments. According to our study, we already excluded 443.0(Raynaud's syndrome) to do the research between PAD and SSc at first. In our opinion Raynaud's syndrome is just a condition where arterial spasm, usually in the fingers, causes episodes of reduced blood flow or secondary to medication use. Raynaud's syndrome is not like the condition of general PAD in our daily medical practices , so we exclude the diagnosis at first in our study.