Systemic sclerosis: can we identify patients at risk?

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Part IV

Appendices

Appendix

Summary, conclusions and future perspectives

SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

The studies described in this thesis contribute to the identification of biomarkers for risk stratification in systemic sclerosis (SSc). Luckily, nowadays many SSc prospective cohorts have been set up worldwide which allows high-quality research. Given the rarity and the heterogeneity of the disease, relatively large cohorts are needed to draw valuable conclusions. For the studies described in the current thesis, I was able to incorporate data from the Leiden prospective SSc cohort and data from other prospective cohorts in Europe, which made it possible to strengthen the data. In this final chapter, I summarize the main findings of the studies presented in this thesis, put our findings in a broader perspective, discuss future perspectives and formulate research questions that are relevant to assess in the years ahead of us.

PART I: IMPACT OF SYSTEMIC SCLEROSIS

Diagnosis of Systemic Sclerosis

SSc can be difficult to diagnose due to its rarity and heterogeneity. In most patients, receiving the diagnosis of SSc takes years as it is often not immediately recognized at time of first symptoms (1, 2). The new ACR/EULAR 2013 criteria and the very early diagnosis of SSc (VEDOSS) classification criteria help us with early diagnosis (3-5). Earlier diagnosis in SSc is necessary to manage and treat patients at a point in their disease where damage of skin and internal organs is still reversible. On the other hand, physicians should be aware that even in patients with early disease, without any organ complications, receiving a diagnosis of SSc can have a major impact on daily life (**chapter 1**)(6).

Patient perception of disease burden

Since early diagnosis lengthens the time window of patients in which the prognosis is unclear, it is necessary to know how this affects the patients (7, 8). A focus group study (**chapter 1)** among 7 patients with a recent diagnoses of SSc showed that patients indeed worry, mainly about the chronic nature, the unpredictable disease course and the negative consequences of the disease (9-13). It is known that these illness perceptions have an impact on physical health, mental health and illness behavior in SSc (14) (15). As illness perceptions influence illness behavior, it is important for physicians to be aware of the decoupling of patients perceptions of disease and objectified disease activity (**chapter 1**). Moreover, these perceptions are associated with the disease course, since a patient's own personal beliefs and emotional responses to symptoms affect disease management. We did not only analyze illness perceptions during the focus group but we also asked patients to make a drawing of their disease. In contrast to the illness perceptions evaluated during the focus group and the questionnaires, which were predefined, drawings can provide an unbiased image of patients' perceptions. The most common features displayed in the drawings were; experienced symptoms, emotional functioning and social functioning. The images drawn by the patients gave us some insights in patients thoughts and concerns and highlighted the importance of psychosocial support. Finally, we learned from this study that patients experienced negative thoughts caused by internet based information and little understanding of the disease in their personal environment. This indicates the importance of patient education after receiving a diagnosis. Patient-centered care that encompasses strategies to promote self-esteem, self-efficacy, and open communication may help to decrease the SSc disease burden.

SSc-related quality of life

Improving patients' quality of life should be one of the main goals for every physician. Health related Quality of Life (HRQoL) includes both physical and mental health, and several validated questionnaires have been developed to assess HRQoL (16-19). HRQoL in SSc patients can vary greatly, independent of disease severity. Even in SSc patients without organ manifestations HRQoL is lower when compared to patients with other chronic diseases (20-22).

Clinical manifestations associated with SSc-related quality of life

Due to the chronic nature of SSc and it's heterogeneity, it is important to know which disease manifestations have the largest impact on HRQoL. A thorough understanding of HRQoL determinants may help treating physicians to identify the unmet needs of SSc patients and the areas where more effective pharmacological or non-pharmacological interventions are indicated. We confirm, in **chapter 2,** that gastrointestinal (GIT) symptom burden, Raynaud phenomenon (RP) symptoms, and digital ulcers are associated with lower HRQoL (13, 23-25). In addition, in SSc, patients with organ involvement experience a lower HRQoL compared to patients without organ involvement. During the disease course and during follow-up, an increase of GIT symptoms and/or RP symptoms were found to be predictive for a decrease in HRQoL in all SSc patients. Skin involvement changes specifically impact HRQoL in patients with early disease (since first non-RP symptom < 24 months), whereas pulmonary arterial hypertension (PAH) had a significant impact on HRQoL in patients with long standing disease. Functional impairments, as shown by a decrease in six-minute-walking distance (6MWT) and hand function, were also associated with impaired HRQoL over time, meaning that loss of function significantly impacts HRQoL. Remarkably, quality of life in SSc patients is significantly affected by troublesome and difficult to control symptoms including RP and GIT, even more than by life threatening complications such as ILD and cardiac involvement. In contrast, treating physicians often focus on life-threatening manifestations. Our results suggest that despite the non-life threatening nature these burdensome disease manifestations deserve attention as these are highly important for the patient. In my opinion, HRQoL assessment measures should play a prominent role also in clinical trials investigating the efficacy of novel therapies for SSc. Future studies should focus on how to address functional impairment, RP and GIT. By improving treatment and care for these symptoms, HRQoL can significantly improve and, consequently, this can have a positive influence on illness and risk perceptions which will also improve disease management and will have a positive effect on the disease course.

PART II: DISEASE PROGRESSION IN SYSTEMIC SCLEROSIS

Disease progression

Clear guidance regarding follow-up is very important for clinicians, not only to identify progression in time but also to limit overdiagnosis and overtreatment in mild patients. Pulmonary, cardiac, gastro-intestinal (GIT), renal, musculoskeletal, functional, and vascular symptoms are annually investigated in our multidisciplinary SSc care pathway, however no evidence based guidelines on the extent and frequency of follow-up exists. Currently, only an expert consensus based guideline exists which describes 55 tools/ measurements to assess on an annual basis in every SSc patient (26). Whether these items are sufficient to identify progression timely is yet to be determined. Approximately 50% of the SSc patients never show any signs of progression and annual follow-up might be redundant in this group of patients (**chapter 3**). On the other hand, also approximately 50% of the patients experiences relevant progression somewhere during their disease course. The most common cause of progression was cardiopulmonary deterioration, which is also the number one cause of death in SSc (27). Although research and guidelines often mention disease progression is most likely to occur in early disease, our data showed that in 24% of the patients progression occurred after a disease duration of > 10 years since first non-RP symptom. We observed that skin progression occurred more frequently in early disease. The proportion of patients with lung, heart or GIT progression was relatively stable over time. Anti-topoisomerase antibody (ATA) positive patients showed progression most often in early disease, while in anti-centromere antibody (ACA) positive patients the proportion of patients with progression seemed to increase over time. This study indicates the importance of follow-up, as half of the patients experience disease progression. The fact that progression can occur both early and late demonstrates why it is difficult to design guidelines on the extent and frequency of follow-up. The fact that half of the patients never show any signs of progression indicates at the same time the importance to identify biomarkers to predict progression in order to enable tailormade follow-up of the individual SSc patient.

Gastrointestinal symptoms and progression; underestimated in SSc

GIT symptoms hamper SSc patients' HRQoL and, after skin involvement, are the most common complications in SSc (28). Approved treatment options for GIT involvement in SSc are very limited, but this may, at least partially, relate to little knowledge and focus. Little is known on GIT progression, and the potential effects on GIT symptom burden by the standard of care treatments in SSc (immune modulating and/or vaso-dilating treatment). Therefore, in **chapter 4**, we performed a multicenter study (Oslo and Leiden) with longitudinal data on patient-reported GIT symptoms and standard of

care treatment. We identified that GIT symptoms are very common in SSc, and a high symptomatic burden from early in the disease course predicted progressive behavior of the GIT symptoms over time. Many patients reported severe reflux and distension/bloating symptoms already at time of SSc diagnosis. All GIT symptoms progressed during the observation period, with highest progression rates for reflux and distension/bloating. Female sex and presence of ACA were significantly associated with total GIT symptom burden and with GIT progression, no other predictors could be identified. With the exception of corticosteroids, standard of care therapies for SSc seem to have little impact on GIT symptoms. This study shows that clinicians should be aware of the high GIT symptom burden at time of SSc diagnosis and should identify patients at risk for progressive GIT disease early to tailor disease management. In addition, more knowledge on the correlation between GIT patient-reported-outcome measurements and objective measurements is necessary. In a very recent study performed by Zampatti et al.(29) the correlation between the UCLA GIT 2.0 score (reflux domain) and esophago-gastro-duodenoscopy (EGD) were investigated, and the reflux subscale was able to discriminate patients with SSc who had an indication for EGD, but this did not correlate with the findings in the EGD. Therefore, this study concluded that the UCLA GIT 2.0 is helpful but should not be used as a stand-alone instrument to identify an indication of EGD (29). We showed that all gastro-intestinal domains can be affected and therefore evaluation of all the different gastro-intestinal domains should be taken into account and should be included in the guideline for follow-up in SSc patients. However, the definition for GIT involvement in SSc patients remains very difficult. Kaniecki et al.(30) published an extended review on the practical approach to the evaluation and management of GIT symptoms in SSc which is of major clinical relevance for physicians following SSc patients (30). Knowledge about severity and the natural behavior of GIT symptoms is a prerequisite to identify patients for inclusion in clinical trials targeting GIT involvement, and to assess treatment effects. This is particularly important in times of evolving new therapeutic options, such as fecal microbiota transplantation. This study helped us to gain knowledge on the severity and evolution of GIT involvement in SSc. A next step would be to identify biomarkers for GIT disease activity or GIT disease progression.

Prediction model

Over 50% of patients with SSc showed disease progression over time, disease progression was very diverse and occurred in a heterogeneous group. To identify which patients were at risk for overall disease progression we developed, with the use of machine learning, a prediction model including 90 variables (100% complete, **chapter 5**). With this model we were able to stratify patients for low, intermediate or high risk of disease progression. Twenty-nine percent of the patients had a low risk of disease progression (negative predictive value [NPV] 1.0), and annual follow-up could be less extensive in these patients.

The Machine-Learning-Assisted prediction model could therefore significantly reduce health-care costs without substantial risk to our patients, and we might be able to reduce the amount of worry in some of the patients. In addition, we compared the Machine-Learning-Assisted driven model with the expert opinion model (26). Where the Machine-Learning-Assisted driven model included 10 variables in the final model, the expert model included 51 variables. Interestingly, the ROC of both models was comparable (ROC of 0.68), however, cutoffs for low, intermediate and high risk of progression were only identifiable in the Machine-Learning-Assisted driven model. This model allows us to confidently identify a subset of patients who can safely reduce their visit frequency. Preferably, in the future we will be able to predict the risk for progression on each specific organ system in every individual patient. We were not able to accomplish this in our cohort due to the sample size and the heterogeneity of the disease. To evaluate organ systems separately in both a test and training set we need a large amount of patients followed over a long period. Besides, predictors for organ progression on one certain domain might be protective for progression on another domain, which means a large amount of predictors are needed in the model. To be able to develop a model with this goal we need to collect data from a few international SSc cohorts (preferable also outside of Europe) and identify models for each organ system and externally validate these models. To be able to accomplish this it is important to identify the most important predictors and evaluate if these predictors are internationally collected in the same manner. If we will be able to develop a model that predicts accurately enough to identify the low and high risk patients we can develop an online tool where physicians can calculate the risk score of every individual patient, and this will help us to provide tailormade follow-up and treatment for every individual patient.

PART III: MICROANGIOPATHY AND SSC SPECIFIC AUTOANTIBODIES

Biomarkers in systemic sclerosis

A better understanding of SSc is the best way to identify important biomarkers, and these biomarkers are the key to improve prediction of the disease course. Currently, the classification criteria for SSc consists out of clinical characteristics, laboratory findings and microvascular abnormalities. Ideal biomarkers are indicators of SSc that can be measured accurately, easily, cheap, and preferably with non-invasive techniques. They are not only helpful for early diagnosis and understanding distinct pathophysiological processes of the disease but are also useful for patient care in terms of prediction of prognosis, and treatment decision-making (31). SSc specific autoantibodies and nailfold capillaroscopy (NC) patterns are used as biomarkers based on significant and sometimes exclusive associations with the disease itself or certain clinical phenotypes of the disease and in this thesis we evaluated these two biomarkers more extensively.

Degree of microangiopathy

Vasculopathy plays an important role in the pathophysiology of SSc (32). The factors that trigger vascular injury in SSc have not been elucidated so far. Antinuclear auto-antibodies (ANAs) have been mentioned as one of the possible triggers for vascular injury (33, 34). In addition, hormonal factors also have been suggested as trigger for microangiopathic manifestations (35). To gain more evidence on this subject we performed a systematic review in **chapter 6** to evaluate whether sex or expression of specific ANA might associate with the degree of microangiopathy in SSc patients. Eleven studies were included that report on the relationship between SSc specific auto-antibodies and microangiopathy, and six studies were included that report on the association between sex and microangiopathy in SSc. The number of included articles already indicates that limited evidence was available for our review. Contradictory results were found on the association between auto-antibodies and microangiopathy, with a trend towards more severe degree of microangiopathy in ATA positive patients. No association was found between sex and microangiopathy based on the current literature. Due to limited evidence on the association between autoantibodies and degree of microangiopathy we decided to evaluate this in our own cohort. In **chapter 8** we demonstrated an association between ACA and ATA specific immune response and degree of microangiopathy (36). We confirmed the association between more severe microangiopathy and organ involvement in SSc patients. Secondly, we showed that ATA positive SSc patients more often have severe microangiopathy compared to ACA positive patients. Finally, and completely novel, was the significant association between ACA-IgG and ATA-IgM levels with a more severe degree of microangiopathy. As ATA positive and ACA positive patients

display clearly different clinical phenotypes, one might hypothesize that behavior of ATA and ACA specific isotypes differs which might impact on their roles in pathophysiology. The continuous presence of IgM indicates a constant trigger of the immune system which might be more obvious in ATA positive patients compared to ACA positive patients. Currently, one of the ideas is that autoimmunity occurs early in the disease course and the auto-immune response is targeting other cell types (endothelial cells). ATA and ACA probably target different cells / pathways which might explain the clinical differences between the two groups. The observation between higher ACA-IgG and ATA-IgM levels and a more severe degree of microangiopathy might indicate that dysregulated B cell responses and microvascular damage interact with each other in the pathophysiology of SSc. To confirm these observations and to identify the possible mechanism behind this association further research is needed. For example, in clinical setting the effect of immunosuppressive therapy affecting B cells on microvascular damage can be evaluated, and a next step would be to isolate the (autoreactive) B cells from SSc patients to be able to evaluate their effect on an in vitro endothelial cell model.

Anti-U3RNP SSc specific autoantibody

Anti-fibrillarin (anti-U3RNP) is a SSc specific autoantibody, which has been described in small subgroups. Previous studies suggested an association with cardiovascular complications, however due to its rarity clear clinical associations remains to be confirmed (37, 38)**.** We evaluated if NC could be of contributive value to identify the anti-U3RNP positive patients with cardiopulmonary involvement (**chapter 7**). We did not observe a higher prevalence of cardiopulmonary involvement in anti-U3RNP positive patients compared to ATA or ACA positive patients, but we did confirm the association between degree of microangiopathy and cardiopulmonary involvement for all the antibody subgroups, which is in line with our results in **chapter 8**. As such, NC can also serve as biomarker in anti-U3RNP positive SSc patients for risk of cardiopulmonary involvement.

SSc specific autoantibodies

ACA generally carries a better prognosis than most other SSc autoantibodies, still 35% of the ACA positive SSc patients develop organ involvement. This already demonstrates that even within one autoantibody group the disease course is very heterogeneous. Therefore, in **chapter 9** we analyzed the ACA isotype levels in ACA-IgG positive SSc patients in relation to clinical disease progression using data from five large and well defined SSc cohorts from European centers of expertise in SSc. We described the ACA isotype levels in patients with very early SSc and in patients with definite SSc, including the association with disease severity and disease progression. Using autoantibodies for risk stratification is not new (33, 39-42), however, evaluating the specific isotypes has never been performed extensively in SSc. Our study showed that in ACA positive SSc patients,

higher ACA-IgG and ACA-IgM levels associated with more severe disease. Moreover, higher ACA-IgG levels associated with disease progression over time in both established SSc and very early, pre-clinical SSc. The continuous presence of ACA-IgM suggests that there is ongoing immune activation triggering continuous production of IgM which is most likely caused by recently activated B cells. Also more mechanistic explanations could be considered. For example, IgM and IgG have the ability to induce inflammation by activating complement, where IgA is a weak complement activator, and therefore might not be involved at the same level. As there is no evidence regarding the nature of ACA-IgA in SSc pathogenesis it is intriguing to hypothesize about its origin and implication. IgA is mostly found in mucous membranes, particularly the respiratory tract and the gastrointestinal tract; as such expression of disease specific ACA-IgA might implicate involvement of these mucous membranes in SSc pathogenesis. The frequent pulmonary and gastro-intestinal involvement in SSc patients supports this hypothesis. We conclude that the ACA isotypes can be seen as biomarker for the underlying immune response, and the presence and levels of the different isotypes can be used as a marker for 'the breadth of the immune response'. In very early SSc disease [pre-disease], two features are present in > 90% of the patients; microangiopathy as clinically shown by RP symptoms, and dysregulated immunity reflected by presence of SSc specific autoantibodies. It is possible that these SSc specific autoantibodies contribute to microangiopathy by endothelial cell damage (34). Taking this in mind it is tempting to speculate that either ACA-IgG, and/or the B-cell responses underlying ACA production are involved in the disease pathogenesis. Based on these data, ACA isotype levels might be considered as a biomarker to predict which SSc patients are at risk for disease progression, and to predict which patients with very early SSc are at risk for future SSc. We believe that the results are therefore highly relevant for clinicians in rheumatology as these findings contribute to risk stratification in SSc using a simple biomarker. Additionally, our findings encourage further evaluation of the contribution of ACA antibodies to the pathogenesis of SSc.

SUMMARY

Can we identify patients at risk for decreased health-related quality of life?
By improving patients' physical functioning, RP symptoms and GIT burden we will be able to influence HRQoL. In order to achieve this, assessment of these symptoms on a regular basis must be performed and pharmacological and non-pharmacological treatment options should be followed according to the EULAR guidelines (43). In addition, further research is needed to increase the treatment options for especially GIT involvement. In SSc, illness perceptions have an important influence on quality of life, independent of disease severity. As physicians we have the possibility to address these perceptions with clear guidance, monitoring and information.

Can we predict SSc disease course?
Unfortunately, prediction of the disease course remains difficult, but we were able to develop a prediction model by means of which patients with a low risk of progression, can be identified in whom annual follow-up can be less extensive. Applying this model to provide tailor made care can influence illness perception, illness behavior and quality of life in SSc importantly. In the future, we need to develop models that can also identify patients with a high risk on specific organ involvement in whom we should interfere timely with the disease course before irreversible damage is done.

Can we identify biomarkers for patients at high risk?
In this thesis we confirmed that the degree of microangiopathy is associated with more severe disease, a next step would be to investigate the predictive role more extensively in a large subset of patients followed over time. We found ACA isotypes and isotype levels to be associated with the disease course which indicates that ACA isotype levels can be used as biomarkers to predict disease progression. Confirmation in larger cohorts with very early SSc patients and established SSc patients is necessary to confirm our observation and to confirm the relevant cut-offs. To be able to investigate this, early recognition of SSc is very important. New biomarkers are identified on a yearly basis and more and more research is and will be performed in the coming years.

FUTURE PERSPECTIVES

Health care

The multidisciplinary approach in SSc patients remains very important and to improve health care outcomes benefiting both patients and health professionals it is necessary to break down barriers and bridge professional boundaries. Ideally a multidisciplinary team involving a rheumatologist, a pulmonologist, a cardiologist, a gastroenterologist and a specialized nurse should determine the best care for every individual SSc patient. To be able to impact as much as possible on HRQoL we also need more information on a patients' illness perceptions, this allows us to individualize our health care system in combination with a patients' need. Illness perceptions should always be taken into account, as all patients are behaving and responding differently on receiving a diagnosis. In my opinion, in the future, SSc care pathways need to be based on the individual risks of a patients stratified for different organ systems; some patients need screening of the pulmonary system where others are more prone for vascular abnormalities. To change or improve the care of patients we need to expand our knowledge on SSc disease course and in order to do that we need to gain more insight on the pathophysiology of SSc. This is one of the examples of how research has a direct influence on health care (see figure). In the end, this will improve the quality of care and will reduce the health care costs.

Research

Despite many advances made in elucidating the pathogenesis of SSc, the exact mechanism remains unsolved. Based on the above background, it is important both clinically and pathologically to elucidate the relationship between microvasculopathy and the immunological heterogeneity of SSc. I would argue for more longitudinal research on the associations between the clinical characteristics and the laboratory findings as these associations might be able to help us with risk stratification in this heterogeneous disease. The most ambitious goal still remains to identify the key elements, in particular in the earlier phases, for targeted intervention and to disease progression and prevent organ complications. Besides targeted therapies, in the future, individualized treatment options may also be dependent of a patients' biomarker profile. This will not only influence daily care, but will also improve the selection of patients for clinical trials. That is how research and healthcare are continuously influencing each other (figure).

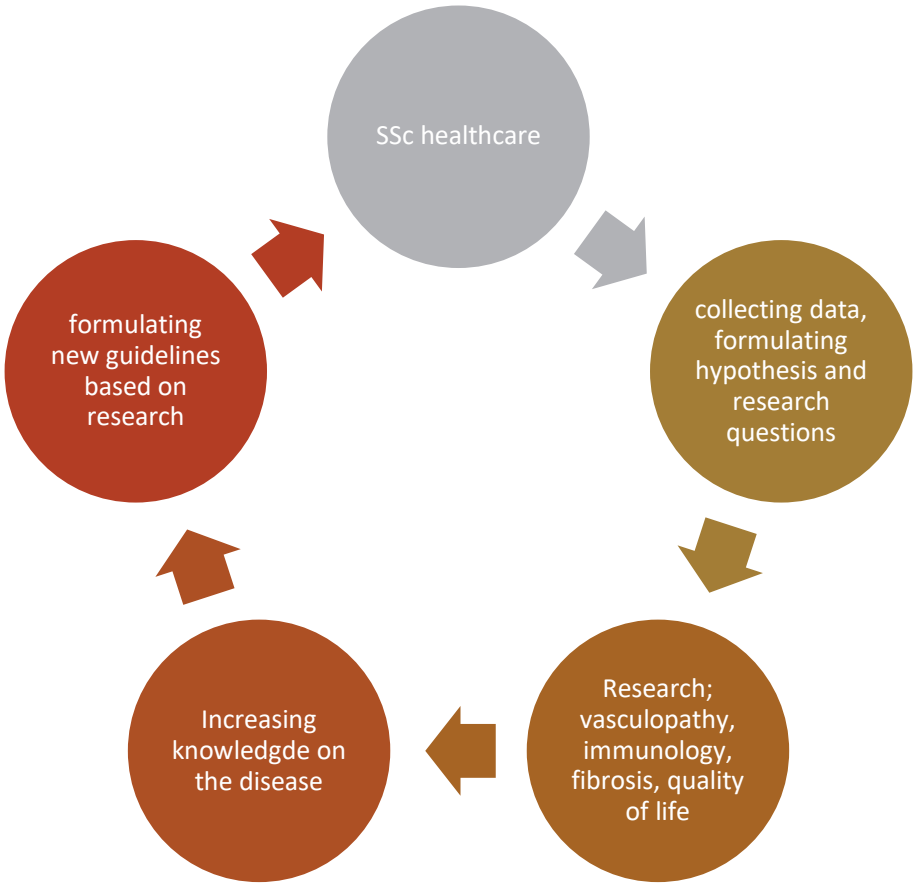

Figure 1. Research and healthcare

REFERENCES

1. Hudson M, Thombs B, Baron M. Time to diagnosis in systemic sclerosis: is sex a factor? Arthritis and rheumatism. 2009;61(2):274-8.
2. Distler O, Allanore Y, Denton CP, Matucci-Cerinic M, Pope JE, Hinzmann B, et al. Factors influencing early referral, early diagnosis and management in patients with diffuse cutaneous systemic sclerosis. Rheumatology. 2018;57(5):813-7.
3. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis and rheumatism. 2013;65(11):2737-47.
4. Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis. 2011;70(3):476-81.
5. Vasile M, Avouac J, Sciarra I, Stefanantoni K, Iannace N, Cravotto E, et al. From VEDOSS to established systemic sclerosis diagnosis according to ACR/EULAR 2013 classification criteria: a French-Italian capillaroscopic survey. Clin Exp Rheumatol. 2018;36 Suppl 113(4):82-7.
6. Minier T, Guiducci S, Bellando-Randone S, Bruni C, Lepri G, Czirjak L, et al. Preliminary analysis of the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Annals of the Rheumatic Diseases. 2014;73(12):2087-93.
7. Amin K, Clarke A, Sivakumar B, Puri A, Fox Z, Brough V, et al. The psychological impact of facial changes in scleroderma. Psychology, health & medicine. 2011;16(3):304-12.
8. Merz EL, Malcarne VL, Roesch SC, Nair DK, Salazar G, Assassi S, et al. Longitudinal patterns of pain in patients with diffuse and limited systemic sclerosis: integrating medical, psychological, and social characteristics. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2017;26(1):85-94.
9. Nakayama A, Tunnicliffe DJ, Thakkar V, Singh-Grewal D, O'Neill S, Craig JC, et al. Patients' Perspectives and Experiences Living with Systemic Sclerosis: A Systematic Review and Thematic Synthesis of Qualitative Studies. J Rheumatol. 2016;43(7):1363-75.
10. Sumpton D, Thakkar V, O'Neill S, Singh-Grewal D, Craig JC, Tong A. "It's Not Me, It's Not Really Me." Insights From Patients on Living With Systemic Sclerosis: An Interview Study. Arthritis Care Res (Hoboken). 2017;69(11):1733-42.
11. Sumpton D, Thakkar V, O'Neill S, Singh-Grewal D, Craig JC, Tong A. "It's not me, it's not really me." Insights from patients on living with systemic sclerosis: An interview study. Arthritis Care Res (Hoboken). 2017.
12. Nakayama A, Tunnicliffe DJ, Thakkar V, Singh-Grewal D, O'Neill S, Craig JC, et al. Patients' perspectives and experiences living with systemic sclerosis: a systematic review and thematic synthesis of qualitative studies. The Journal of rheumatology. 2016;jrheum. 151309.
13. Frantz C, Avouac J, Distler O, Amrouche F, Godard D, Kennedy AT, et al. Impaired quality of life in systemic sclerosis and patient perception of the disease: A large international survey. Seminars in arthritis and rheumatism. 2016;46(1):115-23.
14. Arat S, Verschueren P, De Langhe E, Smith V, Vanthuyne M, Diya L, et al. The association of illness perceptions with physical and mental health in systemic sclerosis patients: an exploratory study. Musculoskeletal care. 2012;10(1):18-28.

15. Richards HL, Herrick AL, Griffin K, Gwilliam PD, Loukes J, Fortune DG. Systemic sclerosis: patients' perceptions of their condition. Arthritis and rheumatism. 2003;49(5):689-96.
16. Cossutta R, Zeni S, Soldi A, Colombelli P, Belotti Masserini A, Fantini F. [Evaluation of quality of life in patients with systemic sclerosis by administering the SF-36 questionnaire]. Reumatismo. 2002;54(2):122-7.
17. Khanna D, Furst DE, Clements PJ, Park GS, Hays RD, Yoon J, et al. Responsiveness of the SF-36 and the Health Assessment Questionnaire Disability Index in a systemic sclerosis clinical trial. The Journal of Rheumatology. 2005;32(5):832.
18. Steen VD, Medsger TA, Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis and rheumatism. 1997;40(11):1984-91.
19. Gualtierotti R, Ingegnoli F, Scalone L, Cortesi P, Bruschi E, Gerosa M, et al. Feasibility, acceptability and construct validity of EQ-5D in systemic sclerosis. Swiss medical weekly. 2016;146:w14394.
20. Hudson M, Thombs BD, Steele R, Panopalis P, Newton E, Baron M. Quality of life in patients with systemic sclerosis compared to the general population and patients with other chronic conditions. J Rheumatol. 2009;36(4):768-72.
21. Park EH, Strand V, Oh YJ, Song YW, Lee EB. Health-related quality of life in systemic sclerosis compared with other rheumatic diseases: a cross-sectional study. Arthritis research & therapy. 2019;21(1):61-.
22. Bullinger M, Quitmann J. Quality of life as patient-reported outcomes: principles of assessment. Dialogues in clinical neuroscience. 2014;16(2):137-45.
23. Georges C, Chassany O, Toledano C, Mouthon L, Tiev K, Meyer O, et al. Impact of pain in health related quality of life of patients with systemic sclerosis. Rheumatology (Oxford, England). 2006;45(10):1298-302.
24. Baron M, Sutton E, Hudson M, Thombs B, Markland J, Pope J, et al. The relationship of dyspnoea to function and quality of life in systemic sclerosis. Ann Rheum Dis. 2008;67(5):644-50.
25. Matucci-Cerinic M, Krieg T, Guillevin L, Schwierin B, Rosenberg D, Cornelisse P, et al. Elucidating the burden of recurrent and chronic digital ulcers in systemic sclerosis: long-term results from the DUO Registry. Ann Rheum Dis. 2016;75(10):1770-6.
26. Hoffmann-Vold AM, Distler O, Murray B, Kowal-Bielecka O, Khanna D, Allanore Y. Setting the international standard for longitudinal follow-up of patients with systemic sclerosis: a Delphi-based expert consensus on core clinical features. RMD open. 2019;5(1):e000826.
27. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis. 2017;76(11):1897-905.
28. Emmanuel A. Current management of the gastrointestinal complications of systemic sclerosis. Nature reviews Gastroenterology & hepatology. 2016;13(8):461-72.
29. Zampatti N, Garaiman A, Jordan S, Dobrota R, Becker MO, Maurer B, et al. Performance of the UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 instrument as a clinical decision aid in the routine clinical care of patients with systemic sclerosis. Arthritis Res Ther. 2021;23(1):125.
30. Kaniecki T, Abdi T, McMahan ZH. A practical approach to the evaluation and management of gastrointestinal symptoms in patients with systemic sclerosis. Best practice & research Clinical rheumatology. 2021:101666.
31. Hummers LK. The current state of biomarkers in systemic sclerosis. Curr Rheumatol Rep. 2010;12(1):34-9.

32. Mostmans Y, Cutolo M, Giddelo C, Decuman S, Melsens K, Declercq H, et al. The role of endothelial cells in the vasculopathy of systemic sclerosis: A systematic review. Autoimmun Rev. 2017;16(8):774-86.
33. Steen VD. Autoantibodies in systemic sclerosis. Seminars in arthritis and rheumatism. 2005;35(1):35-42.
34. Shen CY, Li KJ, Lai PH, Yu CL, Hsieh SC. Anti-CENP-B and anti-TOPO-1-containing sera from systemic sclerosis-related diseases with Raynaud's phenomenon induce vascular endothelial cell senescence not via classical p53-p21 pathway. Clin Rheumatol. 2018;37(3):749-56.
35. Fraenkel L, Zhang Y, Chaisson CE, Evans SR, Wilson PW, Felson DT. The association of estrogen replacement therapy and the Raynaud phenomenon in postmenopausal women. Annals of internal medicine. 1998;129(3):208-11.
36. van Leeuwen NM, Wortel, C.M., Fehres, C.M., Bakker, J.A., Schere, H.U., Toes, R.E.M., Huizinga, T.W.J., de Vries-Bouwstra, J.K. Association between centromere and topoisomerase specific immune responses and the degree of microangiopathy in Systemic Sclerosis. Journal of Rheumatology. 2020.
37. Tormey VJ, Bunn CC, Denton CP, Black CM. Anti-fibrillarin antibodies in systemic sclerosis. Rheumatology. 2001;40(10):1157-62.
38. Mejia Otero C, Assassi S, Hudson M, Mayes MD, Estrada YMR, Pedroza C, et al. Antifibrillarin Antibodies Are Associated with Native North American Ethnicity and Poorer Survival in Systemic Sclerosis. J Rheumatol. 2017;44(6):799-805.
39. Boonstra M, Mertens BJA, Bakker JA, Ninaber MK, Ajmone Marsan N, van der Helm-van Mil AHM, et al. To what extent do autoantibodies help to identify high-risk patients in systemic sclerosis? Clin Exp Rheumatol. 2018;36 Suppl 113(4):109-17.
40. Choi MY, Fritzler MJ. Progress in understanding the diagnostic and pathogenic role of autoantibodies associated with systemic sclerosis. Current opinion in rheumatology. 2016;28(6):586-94.
41. Koenig M, Joyal F, Fritzler MJ, Roussin A, Abrahamowicz M, Boire G, et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis and rheumatism. 2008;58(12):3902-12.
42. Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66(6):754-63.
43. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327-39.