Hand ultrasound for the diagnosis of scleroderma: a scoring strategy including US items and items from the EULAR/ACR classification

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ABSTRACT

Objective. *To evaluate the diagnostic value of hand ultrasound (US) in systemic sclerosis (SSc) and to explore its relevance within a combined diagnostic approach.*

Methods. *224 patients with suspected SSc were consecutively included. They all had US evaluation assessing the presence of fibrotic tenosynovitis (fibrotic TS) and ulnar artery occlusion (UAO). The final diagnosis of SSc was based on the clinical evaluation of a board of experts independently of any pre-established classification criteria.*

Results. *166 patients were finally diagnosed as SSc according to the experts as reference standard. 62 SSc and 8 non-SSc patients had UAO (uni or bilateral) (p=0.001). 23 SSc patients and 1 non-SSc patient had US fibrotic TS (p=0.007). A US SSc-pattern (presence of UAO and/or fibrotic TS) was reported in 73 SSc patients and 9 non-SSc patients (p<0.001). UAO had an area under ROC curve (AUC) for the diagnosis of SSc of 0.618 (95%CI 0.539–0.697); with Se=0.373 (0.304–0.449) and Sp=0.862 (0.751–0.928). Fibrotic TS had an AUC of 0.561 (0.480–0.643); with Se=0.139 (0.094–0.199) and Sp=0.983 (0.909–0.997). The US-SSc pattern had a AUC of 0.641 (0.563–0.695), with Se=0.440 (0.367–0.516) and Sp=0.845 (0.731–0.916). A scoring system including these US parameters and items from ACR/EULAR classification criteria had an AUC of 0.979 (0.962–0.996)) and allows the substitution of capillaroscopy by US parameters with similar performances.*

Conclusion. *The use of hand US parameters may help to refine the diagnostic strategy of SSc and their inclusion in a combined diagnostic approach could be discussed.*

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disorder characterised by vascular hyper-reactivity and fibrosis of skin and internal organs (1). There is a high clinical heterogeneity among SSc patients and various phenotypes are described, based on visceral involvement or skin fibrosis extent, with different prognosis (2). The classification criteria defined by EULAR and ACR in 2013 attempt to cover this heterogeneity of the disease and include both clinical parameters and radiological/paraclinical findings (interstitial lung disease (ILD) and/or pulmonary arterial hypertension (PAH), capillaroscopic features, antibody status) (3). Taken separately the items of this classification have disappointing diagnostic performances. To date, neither ACR nor EULAR recommend the use of these classification criteria as diagnostic criteria, considering that classification criteria are designed for the selection of a homogeneous population of patients for clinical trials whereas diagnostic criteria try to capture the highest number of patients with the suspected disease, reflecting the entire spectrum of the condition (4). Nonetheless, considering that there are no consensual international diagnostic criteria for SSc in daily practice, the combination of clinical parameters and radiological/paraclinical items within the ACR/EULAR classification shows good diagnostic performances and some authors suggest that this classification could serve as a guide to help clinician for the diagnosis (3,5), although the final diagnosis would still rely on clinicians' expertise, since these classification criteria were not initially designed for diagnostic purposes.

The hand is almost always affected by the disease and five items included in this 2013 ACR/EULAR classification criteria are related to hand. Recent studies have highlighted that ultrasound (US) examination could offer a better assessment of hand manifestations of the disease (6-17). Indeed, US allows a simultaneous evaluation of vascular, fibrotic and inflammatory hand features of the disease, capturing all pathologic aspects of the disease in a single examination. Doppler US can indeed explore macrovascular involvement characterised by an obliteration of digital arteries or ulnar arteries (9, 10, 13). Ulnar artery occlusion (UAO) is especially frequent in SSc patients and could be a relevant marker of the severity of SSc-associated vasculopathy (7, 9, 10). Among other hand manifestations of the disease, US evaluation can also explore tenosynovial involvement such as inflammatory and fibrotic tenosynovitis (11). Although inflammatory synovitis or tenosynovitis are not specific to SSc, fibrotic tenosynovitis (TS), characterised by a US concentric alternation, of iso- and/or hyperechoic layers and reflecting a fibrosis of paratendinous tissues, are considered to be SSc-specific. There is growing interest in the use of US in rheumatology and exploring the relevance of including this device in the diagnostic strategy of SSc is therefore mandatory. The 2013 ACR/EULAR classification criteria for SSc do not include any US parameters (3). The diagnostic performances of US parameters have been poorly studied to date in large populations of suspected-SSc patients. Therefore, the objective of this study was to evaluate and discuss the diagnostic value of hand US parameters and to explore their relevance for a combined diagnostic approach.

Methods

Patients

Two hundred and twenty-four patients (n=224) were referred to the Rheumatology or Internal Medicine departments for suspected SSc/SSc-like disorder by their routine practitioner (general practitioner, first-line rheumatologist, internal medicine specialist or dermatologist), were consecutively included in this single-centre observational cross-sectional study (inclusions from March 2011 to October 2018). Patients with suspected overlap syndrome could be included. All patients benefited from global clinical assessment and visceral evaluations according to daily practice (18). All patients also had US evaluation of the hand, performed by the same evaluator (GCo, 5 years of US practice in 2011, blinded from the results of clinical and paraclinical investigations and for the conclusion of the expert for the diagnosis of SSc). The ethics committee of Rennes Hospital approved this observational study (approvals 14.53 and 15.09). The study complied with the recommendations of the Declaration of Helsinki. All patients gave their informed consent prior to investigations.

US evaluation and US outcomes

Hand US evaluation was performed as previously described (6, 10, 11). UAO and fibrotic TS were evaluated by a same examiner in all patients (Supplementary Fig. S1). Our US protocol is fully described in the Supplementary file (US protocol section)

Diagnosis of SSc

For the analysis of the diagnostic accuracy of the 2013 ACR/EULAR classification criteria for SSc, and the diagnostic value of US parameters, the reference standard was a clinical diagnosis of SSc according to a board of experts blinded from the results of US evaluation. A first expert reviewed all cases and proposed a conclusion regarding SSc diagnosis, (AL, 10 years of experience in SSc diagnosis in 2018) based on the evaluation of 34 parameters. Patients were also evaluated and discussed by two other experts (CC & PJ; 25 years of experience in SSc diagnosis in 2018), also blinded from the results of US evaluation, independently of the first expert. In case of inconsistency, a consensus was reached after discussion, supervised by a fourth investigator (MdSR). According to this strategy, patients were classified as "SSc patient" or "other diagnosis than SSc" blinded from the results of US evaluation, and expert decision was not based on any US parameter. Importantly, the expert did not calculate 2013 ACR/EULAR score to give its final diagnostic decision and the expert diagnosis was therefore only based on his own experience in SSc and not on the result of the total score of 2013 ACR/EULAR classification criteria (3). The total score of the 2013 ACR/EULAR classification criteria was separately calculated for all patients as well as the 1980 ACR classification criteria for SSc and patients were classified according to Leroy's classification by an independent investigator (19-21).

This evaluation strategy is in accordance with the STARD strategy (22) and in accordance with the methodology of previous studies evaluating the involvement of US parameters in the diagnostic strategy of systemic diseases such as US evaluation of major salivary glands in primary Sjögren's syndrome (23).

Statistical analyses

We performed all tests with a significance level of $p<0.05$. Statistical analyses are fully described in the supplementary data (section "Statistical analyses").

Combination of US parameters and items from the 2013 EULAR/ACR classification for a combined diagnostic approach

In order to propose a combined diagnostic approach including US parameters (UAO; Fibrotic TS) and items derived from the 2013 EULAR/ACR classification, we evaluated the association of US findings with a 2013 ACR/EULAR score ≥9 and then determined if these parameters were statistically independently of the other items of the 2013 ACR/ EULAR classification using multivariable stepwise logistic regression models (3, 24). The weight of UAO and fibrotic TS was determined according to the value of the LR+ in these logistic regression models, considering UAO and fibrotic TS separately in a first model and the association of these parameters as a "US-SSc pattern" in a second model. In a pragmatic approach, we also analyse the diagnostic performances of our scoring strategy when capillaroscopic findings were suppressed, in order to assess

Table I. Characteristics of the 224 patients (SSc and controls).

	SSc n (%)	Controls n (%)	OR (95%CI)	*p*
General parameters				
n	166 (74.1)	58 (25.9)		
age (years) [a]	60.5 (52-69.5)	54.0 (43-62)	NA	*0.001*
Female	127 (76.5)	43 (74.1)	-	*0.23*
Current smoker	34/149 (22.8)	12/55 (21.8)	-	*0.88*
No smoking ever	77/149 (51.7)	25/55 (45.5)	-	*0.43*
Disease duration since RP[a]	10.0 (4.0-20.0)	4.5 (1.0-9.75)	NA	*0.002*
Clinical parameters				
Raynaud's phenomenon	165 (99.4)	40 (70.0)	5.13 (3.88-6.77)	*<0.001*
Telangiectasia	107 (65.2)	4 (6.9)	25.3 (8.73-73.5)	*<0.001*
Abnormal capillaroscopic pattern	116/127 (91.3)	13/42 (31.0)	23.5 (9.56-57.9)	*<0.001*
Puffy fingers	40 (24.1)	11 (19.0)	-	*0.40*
Sclerodactyly	114 (68.7)	3 (5.2)	41.8 (12.5-140)	*<0.001*
Proximal scleroderma	44 (26.5)	0	+∞	*<0.001*
Modified Rodnan skin score[a]	5.0 (3.0-38.0)	0.0 (0.0-0.0)	NA	*<0.001*
History of digital ulcers	77 (46.4)	6 (10.3)	7.58 (3.09-18.6)	*<0.001*
Calinosis on X-Rays	72 (43.4)	1 (1.7)	40.7 (5.48-302)	*<0.001*
Reflux	102 (61.4)	12 (22.4)	5.70 (2.85-11.4)	*<0.001*
PAH	19 (11.4)	0	+∞	*0.016*
ILD	65 (39.2)	3 (5.2)	9.32 (2.77-31.3)	*<0.001*
History of scleroderma renal crisis	5 (<1)	0	-	*0.33*
Auto-antibodies				
ANA	158 (95.2)	34 (58.6)	12.0 (4.63-30.8)	*<0.001*
Anti-centromere	78 (47.0)	11 (19.0)	3.38 (1.63-7.03)	*0.001*
Anti-topoisomerase I	45 (27.1)	3 (5.2)	6.18 (1.83-20.9)	*0.001*
Anti-RNA-polymerase-III	7 (4.2)	1 (1.7)	-	*0.68*
Other autoantibodies				
Power Doppler US				
UAO (uni- or bilateral)	62 (37.3)	8 (13.8)	3.73 (1.66-8.38)	*0.001*
UAO (bilateral)	41 (24.7)	4 (6.9)	4.43 (1.51-13.0)	*0.004*
Fibrotic tenosynovitis (TS)	23 (13.9)	1 (1.7)	9.17 (1.21-69.5)	*0.007*
UAO or fibrotic TS = scleroderma US pattern	73 (44.0)	9 (15.5)	4.27 (1.97-9.27)	*<0.001*
Classifications				
ACR/EULAR 2013	157 (94.6)	3 (5.2)	319.8 (84-1224)	*<0.001*
ACR 1980	98 (59.0)	0	+∞	*<0.001*
Leroy lcSSc	122 (73.5)	6 (10.3)	27.8 (8.34-92.5)	*<0.001*
Leroy dSSc	44 (26.5)	0	+∞	*<0.001*

[a]median (IQR); NA: non-applicable. SSc: systemic sclerosis; RP: Raynaud's phenomenon ; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease on last computed tomography evaluation; UAO: ulnar artery occlusion; TS: tenosynovitis; lcSSc: limited cutaneous SSc; dSSc: diffuse cutaneous SSc.

the relevance of our scoring strategy without this item evaluating vascular involvement and to test the place of US parameters in comparison with other diagnostic devices used for SSc.

Results

Characteristics of SSc and non-SSc patients, classified according to experts

Two-hundred and twenty-four patients (n=224) were included. Among them, 166 (74.1%) were diagnosed as SSc patients and 58 (25.9%) were considered as non-SSc patients by experts. Clinical, paraclinical and US parameters are summarised in Table I and specified in the supplementary data. Specific final alternative diagnoses for the 58 non-SSc patients are presented in Table II.

Diagnostic values of hand US parameters for the diagnosis of SSc

Using the experts' diagnosis of SSc as the reference standard, the presence of uni or bilateral UAO had an AUC of 0.618 (0.539-0.697) (Fig. 1A-B), with a sensitivity of 0.373 (0.304–0.449), a specificity of 0.862 (0.751–0.928) and a LR+ of 2.71 (1.38–5.31) (Fig. 1A-B). The presence of bilateral UAO had an AUC of 0.589 (0.509–0.669), with a sensitivity of 0.247 (0.188–0.318) and a specificity of 0.931 (0.836–0.973) and a LR+ of 3.58 (1.34–9.56) (Fig. 1A-B). The presence of a fibrotic TS had an AUC of 0.561 (0.480–0.643), with a sensitivity of 0.139 (0.094–0.199), a specificity of 0.983 (0.909–0.997) and a LR+ of 8.04 (95%CI 1.11–58.2). The US-SSc pattern had an AUC of 0.641 (0.563-0.695), with a sensitivity of 0.440 (0.367–0.516), a specificity of 0.845 (0.731–0.916) and a LR+ of 2.83 (1.52–5.29). The diagnostic value of other clinical/paraclinical items from the 2013 ACR/EULAR classification criteria are presented in Supplementary Table S1.

Addition of US parameters in a combined diagnostic approach including the items derived from the 2013 ACR/EULAR classification criteria for SSc

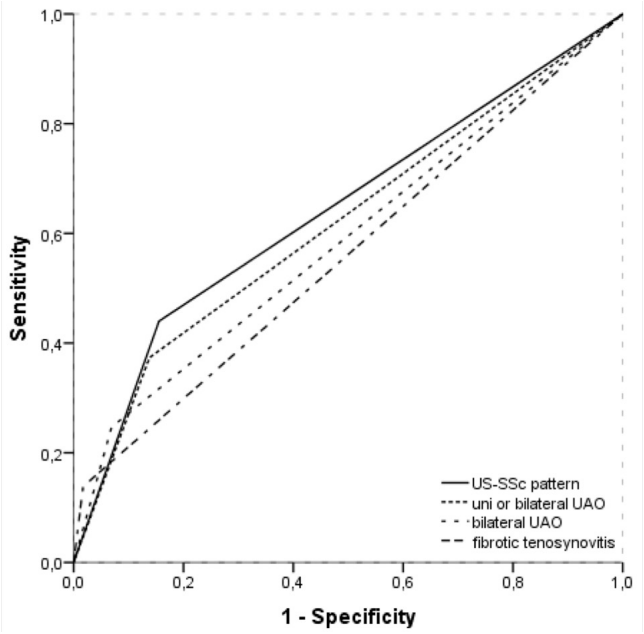
UAO (uni or bilateral) and fibrotic TS were both significantly associated with a ACR/EULAR score above 9 in univariable analysis (Suppl. Table S2).

Table II. Final diagnosis for the 58 non-SSc patients.

Diagnosis	n. (%)
Undifferentiated connective tissue diseases*	21 (36)
Isolated Raynaud's disease	12 (20)
Rheumatoid arthritis	8 (14)
Mixed connective tissue disease	4 (7)
Systemic lupus erythematosus	1 (1.7)
Generalised morphea	1 (1.7)
Thoracic outlet syndrome	3 (5.1)
Buerger's disease	1 (1.7)
Fibromyalgia	1 (1.7)
Antiphospholipid syndrome	1 (1.7)
Isolated positivity of antinuclear antibodies	1 (1.7)
Isolated tenosynovitis	1 (1.7)
Others	3 (5.1)

*The diagnosis of undifferentiated connective tissue diseases (UCTD) was proposed by the expert when patients had autoimmune manifestations but did not have sufficient clinical and/or biological autoimmune features to be diagnosed as a defined connective tissue disease such as SSc or systemic lupus erythematosus or Sjögren's syndrome or rheumatoid arthritis. This heterogeneous group could include patients with pre-scleroderma conditions without sufficient clinical or biological features to be diagnosed as authentic SSc according to the expert opinion and experience.

A. ROC curves



B. Diagnostic performances.

	AUC (95%CI)	Se (95%CI)	Sp (95%CI)	LR+ (95%CI)	Agreement
Uni or bilateral UAO	0.618 (0.539-0.697)	0.373 (0.304-0.449)	0.862 (0.751-0.928)	2.71 (1.38-5.31)	50.0%
Bilateral UAO	0.589 (0.509-0.669)	0.247 (0.188-0.318)	0.931 (0.836-0.973)	3.58 (1.34-9.56)	42.4%
Fibrotic tenosynovitis	0.561 (0.480-0.650)	0.139 (0.094-0.199)	0.983 (0.909-0.997)	8.04 (1.11-58.2)	35.7%
US-SSc Pattern	0.641 (0.563-0.695)	0.440 (0.367-0.516)	0.845 (0.731-0.916)	2.83 (1.52-5.29)	67.9%

[a]Agreement: positive predictive value + negative predictive value/total; [b]US-SSc pattern: UAO and/or fibrotic TS; AUC: area under the curves; Se: sensitivity; Sp: specificity; LR+: positive likelihood ratio; UAO: ulnar artery occlusion.

Fig. 1. Diagnostic performances of US or Doppler parameters for the diagnosis of SSc.

With a LR+ of 3.10, UAO had a LR+ similar to digital ulcers (DUs) (LR+ of 4.28). We therefore proposed that UAO could weigh a similar number of points as DUs (2 points). With a LR+ of 9.20 the presence of a fibrotic TS on US evaluation had a LR+ similar to sclerodactyly (LR+ of 11.2) (Suppl. Table S2). We therefore proposed that TS could add a similar number of points as sclerodactyly (4 points). The presence of a US-SSc pattern was also associated with a ACR/EULAR score above 9 in univariable analysis (Suppl. Table S2) with a LR+ of 3.24.

In multivariable analysis, the significant association between UAO or fibrotic TS, with a total ACR/EULAR score above 9 was not maintained (Additional Table II), demonstrating that these US parameters could not be considered independently of other items of the classification and should more likely be considered as sub-items. US-fibrotic TS was thus included as a third sub-item of digital sclerosis (along with puffy fingers and sclerodactyly) and UAO (uni or bilateral) was included as a third sub-item of digital cutaneous lesions (along with pitting scar and DUs), considering DUs and UAO as vascular cutaneous manifestations of the disease (Additional Table III). In accordance with the calculation of the total score in the 2013 ACR/EULAR classification, only the sub-item adding the highest number of points was considered in each category.

Diagnostic performances of this composite score including US parameters and items from the 2013 EULAR/ACR classification criteria

Using the experts' diagnosis of SSc as reference standard, the combination of items from the 2013 ACR/EULAR classification criteria for SSc, with a diagnostic of SSc for a total score ≥9, had an AUC of 0.982 (0.969–0.996), with a sensitivity of 0.946 (0.900-–.971), a specificity of 0.931 (0.836–0.973) and a LR+ of 13.7 (5.32–35.3) (Fig. 2A-B). Including UAO and fibrotic TS in the calculation of the total score had few impact on these diagnostic performances, as this new composite score including US parameters and items

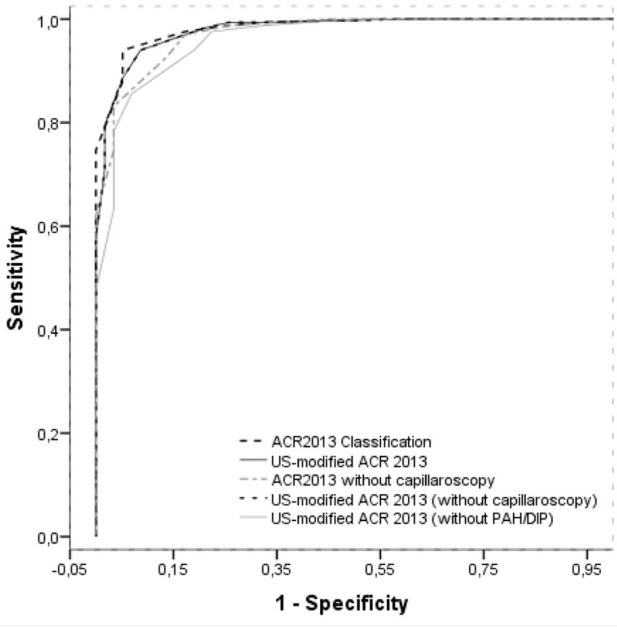
from 2013 ACR/EULAR classification criteria, with a diagnostic of SSc for a total score ≥9, had an AUC of 0.979 (0.962–0.996) with a sensitivity of 0.940 (0.893–0.967), a specificity of 0.931 (0.836–0.973) and a LR+ of 13.6 (5.29–35.1) (Fig. 2A-B).

When the item "capillaroscopy" was suppressed, the diagnostic value of this new composite score was unchanged with an AUC of 0.979 (0.962–0.996) and it was higher than the score of the original items from the 2013 ACR/EULAR classification without the item capillaroscopy (AUC=0.972 (0.952–0.992)) (Fig. 2A and B).

Discussion

This study evaluates the relevance of including US parameters in a combined diagnostic approach for SSc. These US parameters were therefore included in a proof-of-concept scoring system including US parameters and items derived from the 2013 ACR/EULAR classification criteria. It is important to highlight that the strategy proposed here was only designed for diagnostic purposes and not for classification purposes. By no means, this study attempted to improve classification value of the current EULAR/ACR 2013 classification criteria, as this was not the objective of this study and as the method proposed was not adapted for such an aim (25). The diagnostic performances of the proposed US-modified scoring system were similar to the items of the 2013 ACR/EULAR classification criteria when diagnostic of SSc was considered for a total score ≥9. This could lead to the conclusion that US parameters do not bring much to the items derived from the classification criteria as currently proposed and from a certain viewpoint this could lead to consider this study as a negative study. However, supressing some items such as capillaroscopy had no negative impact on the diagnostic performances of this proposed scoring system, suggesting that these US parameters add similar information for the diagnosis of SSc. This validates the relevance of US evaluation in a combined diagnostic approach, in a population of SSc patients that are not restricted to early or very early SSc.

A. ROC curves



B. Diagnostic performances

	AUC (95%CI)	Se (95%CI)	Sp (95%CI)	LR+ (95%CI)	Agreement[a]
ACR/EULAR 2013 classification	0.982 (0.969-0.996)	0.946 (0.900-0.971)	0.931 (0.836-0.973)	13.7	94.2%
ACR/EULAR 2013[b] (without capillaroscopy)	0.972 (0.952-0.992)	-	-	-	-
US-modified ACR/ EULAR 2013	0.979 (0.962-0.996)	0.940 (0.893-0.967)	0.931 (0.836-0.973)	13.6	93.8%
US-modified ACR/EULAR (without capillaroscopy)	0.979 (0.962-0.996)	0.940 (0.893-0.967)	0.931 (0.836-0.973)	13.6	93.8%
US-modified ACR/EULAR (without PAH/ILD)	0.962 (0.936-0.987)	0.855 (0.794-0.901)	0.931 (0.836-0.973)	12.4	87.5%
US-modified ACR/EULAR (without capillaro & PAH/ILD)	0.962 (0.938-0.986)	0.898 (0.842-0.935)	0.897 (0.792-0.952)	8.7	89.7%

[a]Agreement: positive predictive value + negative predictive value/total.
[b]Considering that there is no validated cut-off value for the original ACR/EULAR classification without capillaroscopy, only AUC were evaluated with no calculation Se, Sp, LR+ or agreement.
AUC: area under the curves; Se: sensitivity; Sp: specificity; LR+: positive likelihood ratio.

Fig. 2. Diagnostic performances of a scoring strategy including US parameters and items from the 2013 EULAR/ACR classification criteria for the diagnosis of SSc using a total score ≥9 for the diagnosis of SSc and the experts' diagnosis as reference standard.

This might be all the more relevant as US evaluation also provide information on specific hand manifestations, such as macrovascular involvement and tenosynovial involvement which both a have prognostic value (6, 7, 13, 26). We have kept a diagnosis threshold of 9 for the ACR/EULAR 2013 whereas US parameters were included in the new diagnostic strategy (3). This may have led to dampen the impact of US parameters on the diagnostic performances of the ACR/EULAR 2013 classification criteria. One could argue that we could have proposed a higher threshold, since new items are included. In this case this may have led to change the diagnostic performances of the ACR/EULAR 2013, and we can suspect that the presence of US findings would have improved the diagnostic value of the classification. But this would require a dedicated study, that goes beyond the scope of our work. With a respective specificity of 0.86 and 0.98, both UAO and fibrotic TS were specific for the diagnosis of SSc in this population of patients with suspected SSc. Their sensitivity was less convincing (0.375 for UAO and 0.139 for fibrotic TS), reflecting the

clinical heterogeneity of SSc with a vast range of clinical and hand US manifestations, similarly to visceral manifestations such as PAH and ILD (2).

US evaluation has a much higher sensitivity than clinical non-US assisted Allen-test (27, 28) to detect UAO, and the relevance of US evaluation is all the more supported by the high prevalence of UAO in SSc, referring to previous studies from other groups (7, 8, 17) and in accordance with our results. Although UAO appears to be rather specific, some patients with UAO were not finally diagnosed as SSc by the experts in our study. UAO also exists in the general population, with a prevalence ranging from 9.6% in men to 1% in women (29). This prevalence increases with age. The prevalence of UAO in our population of non-SSc patients (13.8%) was therefore slightly above its prevalence in the general population. This result could be explained by the selected population, as this was a population of patients with suspected-SSc, according to their routine practitioner. This inclusion of only suspected-SSc patients could be considered as a limit of our work, however it reflects the real-life situation and daily practice of a rheumatology department and highlights the pragmatic approach used in this study. This population is also in accordance with previous populations selected for the development of classification criteria for SSc (3, 15). Consequently, although still not considered as established SSc patients by our reference standard, 12 (20.7%) of the 58 non-SSc patients fulfilled the inclusion criteria for the very early diagnosis of SSc (VEDOSS; data not shown) (30). Patients in the non-SSc group had lower duration of Raynaud's phenomenon, we therefore cannot exclude that some of these patients could developed authentic SSc in the future. The predictive value of UAO for the onset of established SSc is still to be evaluated in longitudinal studies.

We did not include a group of "healthy controls" and we only included patients with suspected SSc. We therefore think our results reflect the diagnostic performances of US parameters in real-life conditions. Including patients considered as "healthy controls" *i.e.* patients with no scleroderma-associated parameters, would have limited the external value and relevance of our results. Thus, the inclusion of patients addressed to the Rheumatology or Internal Medicine departments for suspected SSc by their routine practitioner (general practitioner, first-line rheumatologist, internal medicine specialist or dermatologist) could be considered as a limitation, especially considering that there were no specific predefined inclusion criteria. Nonetheless, we believe that this inclusion strategy precisely ensures that our results reflect routine care and can assess the diagnostic value of US for common practice. Interestingly one non-SSc patient had US fibrotic TS. This patient was a woman with a final diagnosis of generalised morphea. This description of "fibrous arthropathy" has indeed also been previously noticed in paediatric Morphea (31) but, to our knowledge, not in adults with Morphea. The precise definition and characteristics of fibrotic TS according to the OMERACT (Outcome Measures in Rheumatology) filter also still need to be validated as it may appear examiner-dependent. Nonetheless, previous studies have compared US evaluations with MRI for the assessment of fibrotic tenosynovitis in SSc, demonstrating the reliability of US evaluation, since all tenosynovitis detected by US assessment in this study were also detected and confirmed by MRI (32).

Hand US evaluation offers the opportunity of simultaneously assessing vascular, inflammatory and fibrotic manifestations of SSc (12, 33). In our work, the prevalence of abnormal US parameters (UAO and/or fibrotic TS) was high, since almost half of SSc-patients had a US-SSc-pattern (44.0%). We did not include inflammatory manifestations of SSc in this study due to the wide range of aetiologies of Doppler positive synovitis and TS in SSc (authentic inflammatory manifestation of the disease, unspecific osteo-arthritis-associated synovitis, calcinosis-related synovitis, calcium pyrophosphate-associated synovitis). This could be considered as a limit of our work and further studies are warranted to clarify this issue. Another limitation is that the sonographer could not be totally blinded from all clinical features of SSc and some of them are quite characteristic (*e.g.* cutaneous thickening of both hands extending proximally to metacarpophalangeal joints) and they could not be easily hidden to the sonographer. This could have influenced the results of US evaluation. Nonetheless, this reflects real-life conditions and the sonographer was not involved in any way in the final diagnosis of SSc, as the final diagnostic relied on an independent board of experts, blinded from the results of US evaluation. Recent studies have also highlighted the relevance of ultra-high-frequency US evaluation (50Mhz) for the assessment of hand skin involvement in patients with SSc (34). We can hypothesis that including skin evaluation in the global US assessment of the hand in SSc may also improve the diagnostic value of US but this hypothesis may deserve further investigations (35, 36).

In our study, the combination of the items from the 2013 ACR/EULAR classification criteria had excellent diagnostic performances, when the diagnostic of SSc was considered for a total score ≥9. This result has already been described previously (5). Adding US parameters to the items of the classification had no positive or negative impact on these diagnostic performances (Fig. 2A. and B). This could be considered as a disappointing result, nonetheless, considering the excellent performances of this combination of items from the existing classification, this result was expected. Changing the weighing of the US items had limited impact on the diagnostic performances of the proposed diagnostic approach (data not shown). In our study the weighing of US parameters was derived using data driven methods based on the LR+, whereas weighing of items from the 2013 EULAR/ACR classification were derived using multicriteria decision analysis (25). This is a limitation of our study. Nonetheless, this methods is adapted for an exploratory study. We thus acknowledge that these results need to be validated in other cohorts to externally confirm the relevance of the proposed weights for US parameters.

Interestingly, suppressing capillaroscopy resulted in unchanged diagnostic performances, suggesting that US evaluation, with a simultaneous assessment of TS involvement and macrovascular features, could possibly constitute an interesting complement to capillaroscopic evaluation. Two future steps are required to clarify this issue: first, our results need to be confirmed on a validation sample as this study is the first study approaching global hand US assessment in a combined diagnostic strategy for SSc. Second, capillaroscopy is a cornerstone for the early diagnosis of SSc. On the contrary, some US features such as UAO may occur more lately in the course of the disease (10). Thus, we do not suggest that US could replace capillaroscopy, especially for early diagnosis (37-39). A dedicated study evaluating the diagnostic value of US in a VEDOSS population is mandatory to answer this question. Nonetheless, in offering this unique opportunity of a combined evaluation of vascular, joint and tenosynovial fibrotic manifestations of the disease, US evaluation shows a multi-functionality that capillaroscopy does not. US evaluation may also have a better sensitivity to change than capillaroscopy. This may be specifically important considering the emergence of composite indices for clinical trials including SSc patients (9, 40, 41). Among hand vascular manifestations, our US protocol only evaluated macrovascular involvement through the assessment of UAO. Other US protocols have recently proposed more detailed vascular evaluations including the assessment of finger pulp blood flow and/or obliteration of digital arteries (6, 9, 17, 41, 42). Their diagnostic performances still need to be evaluated in a population of suspected-SSc patients, as well as their prognostic value (43).

In conclusion, US evaluation is non-radiant, non-invasive, more and more accessible and use in daily practice. Although education and expertise in is needed to master this evaluation tool, US of the hand evaluation should not be neglected in SSc. A global and shared reflection is needed to include this device in the diagnostic and management strategy of SSc in the future (44), as some US features appear specific to this connective tissue disease.

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