Shear wave elastography-derived scoring system: application in the detection, subdivision and evaluation of systemic sclerosis

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Abstract

Objective

To locate the most valuable sites for shear wave elastography (SWE) evaluation and to develop a clinically applicable scoring system based on SWE for systemic sclerosis (SSc) and to verify the accuracy for detection and subdivision and the correlation by modified Rodnan total skin score (mRTSS).

Methods

SSc patients with limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) and symptomatic other rheumatic diseases (ORD) patients were included in this cross-sectional study. We assessed the skin stiffness at forehead, chest, abdomen, and bilateral fingers, hands, forearm, arms, thighs, legs, and feet, by palpation and SWE. Logistic regression was used to screen the most valuable sites for detection of SSc and subdivision of lcSSc and dcSSc, on which a scoring system was developed and verified.

Results

A total of 49 lcSSc, 51 dcSSc, and 36 ORD patients were included. The SWE-derived scoring system, including finger, hand, foot, arm, chest, and abdomen, reached a sensitivity and specificity of 80.0% and 94.4%, respectively, for diagnosing SSc at the cut-off value >24. The scoring system, including arm, chest, and abdomen, reached a sensitivity of 72.5% and specificity of 98.0% for subdividing dcSSc at the cut-off value >11. The kappa coefficient between the SWE-derived diagnosis and clinical diagnosis was 0.636 ($p<0.001$). The SWE-derived total scores of six sites had a strong correlation with mRTSS ($r=0.757$, $p<0.001$).

Conclusion

The SWE-derived scoring system can be valuable in detection and evaluation of SSc in clinical application.

Key words

ultrasound, systemic sclerosis, diagnosis, evaluation

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Introduction

Systemic sclerosis (SSc) is an immune-mediated rheumatic disease characterised by autoimmunity, widespread tissue fibrosis of the skin and internal organs, and vasculopathic alterations (1). SSc can be further subdivided into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) according to the region of the skin involved, which in turn exhibits differences in prognosis and organ involvement (2-4). Thus, assessing the skin involvement for evaluation of disease severity and for clear classification is a critical step in SSc management. Nowadays, the modified Rodnan skin score (mRSS) is the most widely used tool for assessing skin involvement in SSc; however, the unsatisfactory interobserver reliability among doctors with different training experiences needs to be assessed further (5, 6). Also, this method is not sufficiently sensitive for evaluating disease progression or treatment effects in the follow-up (7). Therefore, several studies have focused on finding objective assessment tools.

Ultrasound is a radiation-free imaging examination that has excellent resolution for superficial tissues. Previously, high-frequency ultrasound was utilised to measure skin thickness in SSc, and it was found that skin thickness was related to site-specific skin involvement (8-10). However, the natural history of SSc progression can pose challenges for skin thickness-based ultrasound assessment. The involved skin may thicken in the oedematous phase but tend to thin out in the fibrotic or atrophic phase. Thus, traditional high-frequency ultrasound may misjudge disease severity when evaluating patients with varying disease durations. Shear wave elastography (SWE) is a new acoustic technique that can quantify the stiffness of the tissue according to the physical characteristics of various shear wave propagation speeds in the tissues with different mechanical properties (11, 12); this broadens the evaluation dimension of traditional acoustic technology to the structure and function of the tissue. SWE uses Young's modulus to measure the stiffness of the target tissue, and the larger the value, the higher the stiffness (12). Presently, the quantitative assessment of liver cirrhosis by SWE has achieved clinical application (13). Owing to the technical characteristics, SWE can be a suitable imaging evaluation tool for SSc. Some studies have demonstrated the repeatability and SWE imaging and the potential value of SWE in SSc assessment and follow-up (7, 14-17). Although SWE produces quantitative data with great potential for follow-up and is helpful in differential diagnosis, the previous studies were limited to the comparison of differences between target groups. There are two challenges on the road to make SWE a clinical assessment tool: First, SWE scanning for the whole body is time-consuming, limiting its clinical application. As a systemic disease, SSc can widely affect the skin of the body, but which sites are the most valuable? Second, it is difficult for clinicians to correlate SWE results with actual clinical implications.

Therefore, we aimed to develop a clinically applicable semiquantitative scoring system to retain the quantitative advantage of SWE results and verify the accuracy for detection, subdivision, and the correlation with the traditional modified Rodnan total skin score (mRTSS). Subsequently, we designed this cross-sectional study containing SSc patients composed of lcSSc and dcSSc and patients with symptomatic other rheumatic diseases (ORD). The skin at 17 sites, including forehead, chest, abdomen, and bilateral fingers, hands, forearm, arms, thighs, legs, and feet, was assessed by palpation and SWE, and the mRTSS and Young's modulus were recorded. We used logistic regression to screen valuable sites, and then selected the values of different sensitivities and specificities in the ROC curve as the boundary to set up multiple intervals, and finally used the regression coefficients in logistic regression to assign points to each interval, thus establishing the SWE-based scoring system (Supplementary Fig. S1).

Material and methods

Study participants

Between September 2018 and May 2021, 100 SSc patients, who met the

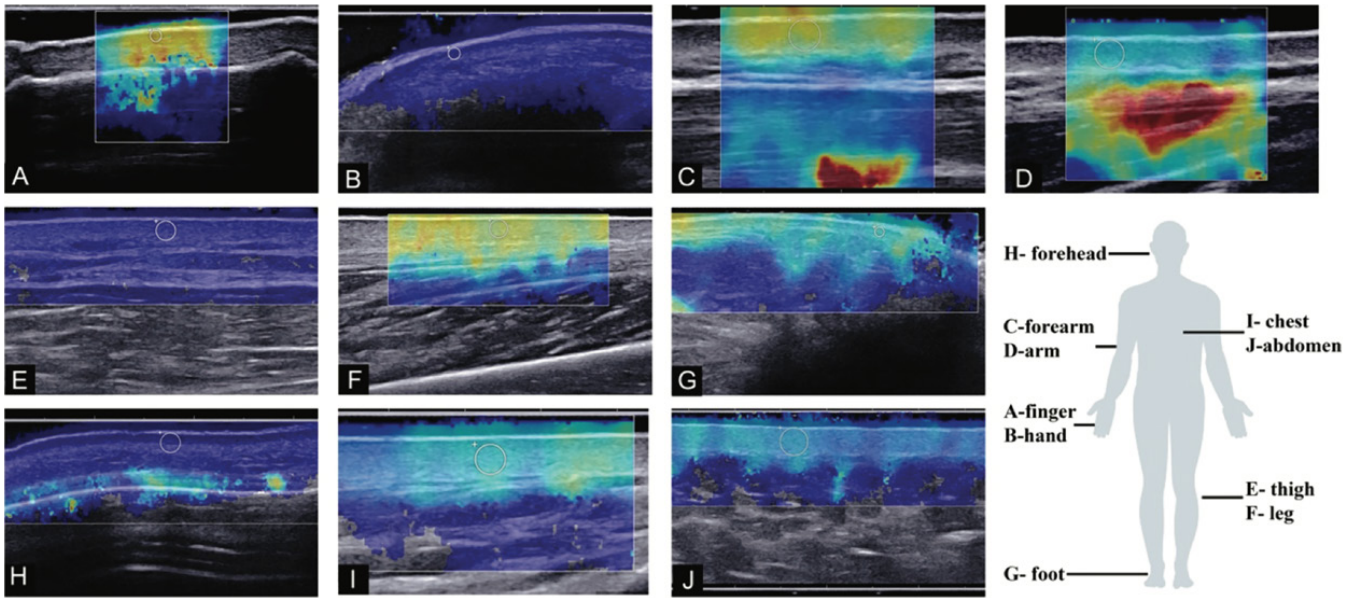

Fig. 1. Standard SWE images of target sites: A-finger; B-hand; C-forearm; D-arm; E- thigh; F- leg; G- foot; H- forehead; I- chest; J-abdomen.

American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2013 criteria for SSc, or the LeRoy's criteria for the classification of early SSc, were included in this cross-sectional study. In addition, 36 clinically suspected SSc patients with swollen fingers, Raynaud's phenomenon, or perceived skin hardening, ultimately diagnosed with ORD, were included in the control group. Skin involvement was scored according to the mRTSS at 17 anatomical sites (18) by an experienced dermatologist trained at the European League Against Rheumatism Scleroderma Trials and Research group course to subdivide SSc into dcSSc and lcSSc (19). Age, sex, and body mass index (BMI) were recorded. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of our institution (No. 2018(210)), and informed consent was obtained from all participants.

Ultrasonography assessments

Ultrasonography assessments were performed before starting treatment. All the patients were instructed not to perform any form of exercise for 2 hours and rest completely for 5 minutes before the examination. The room temperature was maintained at 25°C. One trained sonographer conducted all examinations on an Aixplorer ultrasound system (SuperSonic Imagine, Aix-en-Provence, France) with an SL 15-4 multifrequency linear probe in SWE mode. The instrument settings and scanning process were consistent with previous findings (20). The 17 target sites were consistent with the study of Moore *et al*. (18), and the standard images are exhibited in Figure 1. The results were expressed in kilopascal (kPa) for skin stiffness; for each site, three consecutive values were measured, and the average was calculated. For fingers, hands, forearms, arms, thighs, legs, and feet, the average value of bilateral results was analysed further. During the whole scanning process, the sonographer was unaware of the clinical diagnosis or subdivision.

Table I. Demographic characteristics of ORD, lcSSc, and dcSSc.

	ORD (n=36)	lcSSc (n=49)	dcSSc (n=51)	*p*
Sex (male:female)	6: 30 [a,b]	7: 42 [b]	18: 33 [a]	0.026
Age (years)	45.0 (38.5–51.8)	47.0 (39.0–51.5)	48.0 (35.0–59.0)	0.438
BMI (kg/m^2)	22.7 (20.8–24.8)	22.6 (20.1–24.6)	22.3 (19.3–23.5)	0.210
Duration (≤5y/5-10y/>10y)	/	22/14/13	27/18/6	0.169

[a,b] proportions with the same letter do not differ significantly from each other at the 0.05 level.
SSc: systemic sclerosis; lcSSc: limited SSc; dcSSc: diffused SSc; ORD: other rheumatic diseases; BMI: body mass index.

Statistical analysis

Statistical analyses were performed using SPSS 24.0 software (IBM, Armonk, NY, USA) and MedCalc software 20.0.4 (MedCalc Software Ltd, Ostend, Belgium). Continuous variables that conformed to normal distribution were represented as means ± standard deviations. For non-normally distributed continuous variables, the median (25th percentile–75th percentile) was used and the comparison between multiple groups was performed with a Kruskal-Wallis test, and multiple comparisons were performed in all pairwise method with an adjusted *p*-value. Chi-square test was used for the comparison of sex and disease duration proportions in different groups. Logistic regression with the forward (conditional) method was used to screen the most valuable sites for the detection of SSc and subdivision of lcSSc and dcSSc (excluding parameters with *p*-values >0.10). In the logistic regression, we ensured the sample size was 5–10 times the parameters. Receiver operating char-

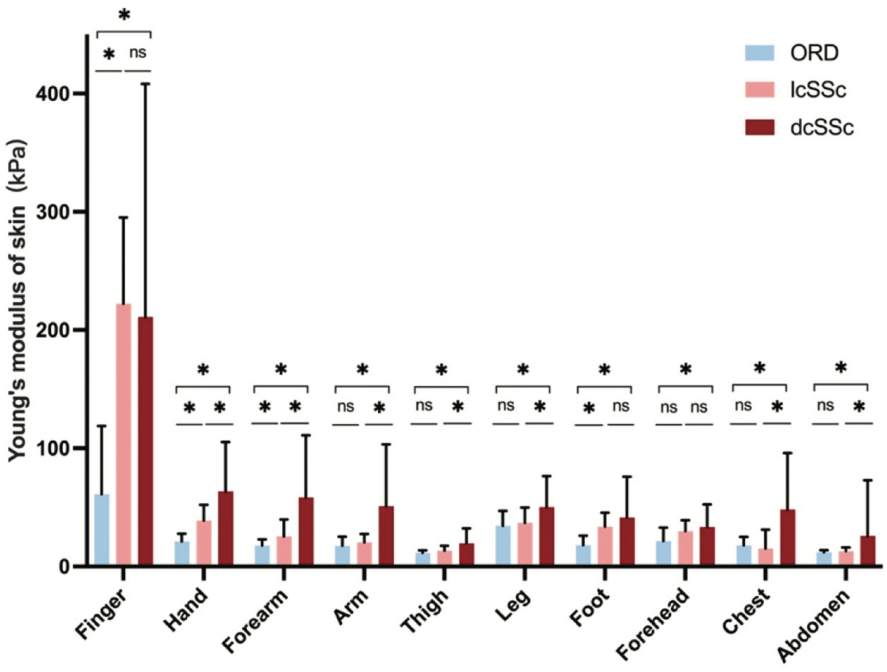

Fig. 2. The skin stiffness of target sites in ORD, lcSSc and dcSSc patients.
SSc: systemic sclerosis; lcSSc: limited SSc; dcSSc: diffused SSc; ORD: other rheumatic diseases; ns: not significant.
*p<0.05.

Table II. Valuable sites of skin stiffness for evaluation and subdivision in logistic regression.

	Valuable sites	Regression coefficient	Odds ratio (95% CI)	p
Regression for dcSSc	Arm	0.050	1.051 (1.014-1.088)	0.006
	Chest	0.027	1.027 (1.004-1.051)	0.020
	Abdomen	0.064	1.066 (1.005-1.131)	0.034
Regression for SSc	Finger	0.024	1.024 (1.014-1.035)	<0.001
	Hand	0.027	1.027 (1.002-1.054)	0.036
	Foot	0.026	1.026 (1.005-1.047)	0.015

SSc: systemic sclerosis; dcSSc: diffused SSc; CI: confidence interval.

acteristic (ROC) curve and area under the curve (AUC) were used to evaluate the diagnostic accuracy. The determination of normal and abnormal intervals is based on the results of the ROC analysis of each site. Next, we selected the values with different sensitivities and specificities for the corresponding positive results as nodes and calculated the weights and scores for each interval based on the regression coefficients (21). The kappa coefficient was used to evaluate the consistency of classification. Spearman's correlation test was used to evaluate the correlation between SWE- derived scores and mRTSS. A p-value <0.05 indicated statistical significance for two-sided tests.

Results

Clinical features and SWE-derived skin stiffness

A total of 49 lcSSc, 51 dcSSc, and 36 ORD patients (20 with rheumatoid arthritis, 6 with eosinophilic fasciitis, 3 with undifferentiated connective tissue disease (UCTD), 2 with mixed connective tissue disease (MCTD), 2 with systemic lupus erythematosus, 2 with polymyositis, 1 with spondyloarthritis.) were included in this cross-sectional study, and the demographic characteristics are compared in Table I. No significant difference was detected in the age, BMI, and the disease duration between ORD, lcSSc, and dcSSc. Female patients comprised the majority in the three groups, indicating a significant difference in sex proportion between the three groups (p=0.026). Moreover, the proportion of women in the lcSSc group was higher than that in the dcSSc group.

For skin stiffness, significant between-groups differences existed at every site (Suppl. Table S1), and the following pairwise comparisons are shown in Figure 2. Overall, the dcSSc group had higher skin stiffness than the lcSSc group, and the lcSSc group had higher stiffness than the ORD group. For specific sites, the dcSSc had higher skin stiffness than the ORD group at all target sites and had higher skin stiffness than lcSSc at hand, forearm, arm, thigh, leg, chest, and abdomen (all p<0.05). The skin stiffness of the lcSSc group was higher than that of ORD at the finger, hand, forearm, and foot (all p<0.05).

Establishment of the scoring system

As shown in Table II, we first screened for valuable sites for dcSSc and found that skin stiffness on the arm, chest, and abdomen were significant parameters. Then, finger, hand, and foot were found to be valuable for diagnosing SSc in the regression. Based on the ROC analysis of each site (Suppl. Table S1), we selected the values with different sensitivities and specificities for the corresponding positive results as nodes and calculated the weights and scores for each interval based on the results of the regression coefficients. The rating and scoring and the corresponding intervals of Young's modulus are listed in Table III.

Then, each subject was scored according to the standard in Table III, and the ROC curves were plotted to diagnose SSc (Fig. 3A) and subdivide dcSSc (Fig. 3B); subsequently, the cut-off values were obtained. While diagnosing SSc, the sum of the scores from all six sites was used in the first step. In the second step to subdivide the dcSSc, the sum of the scores only from the arm, chest, and abdomen was used. This was because the AUC improved from 0.926 to 0.941 after adding the scores from the other three sites compared to that using only the sum of the scores for the

Table III. Rating and scoring and the corresponding intervals of Young's modulus for each valuable site.

Site	Young's modulus (kPa)	Rating	Scoring
Finger	<40	Normal	0
	40–100	Suspicious increased	2
	100–140	Slight increased	4
	140–240	Increased	6
	≥240	Severely increased	20
Hand	<15	Normal	0
	15–25	Suspicious increased	1
	25–35	Slight increased	3
	35–100	Increased	10
	≥100	Severely increased	30
Foot	<10	Normal	0
	10–25	Suspicious increased	1
	25–50	Slight increased	2
	50–150	Increased	3
	≥150	Severely increased	10
Arm	<15	Normal	0
	15–30	Suspicious increased	2
	30–45	Slight increased	4
	45–60	Increased	6
	≥60	Severely increased	20
Chest	<15	Normal	0
	15–30	Suspicious increased	1
	30–60	Slight increased	3
	60–200	Increased	10
	≥200	Severely increased	30
Abdomen	<10	Normal	0
	10–15	Suspicious increased	1
	15–20	Slight increased	2
	20–25	Increased	3
	≥25	Severely increased	10

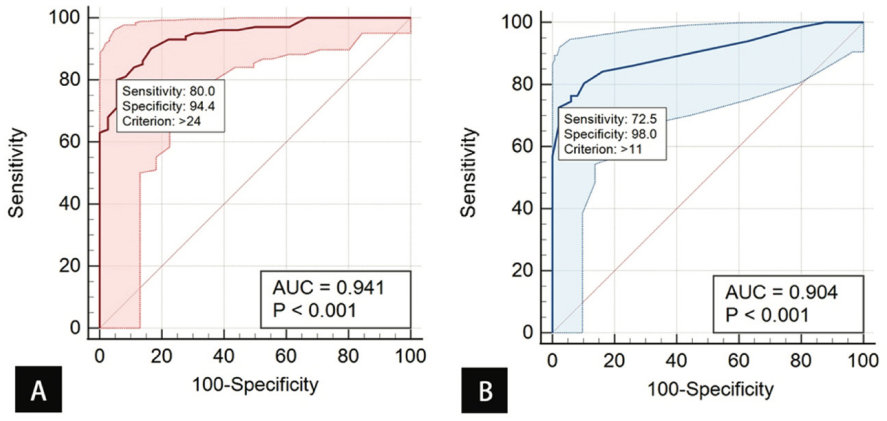

Fig. 3. ROC curves for diagnosing SSc based on the sum of the scores from all six sites (**A**) and for subdividing dcSSc based on the sum of the scores from the arm, chest, and abdomen (**B**).

finger, hand, and foot, although not statistically significant (Suppl. Fig. S2). Without adding any scanning time, rather than using scores from three sites, we speculated that using the total score of six sites might be a good strategy since all six sites need to be evaluated in this protocol. The cut-off value for diagnosing SSc was 24 points, with an AUC of 0.941(0.887-0.974), and a sensitivity of 80.0% and a specificity of 94.4%. The cut-off value for subdividing dcSSc was 11 points, with an AUC of 0.904 (0.828-0.954), and a sensitivity of 72.5% and specificity of 98.0%.

Clinical application of the scoring system

Based on the cut-off values obtained above, all the included subjects were diagnosed sequentially according to the results of the the SWE-derived scores. All patients were first judged whether they were SSc, and the patients diagnosed with SSc were further judged whether they were dcSSc. The final classification results are described in Table IV. The kappa coefficient was 0.636 (p<0.001, and 0.6–0.8 can be considered high agreement), indicating that the SWE-derived scoring system has the potential to diagnose SSc to further subdivide dcSSc.

In addition to diagnosis, the SWE-derived total scores of six sites differed between different intervals of mRTSS (Fig. 4A) (p<0.001) in SSc patients and had a strong correlation with mRTSS (r=0.757, p<0.001) (Fig. 4B).

Discussion

This study included symptomatic ORD patients as controls rather than healthy individuals. The results based on this composition may be closer to the clinical needs since our disease diagnosis should be symptom-driven and based on examination results, SWE is usually not used as a diagnostic or evaluation tool in asymptomatic individuals. Although completely asymptomatic healthy individuals comprised the control group was not in line with clinical practice, the obtained diagnostic value may be overestimated. Thus, we attempted to create a clinically relevant patient composition for our diagnostic tools, but the actual clinical situation may be complex. For example, lcSSc is more common than dcSSc, which accounts for about 66.5% of all SSc (22) rather than the ratio close to 1:1 in this study. In recruited patients, no significant differences were observed in age and BMI, but the sex ratio differed between lcSSc and dcSSc. The female accounts for 85.7% in lcSSc, 64.7% in dcSSc, and 83.3% in the ORD group. In previous studies, higher female proportion has been observed in the lcSSc group (22, 23), while there is no pathogenesis-related evidence to support the sex differences in lcSSc and dcSSc.

Inter group comparison of clinical features and skin stiffness

In the ensuing between-group compari-

Table IV. Classification based on the SWE-derived scoring system compared to clinical diagnosis.

		SWE- derived diagnosis			No.
		ORD	lcSSc	dcSSc	
Clinical diagnosis	ORD	34	2	0	36
	lcSSc	13	35	1	49
	dcSSc	7	8	36	51
	N	54	45	37	136

SSc: systemic sclerosis; lcSSc: limited SSc; dcSSc: diffused SSc; ORD: other rheumatic diseases; SWE: shear wave elastography.

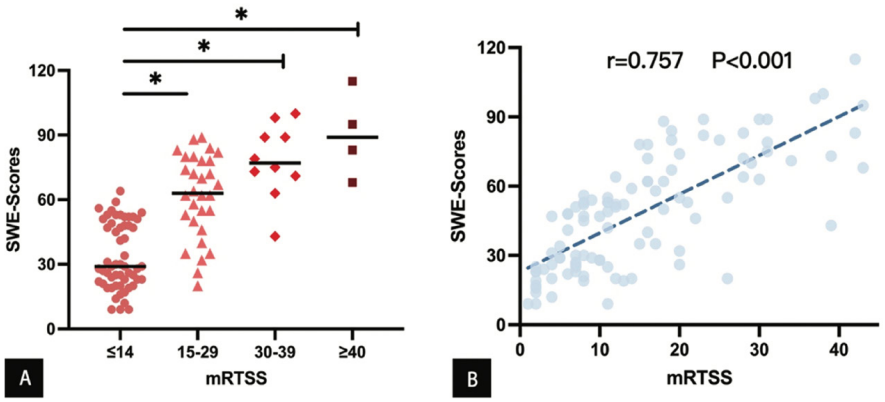

Fig. 4. Distribution of the SWE-derived scores between different mRTSS intervals in SSc patients (**A**), and the correlation between the SWE-derived scores and mRTSS (**B**).
SWE: shear wave elastography; mRTSS: modified Rodnan total skin score; SSc: systemic sclerosis. *p<0.05.

son of skin stiffness, we focused on the pattern of skin involvement and observed differences between ORD and lcSSc at the finger, hand, forearm, and foot, and between lcSSc and dcSSc at the arm, chest, abdomen, thigh, hand, forearm, and leg. According to the definition of the region of skin involvement for lcSSc and dcSSc (24), skin stiffness was observed at the finger, hand, forearm, foot, and leg in lcSSc compared to the control group, but no significant increase was observed in the skin stiffness at leg in lcSSc in this study. This may be partially due to the multiple comparisons between groups, which require a larger sample size to find the differences between the two groups and partially due to the fact that the control group consisted of ORD patients rather than healthy controls in previous studies. Some rheumatic diseases, including rheumatoid arthritis, often have skin involvement (25, 26). Although increased skin stiffness is not a common concern, the presence of skin lesions may indeed attenuate the differences between lcSSc and ORD. In addition, the skin stiffness of the arm, chest, abdomen, and thigh was significantly higher for dcSSc than for lcSSc; also, the skin stiffness of hand, forearm, and leg was higher than that of the lcSSc group, suggesting that compared to lcSSc, dcSSc has a wider range of skin involvement and may be severely involved. This trend has also been found in other studies on skin thickness (9, 27).

Establishment and evaluation of the scoring system

Logistic regression revealed that the most valuable sites for differentiating lcSSc and dcSSc were arm, chest, and abdomen, and the most valuable sites for detecting SSc were finger, hand, and foot. After combining the results of the ROC curves and the actual evaluation protocol, we also added the results of the arm, chest, and abdomen to the detection of SSc. Based on the results of the previous comparison between groups, these three sites mainly play their roles through the differences between dcSSc and ORD. After establishing a scoring system including these six sites, we performed a series of assessments of the diagnostic value of this system. For the ROC curves for diagnosing SSc and dcSSc, we speculated that the AUC of 0.946 and 0.904 was satisfactory, respectively. These results are based on the premise that SWE is the only diagnostic tool, and after combining it with other indicators, such as the laboratory tests of various autoimmune antibodies, the classification efficiency is expected to be improved further (28-31). From a diagnostic point of view, the sensitivity of the current study needs to be improved. In the first step of detecting SSc, some individuals were missed, which also directly led to these cases not entering the step of subdivision, making this issue rather challenging. We can increase the sensitivity by adjusting the cut-off value, which might lead to some ORD patients being misdiagnosed as lcSSc; however, laboratory tests could reduce this risk. Typically, the optimal cut-off value and the final diagnostic performance need to be verified in future studies. From a clinical work perspective, this study provided an unprecedented the SWE-derived scoring system that is easy for patients and clinicians to understand and can serve as a reference tool for future research based on SWE in SSc.

In addition to diagnosis, we also found that the SWE-derived total scores of six sites had a strong correlation with mRTSS (r=0.757, p<0.001). mRTSS is related to pathological findings and can be used to assess disease prognosis (32, 33). In a previous study, our group found Hou *et al*. (14) found that the sum of skin stiffness at 17 sites was correlated with mRTSS (r=0.841), which is similar to the current finding, albeit the correlation was stronger (r=0.841 *vs*. 0.757). This phenomenon could be attributed to the fact that the previous study was only based on dcSSc, and additional homogeneous subjects may improve the correlation. On the other hand, we transformed the quantitative SWE results into semiquantitative scores in this study, leading to the inevitable loss of information in this process. Taken

together, the SWE-derived scores were strongly correlated with clinical scores, indicating that the SWE-derived scoring system can be used for detection and the evaluation of SSc.

Since SWE was applied in evaluation of skin lesions in SSc, many related researches have been studied (7, 20, 27, 32, 34), which are mostly limited to the comparison of differences between groups. Clinicians are still at a loss as to how to translate this technology into diagnostic criteria. We first screened the assessment sites of the whole body, and then established a corresponding scoring system. Finally, we verified the cut-off value of this scoring system, its sensitivity and specificity, and found its correlation with clinical scores. This work will provide clinicians with a more applicable method of assessing SSc.

Limitation

There are some limitations to this work. First, this work is observational study with some diagnostic evaluation approaches, rather than a diagnostic test. Accordingly, there may be some bias in the inclusion of subjects, and some patients with mild symptoms may not be included because they did not seek medical attention. This issue may affect the results of classification effect to some extent. Second, this study focused on the SWE technique, without taking other ultrasound indicators such as skin thickness and laboratory findings into account.

Conclusion

The SWE-derived scoring system help to locate the most valuable sites for SWE evaluation, making it more time-saving. This scoring system can diagnose SSc and further subdivide dcSSc and lcSSc accurately. The total scores are highly correlated with clinical scores that can be utilised for the detection and evaluation of SSc in clinical work.

References

1. DENTON CP, KHANNA D: Systemic sclerosis. *Lancet* 2017; 390: 1685-99. https://doi.org/10.1016/s0140-6736(17)30933-9
2. FOELDVARI I, KLOTSCHE J, KASAPCOPUR O *et al*.: Differences sustained between diffuse and limited forms of juvenile systemic sclerosis in an expanded international cohort. *Arthritis Care Res* 2022; 74(10): 1575-84. https://doi.org/10.1002/acr.24609
3. HUBAC J, GILSON M, GAUDIN P, CLAY M, IMBERT B, CARPENTIER P: Ultrasound prevalence of wrist, hand, ankle and foot synovitis and tenosynovitis in systemic sclerosis, and relationship with disease features and hand disability. *Joint Bone Spine* 2020; 87: 229-33. https://doi.org/10.1016/j.jbspin.2020.01.011
4. KARALILOVA R, KAZAKOVA M, SAPUNDZHIEVA T *et al*.: Serum YKL-40 and IL-6 levels correlate with ultrasound findings of articular and periarticular involvement in patients with systemic sclerosis. *Rheumatol Int* 2019; 39: 1841-8. https://doi.org/10.1007/s00296-019-04402-9
5. CLEMENTS P, LACHENBRUCH P, SIEBOLD J *et al*.: Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. *J Rheumatol* 1995; 22: 1281-5.
6. PARK JW, AHN GY, KIM JW *et al*.: Impact of EUSTAR standardized training on accuracy of modified Rodnan skin score in patients with systemic sclerosis. *Int J Rheum Dis* 2019; 22: 96-102. https://doi.org/10.1111/1756-185x.13433
7. SANTIAGO T, SANTIAGO M, COUTINHO M, SALVADOR MJ, DA SILVA JAP: How much of skin improvement over time in systemic sclerosis is due to normal ageing? A prospective study with shear-wave elastography. *Arthritis Res Ther* 2020; 22: 50. https://doi.org/10.1186/s13075-020-02150-x
8. BALINT PV, KANE D, WILSON H, MCINNES IB, STURROCK RD: Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002; 61: 905-10. https://doi.org/10.1136/ard.61.10.905
9. HESSELSTRAND R, SCHEJA A, WILDT M, AKESSON A: High-frequency ultrasound of skin involvement in systemic sclerosis reflects oedema, extension and severity in early disease. *Rheumatology* (Oxford) 2008; 47: 84-7. https://doi.org/10.1093/rheumatology/kem307
10. LI H, FURST DE, JIN H *et al*.: High-frequency ultrasound of the skin in systemic sclerosis: an exploratory study to examine correlation with disease activity and to define the minimally detectable difference. *Arthritis Res Ther* 2018; 20: 181. https://doi.org/10.1186/s13075-018-1686-9
11. RYU J, JEONG WK: Current status of musculoskeletal application of shear wave elastography. *Ultrasonography* 2017; 36: 185-97. https://doi.org/10.14366/usg.16053
12. OPHIR J, CÉSPEDES I, PONNEKANTI H, YAZDI Y, LI X: Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging* 1991; 13: 111-34. https://doi.org/10.1177/016173469101300201
13. ZHOU X, RAO J, WU X, DENG R, MA Y: Comparison of 2-D shear wave elastography and point shear wave elastography for assessing liver fibrosis. *Ultrasound Med Biol* 2021; 47: 408-27. https://doi.org/10.1016/j.ultrasmedbio.2020.11.013
14. HOU Y, ZHU QL, LIU H *et al*.: A preliminary study of acoustic radiation force impulse quantification for the assessment of skin in diffuse cutaneous systemic sclerosis. *J Rheumatol* 2015; 42: 449-55. https://doi.org/10.3899/jrheum.140873
15. LIU H, HOU Y, ZHU QL *et al*.: A preliminary study of skin ultrasound in diffuse cutaneous systemic sclerosis: does skin echogenicity matter? *PloS One* 2017; 12: e0174481. https://doi.org/10.1371/journal.pone.0174481
16. SANTIAGO T, SANTIAGO M, MOREIRA S, SANTOS L, SALVADOR MJ, DA SILVA JAP: Influence of contextual factors and reliability of ultrasound skin measures in persons with systemic sclerosis and healthy controls. *Clin Exp Rheumatol* 2023; 41: 1599-604. https://doi.org/10.55563/clinexprheumatol/setd1z
17. YANG Y, YAN F, WANG L *et al*.: Quantification of skin stiffness in patients with systemic sclerosis using real-time shear wave elastography: a preliminary study. *Clin Exp Rheumatol* 2018; 36 (Suppl. 113): S118-25.
18. MOORE TL, LUNT M, MCMANUS B, ANDERSON ME, HERRICK AL: Seventeen-point dermal ultrasound scoring system--a reliable measure of skin thickness in patients with systemic sclerosis. *Rheumatology* (Oxford) 2003; 42: 1559-63. https://doi.org/10.1093/rheumatology/keg435
19. TYNDALL A, LADNER UM, MATUCCI-CERINIC M: The EULAR Scleroderma Trials and Research Group (EUSTAR): an international framework for accelerating scleroderma research. *Current Opin Rheumatol* 2008; 20: 703-6. https://doi.org/10.1097/BOR.0b013e328311f841
20. YANG Y, QIU L, WANG L *et al*.: Quantitative assessment of skin stiffness using ultrasound shear wave elastography in systemic sclerosis. *Ultrasound Med Biol* 2019; 45: 902-12. https://doi.org/10.1016/j.ultrasmedbio.2018.11.015
21. WILSON PW, D'AGOSTINO RB, LEVY D, BELANGER AM, SILBERSHATZ H, KANNEL WB: Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97: 1837-47. https://doi.org/10.1161/01.cir.97.18.1837
22. FRANTZ C, HUSCHER D, AVOUAC J *et al*.: Outcomes of limited cutaneous systemic sclerosis patients: results on more than 12,000 patients from the EUSTAR database. *Autoimmun Rev* 2020; 19: 102452. https://doi.org/10.1016/j.autrev.2019.102452
23. DE ALMEIDA CHAVES S, POREL T, MOUNIÉ M *et al*.: Sine scleroderma, limited cutaneous, and diffused cutaneous systemic sclerosis survival and predictors of mortality. *Arthritis Res Ther* 2021; 23: 295. https://doi.org/10.1186/s13075-021-02672-y
24. LEROY EC, MEDSGER TA Jr: Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; 28: 1573-6.
25. HATA T, KAVANAUGH A: Rheumatoid arthritis in dermatology. *Clin Dermatol* 2006; 24: 430-7. https://doi.org/10.1016/j.clindermatol.2006.07.008
26. CHUA-AGUILERA CJ, MÖLLER B, YAWALKAR N: Skin manifestations of rheumatoid arthritis, juvenile idiopathic arthritis, and spondyloarthritides. *Clin Rev Allergy Immunol* 2017; 53: 371-93. https://doi.org/10.1007/s12016-017-8632-5
27. AKESSON A, HESSELSTRAND R, SCHEJA A, WILDT M: Longitudinal development of skin involvement and reliability of high frequency ultrasound in systemic sclerosis. *Ann*

Rheum Dis 2004; 63: 791-6. https://doi.org/10.1136/ard.2003.012146
28. SARI A, ESME M, AYCICEK GS *et al*.: Evaluating skeletal muscle mass with ultrasound in patients with systemic sclerosis. *Nutrition* 2021; 84: 110999. https://doi.org/10.1016/j.nut.2020.110999
29. WIELOSZ E, MAJDAN M, DRYGLEWSKA M, ZWOLAK R: Anti-CCP antibodies and rheumatoid factor in systemic sclerosis: Prevalence and relationships with joint manifestations. *Adv Clin Exp Med* 2018; 27: 1253-7. https://doi.org/10.17219/acem/69921
30. WIELOSZ E, DRYGLEWSKA M, MAJDAN M: The prevalence and significance of anti-PM/Scl antibodies in systemic sclerosis. *Ann Agric Environ Med* 2021; 28: 189-92. https://doi.org/10.26444/aaem/127801
31. BÖRÖCZ K, SIMON D, ERDŐ-BONYÁR S *et al*.: Relationship between natural and infection-induced antibodies in systemic autoimmune diseases (SAD): SLE, SSc and RA. *Clin Exp Immunol* 2021; 203: 32-40. https://doi.org/10.1111/cei.13521
32. CHEN C, CHENG Y, ZHU X *et al*.: Ultrasound assessment of skin thickness and stiffness: the correlation with histology and clinical score in systemic sclerosis. *Arthritis Res Ther* 2020; 22: 197. https://doi.org/10.1186/s13075-020-02285-x
33. NEVSKAYA T, ZHENG B, BAXTER CA, RAMEY DR, POPE JE, BARON M: Skin improvement is a surrogate for favourable changes in other organ systems in early diffuse cutaneous systemic sclerosis. *Rheumatology* (Oxford) 2020; 59: 1715-24. https://doi.org/10.1093/rheumatology/kez529
34. SOBOLEWSKI P, MAŚLIŃSKA M: Applicability of shear wave elastography for the evaluation of skin strain in systemic sclerosis. *Rheumatol Int* 2020; 40: 737-45. https://doi.org/10.1007/s00296-020-04539-y