Risk factors of cognitive function impairment in patients with systemic sclerosis

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Abstract

Objective

Systemic sclerosis (SSc) is characterised by generalised vasculopathy and multi-organ fibrosis. Cognitive impairment may develop among SSc patients, affecting attention, memory and solving complicated tasks. Previous studies have identified microvascular abnormalities in the brain; however, no complex investigation has clarified these cognitive symptoms. This study examined the associations between cognitive functions and detailed clinical parameters regarding SSc.

Methods

One hundred and sixty patients with SSc and 62 age- and sex-matched healthy controls were studied and followed up for a span of twelve months. Clinical data and results of neuropsychological tests were analysed, including the Mini-Mental State Examination (MMSE), Digit Span Forward-Backward, Trail Making A, B and Digit Symbol tests at baseline and one-year follow-up.

Results

In the early stages of the disease, there was no cognitive impairment, even in severe patients with diffuse cutaneous SSc. Based on linear regression models, the cognitive scores were independently influenced by patients' age, degree of education, pain intensity, employment status, presence of hypertension, level of haemoglobin, in addition cardiac function and muscle strength. One-year follow-up results in changes in the six-minute walk distance (6MWT) correlated with changes in the results of MMSE ($p=0.002$, $rho=0.259$).

Conclusion

In addition to age, level of education, employment, presence of chronic hypertension and pain, which are well-known factors affecting cognitive abilities in general population, we have highlighted the role of cardiovascular function, the diastolic dysfunction, the level of haemoglobin and decreased muscle strength in SSc individuals. These cardiovascular function and muscle condition can be characterised by the 6MWT.

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Key words

systemic sclerosis, cognitive function, quality of life, diastolic dysfunction

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Introduction

Systemic sclerosis (SSc) is characterised by generalised microvascular lesions, fibrosis of the skin and variety of internal organs (1). The manifestation of the central nervous system (CNS) is typically not detectable, however, patients afflicted with SSc consistently reported perceived cognitive changes including deficits in short-term memory and difficulties in concentration (2). SSc negatively affects patients' mental health, since individuals more often experience anxiety, depression, persistent pain and mild cognitive dysfunction (3).

Giuliodori *et al*. (4) reported diminished cognitive performances and cerebral vasoreactivity in young scleroderma patients without any symptoms regarding CNS involvement. The authors support the hypothesis regarding endothelial damage in microvasculature, which can cause cerebrovascular dysfunction. Cutolo *et al*. investigated in a clinical study (5), using single photon emission computed tomography and cerebral hypoperfusion was detected and also found magnetic resonance imaging alterations in more than 50% of SSc patients. Bertinotti *et al*. (6) assessing proton magnetic resonance spectroscopy, evaluated in vivo, the ratios of N-acetyl aspartate/creatine and choline/creatine proved significant cerebral neurometabolic modifications in patients with SSc when compared to healthy controls. Notably, these changes were more prominent in patients with limited (lcSSc) than in those with diffuse cutaneous SSc (dcSSc). Sakr *et al*. (7), using transcranial sonography, found increased cerebral vascular tone and resistance in lcSSc patients when compared to dcSSc individuals. There was no cerebral atrophy found among SSc patients, however, cognitive function tests resulted in poor levels for scleroderma patients when compared to healthy controls, using the Trail making A and B tests. Investigators theorise cerebral microvascular damage and hypoperfusion are lurking in the background of cognitive dysfunction (3-7). However, these changes were not closely related to the severity of peripheral deteriorations in the use of nail fold video-capillaroscopy (5, 6). In this follow-up observation, to better comprehend the process of cognitive impairment, detailed clinical characteristics were evaluated among a large patient population. Short-term memory, working memory capacity, attention, psychomotor tempo and central executive function were evaluated at baseline and at the 12-month follow-up. Regarding the one-year follow-up, we investigated the cognitive changes and correlations of the alterations.

Methods

Participants and clinical assessments

One hundred and sixty consecutive Caucasian patients fulfilling the classification criteria for SSc of the 2013 American College of Rheumatology/European League Against Rheumatism (8, 9) were enrolled into the study from 2019 to 2022, originating from the Rheumatology and Immunology Department, University of Pécs, Hungary. Another group, including 62 sex and age-matched healthy individuals were enrolled as controls. Demographical and clinical items were recorded regarding our standard protocol (10).

All at baseline and at the 12-month follow-up, the same clinical parameters and neuropsychological tests were used. The Mini Mental State Examination (MMSE) (4, 11, 12) is the most widely used instrument for evaluating cognitive function and identifying subclinical dementia. MMSE is a 5-dimension measure, including tests for orientation, attention, calculation, memory abilities, analysing-synthesising, and the potential to create quick associations. A maximum of 30 points can be achieved, in which the normal interval is 27-30 and lower points represent cognitive damage. For testing the working memory, in the Digit Span Forward Test (4, 13) participants hear a random series of numbers of different lengths, which they have to state back in the proper order. There are 8 number blocks. Only exact repetition of the number sequence is acceptable, the hiatus, swapping or saying another number is a fault. In the Digit Span Backward Test (4, 13), participants also hear a series of numbers, which

they have to repeat in reverse order. In the Digit Symbol Test (14), there is a number-symbol coding system. Participants have 90 seconds to write as many symbols into the squares as possible. This test examines general psychomotor tempo, span of attention, visuomotor coordination and working memory. Trail Making Tests A and B (4, 13, 14): in Part A participants connect the numbers in ascending order, while in Test B there are numbers and letters which they couple according to a given rule. They must solve both tests in the shortest possible time. Eventually, the measured time corresponds to the point. Test A evaluates visual attention and psychomotor tempo, while Test B shows the flexibility of thinking and working memory.

As part of the clinical examination, family and marital status, level of education, data regarding employment and tobacco use were asked of each participant. Extent of education was scored 1-8 from less than 8 years of education up to university level. To assess general health, the Health Assessment Questionnaire Disability Index (HAQ-DI) and the VASs of the Scleroderma-HAQ and other self-administered questionnaires, the Cochin Hand Function Scale (CHFS) with 18 items and the Short Form Health Survey (SF-36) questionnaire required completion by all participants (15, 16). Functional Assessment of Chronic Illness Therapy 'Emotional Well-Being' (FACIT-EWB) (17), a 6-item questionnaire was used to assess symptoms of anxiety and depression.

Patients underwent spirometry, high resolution computed tomography (18), and echocardiographic examinations. Left ventricular mass index (LVMI) was calculated based on the Devereux formula and then indexed for body surface area (19). Characterisation of left ventricular diastolic function was based on the left atrial size, the mitral inflow pattern (E/A ratio), the LVMI and the calculated right ventricular systolic pressure (19). Based on all these data, an experienced cardiologist (RF) classified participants into 3 categories, with 'normal diastolic function', 'impaired relaxation' and 'pseudo-normal diastolic mitral inflow curve'. Pulmonary arterial hypertension was defined if >20 mm Hg mean pulmonary arterial pressure was detected by right heart catheterisation (19). Cardiorespiratory capacity of the participants was characterised by the Six-minute walk test (6MWT) (20). Presence of hypertension (21) and/or diabetes mellitus (22) of the participants was recorded according to international criteria. Presence of gastrointestinal involvement (GI) was defined according to the University of California, Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (UCLA SCTS GIT 2.0) questionnaire (23). Data of musculoskeletal involvement and the Manual Muscle Testing-8 (MMT8) was performed (24). Pinch strength of I and II digits of the hands was evaluated by using a JAMAR Hy-

Table I. Clinical, demographical characteristics and the results of the cognitive function tests among patients with systemic sclerosis and healthy controls.

Characteristics, results	All SSc (n=160)	Controls (n=62)	*p*
Female subjects, n (%)	138 (86.3)	49 (79.0)	0.186
Age, years, mean (SD)	55.8 (13.0)	54.6 (13.7)	0.411
Disease duration, years, mean (SD)	10.5 (7.6)	NA	-
Diffuse cutaneous SSc, n (%)	88 (55.0)	NA	-
Modified Rodnan skin score >14, n (%)	22 (13.8)	NA	-
Digital ulcer ever (including current), n (%)	52 (32.5)	0	**<0.001**
Cardiac involvement, n (%)‡	117 (73.1)	NA	-
NYHA cardiac state III–IV, n (%)	13 (8.1)	0	**<0.001**
Interstitial lung disease by HRCT, n (%)	97 (60.6)	Not done	-
UCLA SCTC GIT 2.0, (0-3),†	0.2 (0.1; 0.5)	0.04 (0; 0.2)	**<0.001**
Moderate/severe GI by UCLA GIT 2.0, n (%)	37 (23.1	2	**<0.001**
Malabsorption, n (%)	21 (13.1)	0	**<0.001**
Body mass index, kg/m^2, mean (SD)	25.8 (5.1)	27.1 (4.4)	0.326
Scleroderma renal crisis, n (%)	1 (0.6)	0	-
Haemoglobin, g/L,†	130 (124; 139.8)	142 (130.3; 147.8)	**<0.001**
Albumin, g/L,†	43.5 (41.6; 46.0)	48 (45.4; 49.7)	**<0.001**
Six-minute walk test, m,†	428 (347; 523)	600 (510; 660)	**<0.001**
Revised EUSTAR Activity Index,†	2.5 (1.3; 3.9)	NA	-
Microangiopathy Evolution Score (MES),†	2 (1.3; 2.88)	0.4 (0.1; 0.7)	**<0.001**
Treated hypertension, n (%)	72 (45.0)	26 (42)	**<0.001**
Treated type 2 diabetes mellitus, n (%)	10 (6.3)	3 (4.8)	0.787
Corticosteroid treatment, n (%)	23 (14.4)	0	**<0.001**
Conventional DMARDs, n (%)	69 (43.1)	-	-
Biologic or targeted molecular treatment, n (%)	3 (1.8)	-	-
HAQ-DI, (0-3),†	0.75 (0; 1.38)	0 (0; 0)	**<0.001**
Cochin Hand Function Scale, (0-90),†	5 (0; 17)	0 (0; 0)	**<0.001**
Manual Muscle Testing-8, (0-150),†	122 (110; 133)	135 (122.5; 143.5)	**<0.001**
Pinch strength, N,†	61.7 (46.7; 75)	71.6 (60.8; 83.3)	**<0.001**
Smoker ever, n (%)	69 (46.6)	29 (46.8)	0.997
Patients with >12 study years, n (%)	67 (41.9)	48 (77.4)	**<0.001**
Employed, n (%)	50 (31.3)	37 (59.7)	**<0.001**
Living alone, n (%)	67 (41.9)	29 (46.8)	0.596
Sleeping disorder, n (%)	79 (49.4)	17 (27.4)	**0.008**
FACIT-Fatigue Scale (0-52),†	38.5 (29.0; 45.3)	48 (44; 50)	**<0.001**
FACIT-Emotional Well-Being, (0-24),†	19 (16; 22)	21 (19; 23)	**<0.001**
SF36-Mental Summary, (0-100),†	68.1 (40.3; 83.8)	85.7 (74.3; 94.3)	**<0.001**
SF36-Physical Summary, (0-100),†	46.5 (27.3; 72.8)	91,7 (76.4; 96)	**<0.001**
Mini-Mental State Examination, (0-30),†	28 (27; 29)	29.0 (28.0; 29)	**0.014**
Digit Span Forward Test, (0-16),†	8 (7; 10)	9 (7; 11)	**0.043**
Digit Span Backward Test, (0-14),†	5 (4; 6)	6 (4; 6)	**0.017**
Digit Symbol Test, (0-90),†	40 (32; 50)	55.5 (41.8; 63)	**<0.001**
Trail Making A Test, (s),†	41.3 (31; 56)	29 (22; 40.5)	**<0.001**
Trail Making B Test, (s),†	107 (68; 149)	61 (46; 91.8)	**<0.001**

†Median (25th; 75th percentiles); ‡Conduction defects, arrhythmias, pericarditis, myocardial ischaemia on ECG, diastolic dysfunction and/or pulmonary arterial hypertension.

NYHA: New York Heart Association; UCLA SCTC GIT 2.0: University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument 2.0; EUSTAR: European Scleroderma Trials and Research Group; DMARDs: Disease-modifying anti rheumatic drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; FACIT: Functional Assessment of Chronic Illness Therapy; SF36: Short Form 36.

draulic Pinch Gauge (Lafayette Instrument, USA). The degree of skin thickening was assessed using the modified Rodnan skin score (mRSS; range 0–51) (25) Nailfold video capillaroscopy was used to evaluate capillary morphology, density and Microangiopathy Evaluation Score (MES) was calculated for each participant (26).

Ethics

The study protocol fully adhered to the 'Principles of the Declaration of Helsinki', 1964, and later amendments. The National Ethics Committee of Hungary submitted its approval for conducting the study 35147-3/2020/EÜIG. All authorised participants gave their written consent to the study.

Statistical analysis

Depending on the distribution of continuous variables, the results were counted in mean ± standard deviation or median (25th; 75th percentiles) values. To compare the categorical variables, Pearson-χ^2 test or Fisher's exact test were used. In the case of normally distributed continuous variables, an independent sample t-test was used, while the non-normal variables were compared to the Mann-Whitney U-test. In case of comparing more than two groups Kruskal-Wallis rank sum test was applied. For *post-hoc* pairwise comparison Bonferroni-Holm correction were used. Comparison of the test results and differences between baseline and 12-month follow-up values were analysed using the Wilcoxon signed-rank test.

Correlations between the cognitive tests and the other measured variables were determined using Spearman's correlation coefficient. Statistically significant results were considered at a level of 5% ($p<0.05$). The 'Random Forest' (RF) method (27) was used to establish the potential influencing factors of cognitive function. The Y-axis represents the feature importance in arbitrary units, where the values are meaningful only in comparison to each other. The factors gathered from RF were used in linear regression models, to define independent influencing factors (28). To reduce the model component and to avoid overfitting stepwise Akaike Information Criterion (StepAIC) procedure was used (28). The calculations and the figures were computed using the IBM SPSS Statistics v. 23. programme and the R statistical software (v. 4.2.1; package: 'RandomForest'; R Core Team, Vienna, Austria).

Table II. Spearman correlations between clinical data and the results of cognitive and general health measures among patients with systemic sclerosis at baseline.

All SSc (n=160)	Mini-Mental	Digit Span Forward	Digit Span Backward	Digit Symbol	Trail Making A	Trail Making B
Age	-0.349**	-.0331**	-0.383**	-0.615**	0.658**	0.524**
Duration time	-0.252**	-0.191*	-0.160*	-0.330**	0.367**	0.316**
Study years	0.564**	0.385**	0.450**	0.557**	-0.382**	-0.348**
Body mass index	-0.094	-0.121	-0.123	-0.104	0.154	0.074
Rodnan skin score	0.254**	0.286**	0.279**	0.323**	-0.248**	-0.349**
Forced vital capacity	-0.091	-0.067	-0.224**	-0.119	0.069	0.094
DLCO	0.060	0.035	0.001	0.123	-0.167*	-0.087
Ejection fraction	0.038	0.208*	0.123	0.095	0.015	-0.031
Left ventricular mass index	-0.345**	-0.281**	-0.337**	-0.405**	0.428**	0.358**
Six-minute walk test	0.383**	0.227**	0.221**	0.539**	-0.536**	-0.486**
ESR	-0.092	-0.108	-0.210**	-0.222**	0.220**	0.184*
Albumin	0.062	-0.144	-0.035	0.067	-0.146	-0.124
Haemoglobin	-0.013	-0.010	0.011	-0.001	-0.148	-0.137
Manual Muscle Testing-8	0.298**	0.264**	0.234**	0.519**	-0.524**	-0.539**
Pinch strength	0.148	0.167*	0.154	0.336**	-0.341**	-0.339**
HAQ-DI	-0.242**	-0.298**	-0.158*	-0.363**	0.386**	0.357**
HAQ VAS-Pain	-0.219**	-0.156*	-0.116	-0.289**	0.331**	0.251**
sHAQ VAS-Raynaud's	-0.210**	-0.190*	-0.167*	-0.365**	0.318**	0.323**
VAS-Digital ulcer	-0.048	-0.067	0.047	-0.196*	0.158*	0.158*
VAS-Gastrointestinal	-0.124	-0.020	-0.010	-0.137	0.099	0.150
VAS-Lung function	-0.163*	-0.140	0.020	-0.193*	0.192*	0.153
VAS-Overall	-0.161*	-0.129	-0.017	-0.218**	0.245**	0.208**
VAS-Fatigue	-0.262**	-0.145	-0.176*	-0.327**	0.260**	0.291**
SF36-MCS	0.286**	0.254**	0.201*	0.444**	-0.445**	-0.347**
SF36-PCS	0.252**	0.253**	0.136	0.362**	-0.302**	-0.222**
Cochin Hand Scale	-0.178*	-0.193*	-0.153	-0.291**	0.283**	0.264**
Mouth Handicap in SSc	-0.087	-0.084	-0.011	-0.177*	0.213**	0.249**
FACIT-EWB	0.047	0.148	-0.043	0.068	-0.101	-0.085
FACIT-Fatigue Scale	0.186*	0.218**	0.157	0.308**	-0.283**	-0.222**
UCLA SCTC GIT 2.0	-0.070	-0.072	-0.019	-0.118	0.104	0.115
MES	0.006	0.137	0.101	0.070	-0.032	-0.034

Spearman correlation coefficient (rho), significance level **<0.01; *<0.05.
DLCO: diffusion capacity of carbon monoxide; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; sHAQ: scleroderma HAQ; VAS: visual analogue scale, SF36-MCS and PCS: Short Form 36: Mental and Physical Component Summary; FACIT: Functional Assessment of Chronic Illness Therapy; EWB: Emotional Well-Being; UCLA SCTC GIT 2.0: University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument 2.0; MES: Microangiopathy evolution score by nailfold video-capillaroscopy.

Results

Demographic data, clinical characteristics and the results of the cognitive tests of all participants are depicted in Table I. Parameters of physical condition, social indicators and results of all cognitive function tests showed significantly worse values for scleroderma patients when compared to controls. However, the differences between the SSc and healthy groups were more remarkable in tests, in which the participants relied on using their hands.

Patients' test results demonstrated inverse correlations with their age, SSc duration, visual analogue scales (VAS) indicating pain and Raynaud phenomenon, the left ventricular mass index and positive associations with educational levels, the extent of the Rodnan skin score, the muscle strength measurements, the 6MWT, the Mental Component Score of SF-36 and the physical functional indices ($p<0.01$, respectively) (Table II).

Regarding the Kruskal-Wallis test there was a significant difference in comparing the results of each cognitive test between the three SSc subgroups with

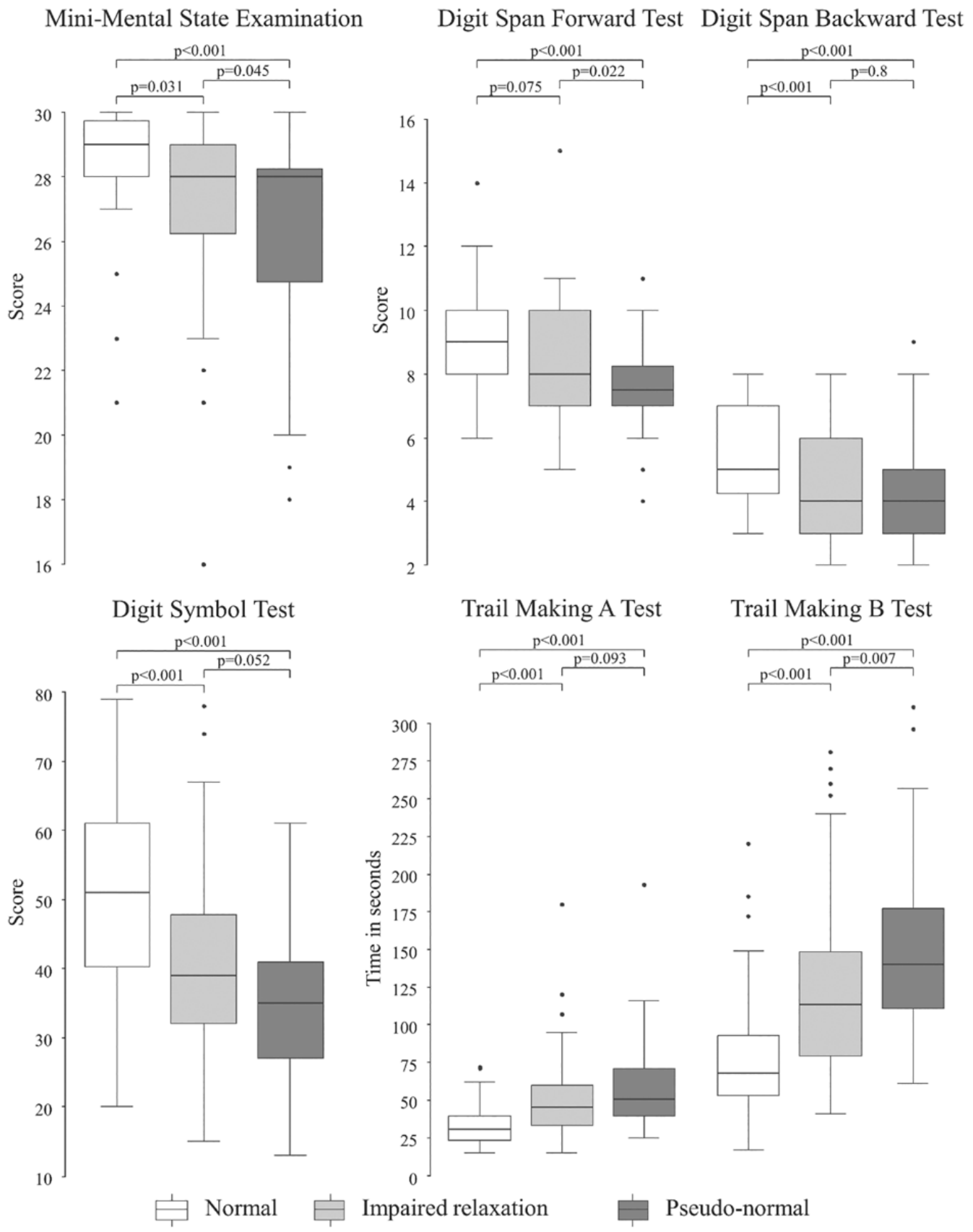

Fig. 1. Comparing the cognitive scores between the three subgroups suffering systemic sclerosis with normal diastolic function (n=50), impaired relaxation (n=66) and pseudo-normal diastolic mitral inflow curve (n=44).

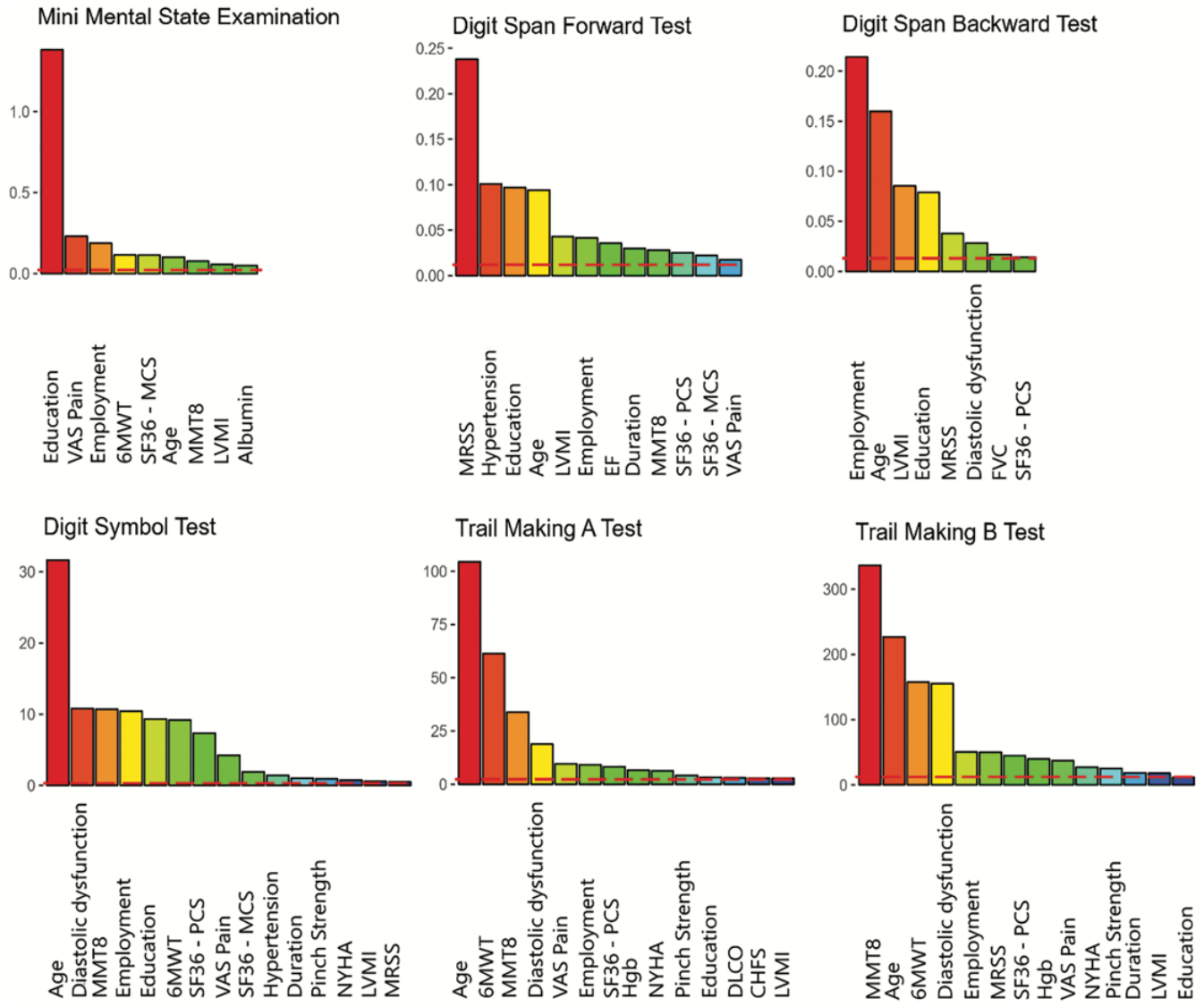

Fig. 2. Feature importance result of the Random Forest algorithm regarding cognitive test scores among 160 patients afflicted with systemic sclerosis. Feature importance values are given in arbitrary units. Only factors, which have significant impact on cognitive test scores are shown.
Diastolic dysfunction: based on left atrial size, left ventricular mass index (LVMI), mitral inflow pattern (E/A ratio) and calculated right ventricular systolic pressure.
VAS: visual analogue scale; 6MWT: Six-minute walk test; SF36-MCS and PCS: Short Form 36: Mental and Physical Component Summary; MMT8: Manual Muscle Testing-8; EF: ejection fraction; CHFS: Cochin Hand Function Scale; MRSS: modified Rodnan skin score; FVC: forced vital capacity; DLCO: diffusion capacity of carbon monoxide; NYHA: Stage of the New York Heart Association.

'normal diastolic function', 'impaired relaxation' and 'pseudo-normal diastolic mitral inflow curve' (Fig. 1).

All the continuous and categorical clinical variables of SSc patients depicted in Table 1 were ranked using a Random Forest algorithm regarding each investigated cognitive test. The order of importance of the factors significantly affecting the results of each test is presented in Figure 2. For each test, linear regression was performed with the selected significant factors. The level of education and the age of the individuals with SSc were independent influencing factors in the assessment of most tests (Table III). Perceived pain-VAS, muscle status determined by MMT8, the modified Rodnan's skin score showed independent influence for two cognitive tests, while hypertension, presence of NYHA III. cardiac stage, low left ventricular ejection fraction level, unemployment status, short 6MWT distance and low haemoglobin level showed independent risk for one test each, respectively. Of note, there were no correlations between the cognitive results and the gastrointestinal test scores, the presence of diabetes mellitus, the corticosteroid use, nor the conventional disease-modifying anti-rheumatic drugs (DMARDs) nor biological treatments.

It is noteworthy that mRSS was also an independent influencing factor for the Digit Span Forward and Trail Making B tests (Table III), so that those with higher skin scores had better cognitive test scores. However, SSc patients with higher skin score (mRSS≥10, n=50) were younger, had significantly shorter SSc duration, higher levels of education and their 6MWT distance were longer than the other patients, 474±136 *versus* 408±135 metre (p=0.001).

Table III. Linear regression models to define independent influential factors based on Random Forest analysis (Fig. 2) of the cognitive test results among160 patients with systemic sclerosis.

Mini-Mental State Examination

Predictors	Estimates	95% CI	*p*
Education	2.07	1.27, 2.87	**<0.001**
VAS - Pain	-0.011	-0.027, 0.005	0.166
Employment	-0.684	-1.62, 0.247	0.149
SF36 - MCS	0.015	-0.002, 0.033	0.089
LVMI	-0.013	-0.030, 0.005	0.149

R^2 = 0.338; Adjusted R^2 = 0.314; no. Obs. = 143

Digit Span Forward Test

Predictors	Estimates	95% CI	*p*
Education	0.962	0.344, 1.58	**0.003**
EF	0.079	0.018, 0.139	**0.011**
Hypertension	-0.856	-1.44, -0.267	**0.005**
mRSS	0.062	0.017, 0.107	**0.007**

R^2 = 0.267; Adjusted R^2 = 0.246; no. Obs. = 141

Digit Span Backward Test

Predictors	Estimates	95% CI	*p*
Education	0.938	0.429, 1.45	**<0.001**
Employment	-0.758	-1.38, -0.140	**0.017**
Age	-0.018	-0.041, 0.006	0.135
LVMI	-0.009	-0.020, 0.001	0.087

R^2 = 0.311; Adjusted R^2 = 0.291; no. Obs. = 144

Digit Symbol Test

Predictors	Estimates	95% CI	*p*
Education	7.42	3.76, 11.1	**<0.001**
VAS - Pain	-0.077	-0.141, -0.013	**0.019**
Age	-0.377	-0.535, -0.219	**<0.001**
MMT-8	0.232	0.097, 0.366	**<0.001**

R^2 = 0.525; Adjusted R^2 = 0.511; no. Obs. = 143

Trail Making A Test

Predictors	Estimates	95% CI	*p*
VAS - Pain	0.149	0.003, 0.296	**0.046**
6MWT	-0.039	-0.073, -0.005	**0.026**
Age	0.828	0.496, 1.16	**<0.001**
DLCO	-0.155	-0.373, 0.063	0.162

R^2 = 0.372; Adjusted R^2 = 0.354; no. Obs. = 143

Trail Making B Test

Predictors	Estimates	95% CI	*p*
Education	-13.8	-32.2, 4.62	0.141
Age	0.936	0.127, 1.75	**0.024**
MMT-8	-1.21	-1.86, -0.554	**<0.001**
mRSS	-1.51	-2.82, -0.190	**0.025**
Haemoglobin	-0.603	-1.20, -0.004	**0.049**
NYHA *st. 1*	0.000	—	
st. 2	-9.71	-29.3, 9.89	0.329
st. 3	35.4	2.86, 68.0	**0.033**

R^2 = 0.383; Adjusted R^2 = 0.355; no. Obs. = 142

Statistically significant results are highlighted in bold font.
VAS: visual analogue scale, SF36-MCS and PCS: Short Form 36 - Mental and Physical Component Summary; LVMI: left ventricular mass index; EF: ejection fraction; Diastolic dysfunction: based on left atrial size, LVMI, mitral inflow pattern (E/A ratio) and calculated right ventricular systolic pressure; mRSS: modified Rodnan skin score; 6MWT: Six-minute walk test; MMT8: Manual Muscle Testing-8; DLCO: diffusion capacity of carbon monoxide; NYHA: New York Heart Association.

Notably, using the MMSE test 37 (23%) out of the 160 individuals with SSc did not achieve the appropriate score (≥27 points out of 30), compared to healthy controls (5 out of 58), who reached a lower score. Those patients who scored below 27 points were older (61.4±7.9 *vs*. 54.1±13.8 years), their disease duration was longer (13.7±8.4 *vs*. 9.6±7.1 years), and there was a significant difference in the 6MWT distance, MMT8 and LVMI (p<0.01, respectively), VAS-pain and the HAQ-DI (p<0.05, respectively). However, there were no differences in other investigated parameters including the degree of education compared to other patients.

There were no associations between cognitive results and the MES, the capillary density and early-active-late capillaroscopic pattern among participants (data not shown).

All cognitive tests were performed with better results by those who were employed (n=47), compared to those who were unemployed (n=47) among the 94 SSc patients in working age (<62 years), as follows: in MMSE p=0.006, in Digit Span Forward p=0.046, in Digit Span Backward, in Digit Symbol and Trail Making B p<0.001, respectively, and in Trail Making A p=0.001.

SSc patients, with shorter disease duration (≤4 years, n=51), performed better when compared to individuals with longer duration (n=109) in tests including the MMSE (p=0.002), the Digit Symbol (p=0.002), the Trail Making A (p<0.001) and B (p=0.001) tests, while at the Digit Span Forward and Backward tests, there were no differences (data not shown).

Among the 72 patients with lcSSc, their average age and disease duration (59.9±9.7 and 12.8±8.0 years) were several years higher than the 88 patients with dcSSc (52.3±14.6 and 8.7±6.7) (p<0.001 in both cases). DcSSc patients achieved significantly better results in tests than lcSSc individuals, except for the MMSE, which were similar in both groups. The dcSSc group achieved higher scores in both summary scores of the SF-36 (p<0.05) and were able to walk longer distances, 478 (173) *versus* 400 (183) meter median (IQR), (p=0.036) during the 6MWT, than the lcSSc group.

Table IV. Clinical, demographical characteristics and cognitive tests' results of high-school graduated patients with systemic sclerosis (SSc) and healthy controls.

	SSc (n=67)	Controls (n=48)	*p*
Female subjects, n (%)	56 (83.6)	40 (83.3)	0.972
Age, years, mean (SD)	49.7 (15.1)	52.1 (13.5)	0.379
Disease duration, years, mean (SD)	8.6 (6.3)	NA	-
Diffuse cutaneous SSc, n (%)	47 (70.1)	NA	-
Body mass index, kg/m^2, mean (SD)	25.5 (5.2)	26.6 (4.6)	0.262
Modified Rodnan skin score ≥14, n (%)	19 (28.4)	NA	-
Cardiac involvement, n (%)‡	43 (64.2)	NA	-
Interstitial lung disease by HRCT, n (%)	46 (68.7)	Not done	-
Six-minute walk test, m†	491 (391; 572)	615 (564; 638)	**<0.001**
UCLA SCTC GIT 2.0, (0-3)†	0.2 (0.1; 0.4)	0.04 (0; 0.2)	**0.001**
Haemoglobin, g/L†	136 (126.0; 144.0)	142 (131.0; 148.0)	**0.017**
Albumin, g/L†	45.1 (43.1; 48.3)	48 (45.2; 49.6)	**0.005**
Revised EUSTAR Activity Index†	2.5 (1.3; 4.2)	NA	-
HAQ-DI, (0-3)†	0.3 (0; 1.1)	0 (0; 0)	**<0.001**
Manual Muscle Testing-8, (0-150)†	126 (115; 134)	139 (124; 143.5)	**<0.001**
Pinch strength, N†	66.7 (46.7; 78.3)	70.0 (61.7; 78.3)	0.137
Cochin Hand Function Scale, (0-90)†	2 (0; 10)	0 (0; 0)	**<0.001**
Smoker ever, n (%)	28 (41.8)	21 (45.7)	0.684
Employed, n (%)	33 (49.3)	32 (66.7)	0.063
Living alone, n (%)	27 (40.3)	20 (41.7)	0.883
Sleeping disorder, n (%)	23 (34.3)	14 (31.8)	0.784
FACIT-Fatigue Scale, (0-52)†	40.5 (30; 49)	48 (44.5; 50)	**0.001**
FACIT-Emotional Well-Being, (0-24)†	19.6 (16; 22)	21 (20; 23)	**0.007**
SF36-Mental Summary, (0-100)†	75.9 (46; 88)	85.7 (75.0; 94.3)	**0.002**
SF36-Physical Summary, (0-100)†	58.3 (34; 83.6)	92.9 (81.4; 95.6)	**<0.001**
Mini-Mental State Examination, (0-30)†	29 (28; 30)	29 (28; 29)	0.792
Digit Span Forward Test, (0-16)†	9 (8; 11)	10 (8; 11)	0.390
Digit Span Backward Test, (0-14)†	6 (5; 7)	6 (5; 7)	0.441
Digit Symbol Test, (0-90)†	48 (40.5; 61)	58 (48.5; 64)	**0.006**
Trail Making A Test, (s)†	36 (25; 46.9)	25 (21; 35.5)	**0.004**
Trail Making B Test, (s)†	85 (60; 120)	56 (45; 84)	**<0.001**

†Median (25th; 75th percentiles); statistically significant results are highlighted in bold font.
‡Conduction defects, arrhythmias, pericarditis, myocardial ischaemia on ECG, diastolic dysfunction and/or pulmonary arterial hypertension.
HRCT: high-resolution computed tomography; EUSTAR: European Scleroderma Trials and Research Group; DLCO: diffusion capacity of carbon monoxide; UCLA SCTC GIT 2.0: University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument 2.0; HAQ-DI: Health Assessment Questionnaire Disability Index; FACIT: Functional Assessment of Chronic Illness Therapy; SF36: Short Form 36.

There was no significant difference in the cognitive values between the serological subsets, as seen in the following, SSc patients with the presence of anti-DNA-topoisomerase1 (n=38), with anticentromere (n=33), with RNA-polymerase 3 (n=21).

Comparison of the high school graduate groups

To eliminate the influence of education, regarding the results of the cognitive tests, only high school graduated scleroderma patients (n=67) and healthy controls (n=48), were compared and are presented in Table IV. The average age, gender rate, prevalence of social and emotional factors did not differ in these higher-educated groups. Mostly, the Trail Making A, B and the Digit Symbol Tests showed (p<0.05) worse results in the SSc group.

The cognitive test results of high school graduated SSc patients with good hand functionality (CHFS<2, n=34) were also compared to healthy individuals (CHFS=0, n=48), and only the Trail Making A and B Tests exhibited (p<0.05) worse results, again in the SSc group (data not shown). However, the results of the other tests were similar in patients and healthy subjects.

Repeated cognitive results following 12 months in patients with SSc (n=142)

Median values of the MMSE and the Digit Span Backward tests were not altered among the patients following the first year. However, the Digit Span Forward, the Digit symbol and the Trail Making A and B tests' results all showed notable improvement (p<0.001, respectively). In reviewing the differences in the MMSE, it's delta-value was significantly correlated with the delta-value of the 6MWT of the patients (p=0.002, rho=0.259).

Discussion

In this single-centre investigation, SSc individuals performed cognitive tests generally worse when compared to healthy matched controls. Furthermore, patients' age, the level of education, disease duration and presence of hypertension are commonly known influential factors of the cognitive abilities in chronic diseases (11, 29, 30, 31), which we confirmed in our study. In this current research, in addition to these, the strength of patients' pain perception, their employment, indicators of the physical condition, level of haemoglobin and cardiac function were independent factors affecting their cognitive abilities (Table III). After the one-year follow-up, changes in the MMSE results were significantly correlated with the changes in the 6MWT in SSc patients.

In previous clinical studies, the prevalence of cognitive impairment ranged from 8.5 to 65% (3-5, 11, 29) among individuals with SSc. The wide range may be explained due to the variable methods and interpretation of results. In 2020, Khedr *et al*. (11) reported using the MMSE in which 13 of 20 patients with SSc (65%) scored below the normal range. Cognitive impairment was significantly associated with the Medsger vascular severity score and duration of the illness. In our study, cognitive dysfunction was found in 23% of SSc patients based on the MMSE. This is also considerably a high rate; however, our patients were much better educated, all literate, and clinical data showed that more of our patients were less severe.

Chen *et al*. (29) detected mild cognitive impairment in 56% of 106 SSc patients using the Patient-Reported Outcomes Measurement Information System 8a Short Form (PROMIS SF 8a). In their study, elderly age, work disability and

fatigue were strongly associated with cognitive impairment (29). In our study, age and unemployment status had great influence and fatigue only a mild effect on cognitive decline. (Table II and III).

Since late-stage (>4 years) SSc individuals performed worse on several tests than early-stage SSc patients, cognitive function is certainly not an early complication.

Previous research identified cerebral microvascular damage as the underlying cause of cognitive impairment (4-7). Patients with SSc have an increased risk of generalised vascular injury, chronic anaemia, cardiac and muscle fibrosis, which may also cause a certain level of chronic hypoxia in the brain. In our observation, the presence of systemic hypertension, the consequently increased left ventricular mass index (LVMI) (32) and diastolic dysfunction were also significantly associated with lower cognitive abilities (Table II, Fig. 1). Additionally, cardiovascular performance can be measured using the 6MWT (33), which also showed a consistent correlation with the result of each cognitive test (Table II).

Similarly, to earlier investigations (5, 6), in this study, the cognitive results were not associated with the morphological parameters of the peripheral microvasculature, which were investigated by nailfold video-capillaroscopy.

Sociodemographic and psychological factors have also been shown to influence cognitive test performance (31, 34). Alexopoulos *et al*. (31) reported that depression symptoms were inversely related to performance on tasks assessing prospective memory, working memory, verbal fluency and concentration in patients with SSc. Santiago and colleagues (34) showed that happiness is related to the perceived impact of illness, which is buffered by the effects of "positive" personality, as observed in their clinical trial. In our study, cognitive results and parameters of the mental health score had positive correlations using the SF-36 questionnaire. However, we observed that there were only mild level correlations between the cognitive test scores and the severity of emotional disorders using the FACIT-EWB and FACIT-Fatigue Scale questionnaires. Based on the Mouth Handicap in SSc (MHISS) the difficulties of self-acceptance also had only a slight influence on the success of the cognitive tasks (Table II, III, Fig. 2).

The Mini-Mental test is primarily used to detect early dementia (35). SSc patients' difficulties in solving complicated tasks was a typical abnormality similar to other patients with chronic rheumatic diseases (36-38). The educational and SSc duration bore the greatest impact on the results of MMSE, which our study confirmed. When comparing the higher-educated subgroups of SSc and healthy controls, there was no difference in the results of MMSE (Table IV).

The simple short-term working memory was relatively spared in patients with SSc (Table IV), similarly in study of Giuliodori *et al*. (4), as all subsets showed good results in the Digit Span Forward test. However, in investigation of Yilmaz *et al*. (38), both rheumatoid arthritis and SSc patient groups had shorter forward and backward digit spans than did the healthy controls, an indication of poorer global attention or vigilance.

The Digit Span Backward was the most difficult in measuring working memory and may be the most efficient in differentiating regarding this aspect (4, 38). Solving the Digit Symbol and Trail Making A and B tests requires greater concentration and a higher level of thinking, which were performed slower and poorer, even among scleroderma patients with good hand function, when compared to the healthy groups. The performance of SSc patients in these two particular tests, strongly correlated with 6MWT, suggesting that impaired cardiorespiratory function caused may be an important contributor to the poor performance in these particular cognitive tests (Table II).

Among our SSc patients with poorer cognitive function based on all tests' scores had significantly poorer muscle strength measured by MMT8. Decreased MMT performance may be an indicator of hypoxia (Table II, III, Fig. 1). The literature suggests that sarcopenia and cognitive decline share pathophysiological pathways (39). We confirmed these observations. Microangiopathy and consequent tissue hypoxia is an important contributing factor of scleroderma myopathy in patients with SSc (40).

Limitations of this study include the relatively small number of cases in a single centre, considering the many subgroups. The strength of the study is the extensive cognitive and clinical investigations of the SSc patients in two sessions in a one-year follow-up study.

Conclusion

Simple memory functions were well preserved in SSc patients when compared to healthy controls. However, more difficult cognitive tasks, which require rapid psychomotor tempo and increased concentration, showed worse performance, especially in elderly SSc individuals. Previous research has identified cerebral microvascular damage as underlying cognitive impairment. This study highlights also the risks of chronic hypertension, diastolic dysfunction, anaemia and deteriorated muscle function in the development of cognitive deterioration. At the onset of the disease, there is no cognitive impairment, even in severe patients with dcSSc. However, later on, generalised vascular injury gradually develops, leading to a degree of chronic hypoxia affecting the muscles of the entire body, which contributes to the development of mild cognitive impairment in patients with SSc. This explains why cognitive function results showed a significant correlation with hypoxia-related factors including haemoglobin level, hypertension, the impaired diastolic function, cardiovascular function and muscle strength.

Key messages

- In the early stages of the disease, no cognitive impairment was present, even in patients with diffuse cutaneous systemic sclerosis (SSc).
- Simple memory functions were well preserved in SSc patients.
- In addition to known factors, the cognitive abilities of SSc patients were strongly correlated with their pain perception, employment, cardiovascular and physical function.

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