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# Six-minute walk distance as a marker for disability and complaints in patients with systemic sclerosis

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**Key words:** six-minute walk test, six-minute walk distance, SHAQ, systemic sclerosis, quality of life

## ABSTRACT

**Background.** The role of the six-minute walk distance (6MWD), measured by a six-minute walk test (6MWT), in the assessment of systemic sclerosis (SSc) patients remains to be evaluated. Here, we have analysed whether 6MWD is associated with clinical parameters obtained by an extended standardised assessment of SSc patients.

**Methods.** In 101 consecutive SSc patients, 6MWD was correlated with disease activity, Scleroderma Health Assessment Questionnaire (SHAQ) score, nutrition status, age, ESR, haemoglobin values, and several lung function parameters.

**Results.** Of the 101 SSc patients, 6 patients were excluded because of diseases that could influence the result of the 6MWT, such as asthma, COPD or peripheral vascular disease. In the remaining 95 patients the median 6MWD was 491.0 m (range 86.0–664.5 m). 6MWD weakly-to-moderately correlated with predicted FVC, FEV1, TLC, DLCO and nutrition status. Moderate negative correlations were found for the SHAQ score and disease activity, weaker correlations for age and BMI. Exclusion of patients with musculoskeletal limitations revealed similar results. Training status of the patients did not affect 6MWD. Multivariate analyses revealed SHAQ score and predicted DLCO values as the best parameters predicting 6MWD. Optimal 6MWD cut-off values for the presence of PAH, predicted FVC values <80%, and dyspnea NYHA III / IV were between 465 m and 480 m.

**Conclusion.** 6MWD is a surrogate marker for disability and complaints in SSc patients. Therefore, 6MWT could provide a valuable outcome parameter although it lacks organ specificity.

## Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease characterised by

tissue fibrosis leading to vascular injury, skin fibrosis, and involvement of heart, lung, kidney, and the gastrointestinal tract (1). Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading causes of disease-related morbidity and mortality (2). Therefore, early detection and management of pulmonary and cardiac involvement and accurate measures for therapeutic outcome are required.

SSc patients, especially those with pulmonary involvement, have a reduced exercise capacity (3–5). A simple test to evaluate submaximal exercise capacity is the 6-minute walk test (6MWT) which is a safe, non-invasive and reproducible test reflecting the effort required for daily physical activities (6). Originally developed for patients with heart failure and pulmonary diseases, the 6MWT has been increasingly used as an outcome measure in clinical trials for SSc (7, 8). Correlations between clinical parameters and 6MWD are weak if present at all (9–11). This could reflect the individual combination and severity of cardiac, pulmonary, or other organ involvements. The different confounders probably limit specificity for PAH or ILD and, therefore, the value as an outcome parameter in clinical studies addressing one particular disease manifestation. On the other hand, 6MWT is easily performed and highly reproducible in SSc patients. Furthermore, lung function parameters, often used as outcome parameter in clinical studies, do not correlate with disability and quality of life (12). Therefore, there is a need for better outcome parameters addressing quality of life and disability (13, 14). We hypothesize that the result of the 6MWT would reflect disability as assessed by the SHAQ score and could be used as a surrogate marker for the patients' multiple complaints.

There are only few studies analysing the cut-off value to identify an abnor-

Competing interests: none declared.

mal 6MWD and most authors use the reference equation by Enright *et al.* analysing data of 117 male and 173 female healthy Americans (15). It remains to be discussed whether these cut-off values can also be used in SSc patients or whether SSc-specific cut-off levels would add further information. At present, these data on consecutive SSc patients are missing.

Therefore, the aim of this study was to evaluate the 6MWT in a consecutive cohort of 101 SSc patients to identify clinical or laboratory parameters including the nutrition status or the physical activity with impact on 6MWD and to identify disease-specific cut-off values useful for risk stratification.

## Materials and methods

### Patient population

We performed a 6MWT in 101 consecutive Caucasian patients diagnosed with SSc according to the American College of Rheumatology criteria (16) who attended the Scleroderma Outpatient Clinic between October 2006 and March 2007. The patients were classified as diffuse or limited SSc (17). The study was approved by the local ethics committee (EA1/103/07) and the patients were included in the study after informed consent.

6MWT was performed and documented according to the American Thoracic Society guidelines (6). It was undertaken at room air conditions without additional oxygen by the same tester throughout the study. Blood pressure, heart rate and Borg Dyspnea Indices were measured at baseline and after the 6MWT, and the body mass index (BMI) was calculated.

After the test the patients were asked what, if anything, would have kept them from walking farther. Answer categories were (1) no limitation, (2) dyspnea, (3) lower body pain, (4) dizziness, (5) angina pectoris.

Furthermore the patients were asked about their smoking habits and regular physical activity and categorised into three groups: (1) no endurance sports, (2) endurance sports less than 1 hour per week, (3) endurance sports more than 1 hour per week. Disciplines such as running, walking, swimming or cy-

**Table I.** Patient characteristics and epidemiologic data.

|                                                                            |                    |
|----------------------------------------------------------------------------|--------------------|
| Males / females                                                            | 10 / 85            |
| ISSc / dSSc                                                                | 61 / 34            |
| Age (years), median (range)                                                | 56.0 (25–80)       |
| Disease duration since Raynaud's phenomenon (years), median (range)        | 10.0 (0–46)        |
| Disease duration since first non-Raynaud's symptom (years), median (range) | 7.0 (0–34)         |
| BMI (kg/m <sup>2</sup> ), median (range)                                   | 23.0 (18–38)       |
| Phase angle values, median (range)                                         | 5.2 (3.2–6.3)      |
| Haemoglobin (g/dl), median (range)                                         | 13.3 (9.5–16.4)    |
| ESR (mm/1 hour), median (range)                                            | 18.0 (4–100)       |
| CRP elevated, n (%)                                                        | 7 (7.4)            |
| Creatine kinase elevated, n (%)                                            | 1 (1.1)            |
| Antinuclear antibodies, n (%)                                              | 90 (94.7)          |
| Anti-Centromere antibodies, n (%)                                          | 32 (33.7)          |
| Anti-Topoisomerase I- antibodies, n (%)                                    | 14 (14.7)          |
| NYHA classification I, n (%)                                               | 44 (46.3)          |
| II                                                                         | 24 (25.3)          |
| III                                                                        | 5 (5.3)            |
| IV                                                                         | 22 (23.2)          |
| % pred FVC, median (range)                                                 | 98.95 (55.6–128.2) |
| % pred FEV1, median (range)                                                | 99.4 (56.7–137.1)  |
| % pred TLC, median (range)                                                 | 99.0 (58.7–144.6)  |
| % pred DLCO, median (range)                                                | 71.9 (20.7–112.2)  |
| % pred DLCO / VA, median (range)                                           | 83.0 (29.2–108.6)  |
| Interstitial lung disease, n (%)                                           | 31 (32.6)          |
| PAH by echocardiography, n (%)                                             | 19 (20.0)          |
| EF (%), median (range)                                                     | 60 (20.0–77.0)     |
| Reduced EF, n (%)                                                          | 2 (2.1)            |
| Left ventricular diastolic dysfunction, n (%)                              | 42 (44.2)          |
| MRSS, median (range)                                                       | 4.0 (0–26)         |
| Musculoskeletal involvement, n (%)                                         | 64.0 (67.4)        |
| Active digital ulcers, n (%)                                               | 11 (11.6)          |
| Digital ulcers in the past, n (%)                                          | 45 (47.4)          |
| Disease activity, median (range)                                           | 1.0 (0–7.5)        |
| SHAQ score, median (range)                                                 | 0.68 (0–2.73)      |

cling were considered as endurance sports.

We retrospectively evaluated clinical parameters within 6 months of the 6MWT including pulmonary function testing, echocardiography, chest x-ray and high resolution computer tomography. Pulmonary function test included FVC, FEV1, RV, TLC, DLCO and DLCO/VA. Pulmonary arterial hypertension was diagnosed by echocardiography (pulmonary arterial systolic pressure  $\geq 45$  mmHg and sign for right heart failure) as right heart catheterisation was not available in all patients. Furthermore, bioelectrical impedance analysis (BIA) was performed in some patients (n=40) providing phase angle (PhA) values to measure nutrition sta-

tus and body composition. As already shown, PhA values predict mortality better than several other parameters in SSc (18).

Quality of life was evaluated using the Scleroderma Health Assessment Questionnaire (SHAQ) (19, 20). SHAQ score was calculated as described (21). Briefly, 5 visual analogue scales, addressing the complaints in scleroderma, were added to HAQ-DI, originally developed for patients with rheumatoid arthritis. The total sum was divided by the number of answered categories. For the visual analogue scales, each scale a 15 cm, 1 cm was defined as 0.2 points. Disease activity was examined using the Valentini Disease Activity Index (22). Skin involvement was evaluated

using the Modified Rodnan Skin Score (MRSS) (23). Musculoskeletal involvement was defined as synovitis, tendon friction rubs, joint contractures, muscle weakness, muscle atrophy or CK elevation more than 3 times above upper limits. Laboratory parameters included hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine kinase (CK), and autoantibodies. Patient's characteristics and epidemiologic data are shown in Table I.

### Statistical analyses

As the data failed to be distributed normally, median and range were calculated. Comparisons among different groups were made using Mann-Whitney-U or Kruskal-Wallis test. Spearman's correlation test was used to determine any correlation between the 6MWD and clinical parameters. To analyse the contributive factors to the 6MWD clinical and laboratory parameters were inserted in a logistic regression model as independent variables and stepwise logistic regression was performed as described (15). Receiver operating characteristic curves were plotted and respective cut-off levels for the presence of PAH or other parameters were determined.

## Results

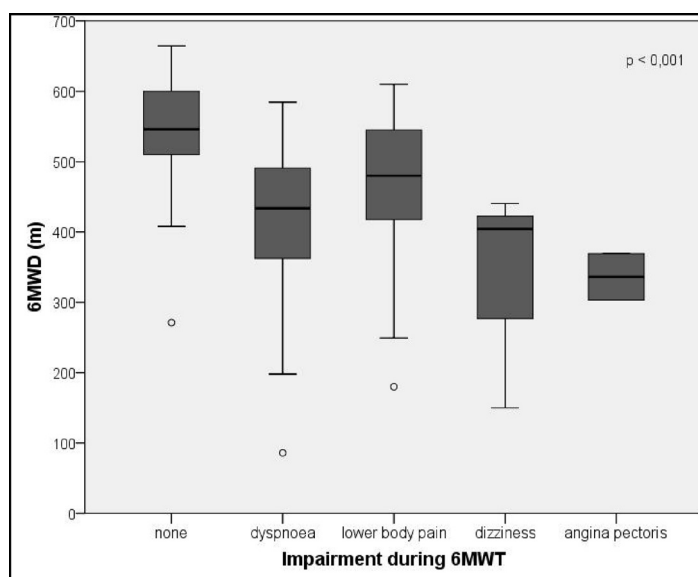
### Results of 6MWT

Of the 101 patients studied by 6MWT, 6 were excluded because of concomitant diseases such as asthma, COPD, or peripheral vascular disease.

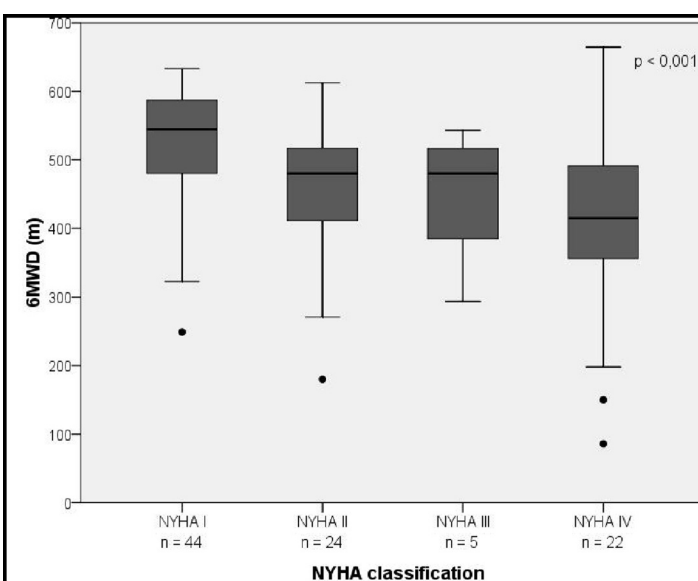
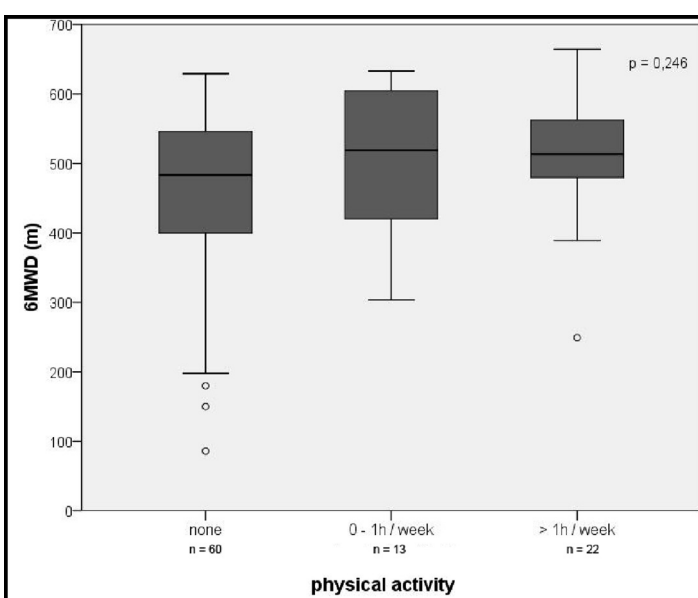
Median 6MWD was 491.0 m (range 86.0–664.5). As expected, there were significant differences in the Borg Dyspnea Index, heart rate (HR), and in the systolic and diastolic blood pressure before and after 6MWT (data not shown). Median Borg Dyspnea Index was 0 (range 0–5.0) before and 2.0 (range 0–8.0) after the walking test ( $p < 0.001$ ). 6MWD correlated negatively with Borg Dyspnea Index before ( $r = -0.357$ ;  $p < 0.001$ ) and after ( $r = -0.337$ ;  $p < 0.01$ ) 6MWT (data not shown).

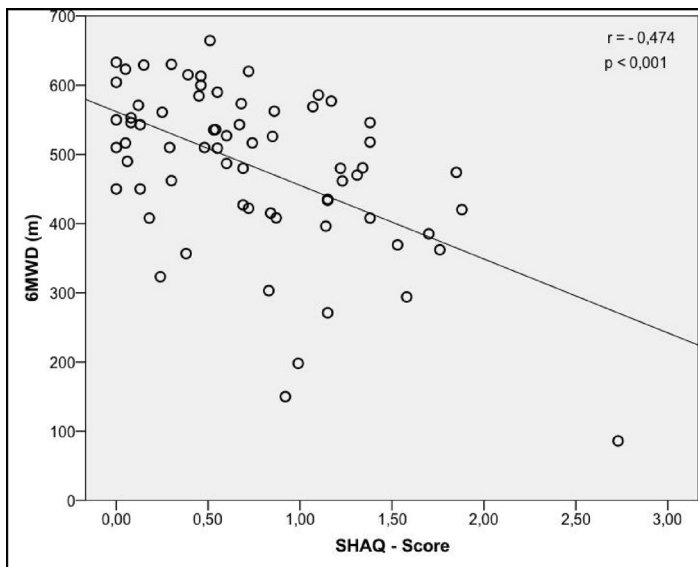
When asked what impaired them the most during the 6MWT, 38 patients felt no impairment (40%), 25 patients felt dyspnea (26.3%), 27 patients had lower body pain (28.4%), 3 felt dizzy

**Fig. 1.** Relation between 6MWD and the clinical symptoms that limited most the result of the 6MWT. Significance was tested by Kruskal – Wallis test.



**Fig. 2.** 6MWD is not significantly influenced by the level of physical activity that is in general low in systemic sclerosis (Fig. 2a). In contrast, there is an association between NYHA class and the results of 6MWT (Fig. 2b).





**Fig. 3.** Correlation between 6MWD and SHAQ score

**Table II.** Spearman's correlation between 6MWD and pulmonary function parameters. Correlation coefficient (r) and *p*-value levels (p) are shown.

|                                                                                       | FVC                        | FEV1                       | RV                          | TLC                        | DLCO                       | DLCO/VA                     |
|---------------------------------------------------------------------------------------|----------------------------|----------------------------|-----------------------------|----------------------------|----------------------------|-----------------------------|
| 6MWD                                                                                  | r=0.309;<br><i>p</i> <0.01 | r=0.225;<br><i>p</i> <0.05 | r=0.168;<br><i>p</i> =0.145 | r=0.348;<br><i>p</i> <0.01 | r=0.336;<br><i>p</i> <0.01 | r=0.125;<br><i>p</i> =0.314 |
| Correlation after exclusion of all patients with lower body pain during 6MWT (n = 68) |                            |                            |                             |                            |                            |                             |
| 6MWD                                                                                  | r=0.293;<br><i>p</i> <0.05 | r=0.270;<br><i>p</i> <0.05 | r=0.232;<br><i>p</i> =0.091 | r=0.417;<br><i>p</i> <0.01 | r=0.354;<br><i>p</i> <0.01 | r=0.192;<br><i>p</i> =0.208 |

(3.2%) and 2 suffered from angina pectoris (2.1%). The Kruskal-Wallis test showed significant differences in 6MWD between these five groups (*p*<0.001, Fig. 1).

#### General determinants of 6MWT

6MWD correlated negatively with age (*r*=−0.293; *p*<0.01) and BMI (*r*=−0.312; *p*<0.01). In line with this, there was a moderate correlation between 6MWD and phase angle values (*r*=0.350; *p*<0.05) for those few patients in which this parameter was obtained. No significant differences in 6MWD were evident between men and women or smokers and non-smokers.

When asked about their physical activity 60 patients (63.2%) did no endurance sports at all, 13 patients (12.7%) did up to one hour a week and 22 patients (23.2%) more than one hour a week (Fig. 2a). No significant differences in 6MWD could be detected in patients practicing regular physical activity compared to patients who did no endurance sports (*p*=0.25, Fig.

2a). In contrast, the 6MWD decreased from NYHA functional class I to IV (*p*<0.001, Fig. 2b).

#### Disease-specific determinants of 6MWT

There were no significant differences in 6MWD between patients with ISSc and dSSc although patients with dSSc complained more about dyspnea and lower body pain during the 6MWT. Disease duration since first Raynaud's phenomenon and disease duration since first non-Raynaud's symptom did not correlate with 6MWD.

In contrast, 6MWD correlated negatively with disease activity (*r*=−0.321; *p*<0.01) and the SHAQ score (*r*=−0.474; *p*<0.001, Fig. 3). Furthermore, 6MWD weakly correlated with predicted FVC (*r*=0.309; *p*<0.01), FEV1 (*r*=0.225; *p*<0.05), TLC (*r*=0.348; *p*<0.01), and DLCO values (*r*=0.336; *p*<0.01). There was no correlation between 6MWD and predicted DLCO/VA (Table II).

After exclusion of all patients that suffered from lower body pain during the

6MWT correlations between 6MWD and pulmonary function parameters did not change much (Table II).

Patients with PAH revealed a lower 6MWD compared to patients without PAH (median 433.4 m; range 150.0–620.0 m versus 512.9 m; range 86.0–664.5 m, respectively, *p*<0.01). There were no significant differences in 6MWD between patients with interstitial lung disease or left ventricular diastolic dysfunction compared to patients without these disease manifestations. Furthermore we found no correlation between 6MWD and the ejection fraction.

Patients with musculoskeletal involvement achieved a shorter 6MWD (median 480.3 m) compared to patients without musculoskeletal involvement (median 536.0 m), although this difference was not significant (*p*=0.072). No correlation was evident between 6MWD and the modified Rodnan Skin Score, and the 6MWD was not significantly lower in patients with active digital ulcers or digital ulcers in the past. 6MWD also did not correlate with haemoglobin levels or ESR and there were no significant differences in 6MWD depending on autoantibody profiles or elevation of CRP or CK.

#### Prediction value of 6MWD

Stepwise multivariate logistic regression for prediction of the 6MWD as a categorical variable (normal vs. abnormal according to Enright *et al.* (15)) showed a significant (*p*<0.001) model consisting of SHAQ score and predicted DLCO levels (Table III). The Odds ratio was 10.8 for having an abnormal 6MWD. Increase in SHAQ values by one unit would increase the risk for abnormal 6MWD about 10-fold. In addition, reduction in the predicted DLCO values by 1% would increase the risk for abnormal 6MWD (OR 0.95). This model reached a variance explanation of 45.4% and predicted 80.7% of the values for the dependent variable correctly.

As detected by ROC analysis, 6MWD of 466.5 m was the best cut-off to identify patients with predicted FVC values <80% with the optimal sensitivity of 71.2% and the optimal specificity

**Table III.** Logistic regression for prediction of the 6MWD as a categorical variable.

|            | Regression coefficient B | standard error | p-value | Odds Ratio | 95 % CI for Exp (B) |
|------------|--------------------------|----------------|---------|------------|---------------------|
| SHAQ score | 2.383                    | 0.757          | 0.002   | 10.832     | 2.457 – 47.759      |
| DLCO       | - 0.50                   | 0.025          | 0.045   | 0.951      | 0.906 – 0.999       |

city of 75% (Fig. 4a). Similar results were also obtained for the prediction of NYHA class III or IV for which the optimal cut-off was 477 m (sensitivity 69.1% and specificity 66.1%, Fig. 4b). Here, optimal 6MWD cut-off with the highest specificity (77.8%) was 509.5 m providing a sensitivity of 57.4%. The best sensitivity was 80.9% when a 6MWD cut-off of 434.2 m was chosen (specificity 55.6%). For the identification of patients with PAH, a 6MWD of 473 m was the optimal cut-off (Fig. 4c) providing the best sensitivity and specificity (68.4% and 73.7%). However, the most predictive values found were relatively low.

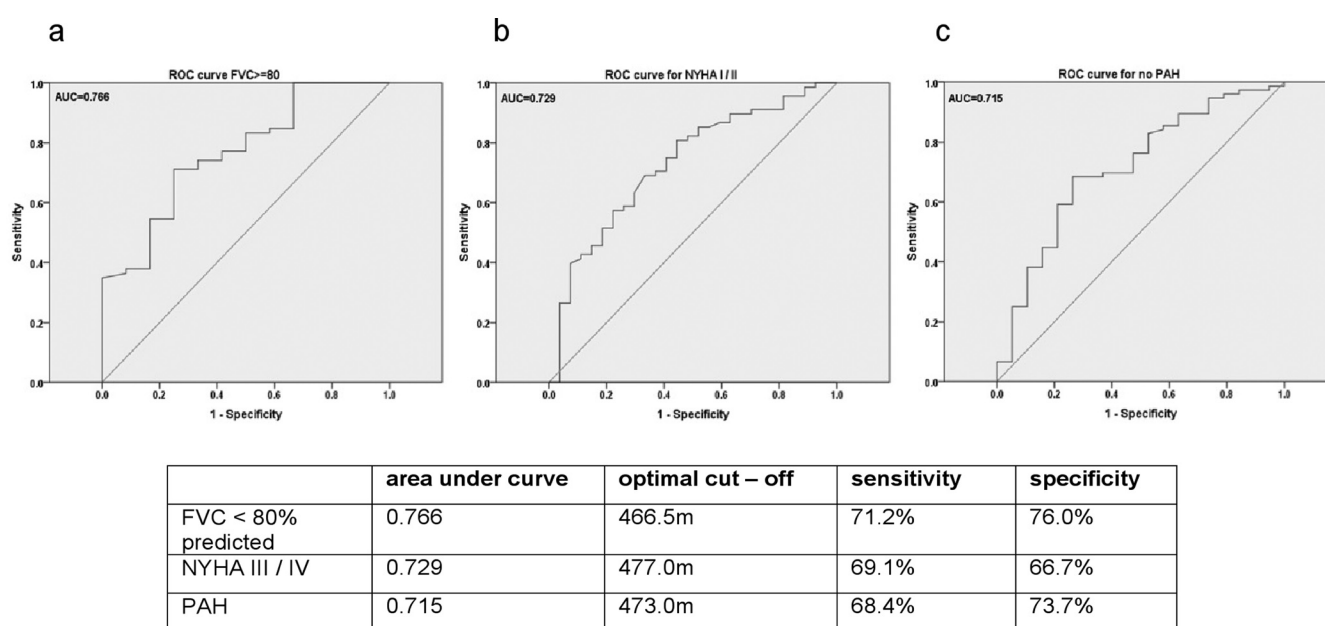
### Discussion

The 6MWT is a simple test to evaluate exercise capacity and is an often used instrument in clinical trials on cardiac and pulmonary disease manifestations. In SSs, 6MWT might not be suitable for the assessment of specific organ dam-

age, as suggested by the lack of specificity, as an outcome parameter which is influenced by multiple disease-specific confounding factors (24). On the other hand, there is a need for outcome parameters that really meet the disability and the multiple problems of SS patients (14). For this purpose, we have compared the results of the 6MWT with several clinical and laboratory data including NYHA class and SHAQ scores in a large group of consecutive SS patients not performed before. We also have assessed the physical activity in SS patients, their musculoskeletal complaints, and the limitation of the patients keeping them from walking farther. As shown here, 6MWD correlated well with SHAQ score. Furthermore, there was a moderate correlation with phase angle values as marker for body composition and nutrition status. There were only weak associations with lung function parameters. Musculoskeletal involvement was no major

confounder for a reduced 6MWD. In addition, physical activity did not affect 6MWD in our patients. Exclusion of all patients with lower body pain did not change the results significantly and correlations with clinical markers did not change. In the assessed cohort 6MWD reflected NYHA classification in SS patients which has not been reported before. Stepwise logistic regression revealed SHAQ score and predicted DLCO levels as the best parameters to identify abnormal 6MWT. 6MWD has moderate capacity to identify patients with signs of severe organ involvement such as restrictive ILD (reflected by FVC values <80%), PAH, or dyspnea NYHA class III or IV.

At present, 6MWT in SS patients is mainly performed as outcome parameter in clinical studies for therapies of certain disease manifestations such as ILD or PAH or in a subgroup of SS patients without confounding factors such as articular disabilities (9-11). At present, there is only one study analyzing 6MWT in 87 consecutive SS patients that were broadly assessed for different clinical parameters (24). In this study from a French cohort, 6MWD was categorised into normal or abnormal according to the first ref-



**Fig. 4.** Receiver operating characteristic curves assessing the best cut-off levels for 6MWD to identify patients with predicted FVC values <80%, dyspnea NYHA III / IV, or PAH. Area under curve and mathematical optimal 6MWD cut-off levels with the corresponding sensitivity and specificity are shown in the table.

erence equation by Enright and Sherill analysing data of 117 male and 173 female healthy Americans (15). C-reactive protein and calcinosis were the only independent variables associated with abnormal 6MWT (24). Therefore, the authors raised doubts about the specificity of the 6MWD in SSc. Although the cut-off levels provided by Enright *et al.* are often used, there is a relative lack of reference values for 6MWT. The results of 6MWT depend on height, weight and age, however; the authors also stated that about 60% of the variance in 6MWD remains unexplained and in this group of healthy persons, exercise habits, conditioning, and presence of musculoskeletal problems were not assessed (15). Similar to other studies, age and BMI were general determinants of the 6MWD (10, 15, 25). As shown here, 6MWD correlated with nutrition status and body composition which is also variable in different cultures. Furthermore, the results of the 6MWT in healthy persons differ between different studies and ethnicity may also have an influence (26–28). Therefore, we used the 6MWD as continuous variable to identify clinical confounders. According to this, gender, smoking habits or physical training had no significant influence on the 6MWD, which argues against these parameters as confounders for the analysis of associations between 6MWD and clinical parameters at least in SSc patients. Furthermore, we have investigated the limitations of the patients influencing the results of 6MWT from patient's perspective and have analysed whether those complaints affect the 6MWD and associations with disease manifestations. Although differences in 6MWD between patients with and without musculoskeletal involvement were marginally non-significant, which is likely due to the small sample size, patients who complained about lower body pain during the 6MWT achieved a significant shorter 6MWD compared to patients who felt no impairment. Apart from the possible influence of musculoskeletal symptoms on 6MWD, similar clinical correlations were found after exclusion of patients with musculoskeletal problems during 6MWT suggesting further

important factors determining 6MWD (Table II).

Concerning disease-related determinants, we could find weak-to-moderate correlations between the 6MWD and predicted TLC, FVC and DLCO values. The correlation with TLC had not been not studied before in SSc, however, similar correlations between 6MWD and predicted FVC and DLCO/VA levels were also found in the French consecutive cohort showing similar disease characteristics as our cohort (24).

In patients with SSc-ILD, there was also a weak correlation between FVC and 6MWD, further suggesting lung fibrosis as a confounder for 6MWT (9). Nevertheless, the relative weak correlations indicate the multifactorial basis for limited exercise capacity in SSc patients and a lower contribution of ILD in our cohort with relative mild ILD (24).

As shown here, there was a good correlation between the 6MWD and the SHAQ score which, to our knowledge, has not been reported before. Schoindre *et al.* found an association between oxygen desaturation during 6MWT and a SHAQ score >1 also suggesting a relation between 6MWT and SHAQ score (24). Using multivariate logistic regression we could identify a significant model for prediction of the 6MWD consisting of SHAQ score and DLCO, which has not been reported before. Schoindre *et al.* also found lower 6MWD in patients with PAH that was also confirmed here. In addition, we have identified a cut-off value of 473 m in 6MWT best discriminating SSc patients with and without PAH with moderate sensitivity and specificity that could help for risk stratification. Unfortunately, NTpro-BNP levels were analysed in only 26 patients at the time point of 6MWT. In these patients, there was a good correlation between 6MWD and NTpro-BNP levels ( $r=0.520$ ;  $p<0.01$ , data not shown), but the data are too scarce to draw any conclusions. However, NTpro-BNP levels could improve the value of non-invasive tests for PAH assessment as suggested before (29).

In the studied cohort, the results of 6MWT reflect NYHA classification also

illustrated by the correlations between 6MWD and Borg Dyspnea Index. The data indicate the high diagnostic value of 6MWT to identify cardiac stretch and subjective complaints of dyspnea, a strong determinant of quality of life in SSc (30). The 6MWT reflects, especially in combination with the SHAQ score, the overall well-being of a patient. Therefore, the 6MWT can help to decide on further tests to be carried out, including pulmonary function, echocardiography and, in case of suspected PAH, right heart catheterisation.

In contrast, digital ulcers, another confounder for the quality of life, did not influence 6MWD what was also found in other studies (24). We also did not find an association between increased CRP values and 6MWD found by Schoindre *et al.* In contrast to this work, we have analysed CRP values only as categorised variable (normal or abnormal) and the number of patients with increased CRP values was low reflecting different cohorts of patients. Nevertheless, the weak correlation between disease activity and 6MWD suggests inflammation and disease activity as further confounding factors.

A limitation of the study is the small sample size. In addition, diagnosis of PAH was made by echocardiography as right heart catheter results were only available in 6 patients weakening the significance of the results. Furthermore, prospective data are missing to identify the prognostic value of 6MWD that would be the best argument for a regular use of the 6MWT. So far two of our patients have died but we will follow-up our patients to identify the predictive value of 6MWT. The assessment period in our cohort was 6 months before or after 6MWT. However, the patients were relative stable and, therefore, it was reasonable not to do any additional diagnostic procedures.

In conclusion, 6MWD reflects disability due to systemic sclerosis and their confounders. Therefore, while not specific for a certain disease manifestation, assessing 6MWD seems to be very relevant since it addresses important complaints of the patients. Therefore, a regular assessment of the 6MWD is suggested.

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