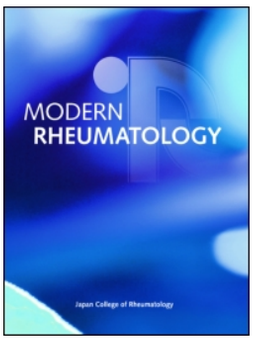

Modern Rheumatology

ISSN: 1439-7595 (Print) 1439-7609 (Online) Journal homepage: https://www.tandfonline.com/loi/imor20

Availability of EuroQol-5-Dimensions-5-Level (EQ-5D-5L) as health-related QOL assessment for Japanese systemic sclerosis patients

Naoki Mugii, Fujiko Someya, Shinichi Noto, Yasuhito Hamaguchi, Takashi Matsushita & Kazuhiko Takehara

To cite this article: Naoki Mugii, Fujiko Someya, Shinichi Noto, Yasuhito Hamaguchi, Takashi Matsushita & Kazuhiko Takehara (2019): Availability of EuroQol-5-Dimensions-5-Level (EQ-5D-5L) as health-related QOL assessment for Japanese systemic sclerosis patients, Modern Rheumatology, DOI: 10.1080/14397595.2019.1640409

To link to this article: https://doi.org/10.1080/14397595.2019.1640409

Accepted author version posted online: 04 Jul 2019.

MORH-D-19-00149 Received: 24-Apr-2019; Accepted: 2-Jul-2019

Original Article

Availability of EuroQol-5-Dimensions-5-Level (EQ-5D-5L) as health-related QOL assessment for Japanese systemic sclerosis patients

Naoki Mugii[a,b], Fujiko Someya[c], Shinichi Noto[d], Yasuhito Hamaguchi[e], Takashi Matsushita[e], Kazuhiko Takehara [e]

a) Department of Rehabilitation, Kanazawa University Hospital,

b) Division of Health Science, Kanazawa University Graduate School of Medical Science.

c) School of Health Science, Kanazawa University

d) Department of Health Science, Niigata University of Health and Welfare

e) Department of Dermatology, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University

Keywords: EQ-5D-5L, HAQ-DI, HRQOL, Japanese patients, systemic sclerosis.

Address correspondence and reprint requests to: Naoki Mugii,

Department of Rehabilitation, Kanazawa University Hospital,

13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan

Phone: 81-76-265-2013, Fax: 81-76-234-4308, E-mail: mugii@med.kanazawa-u.ac.jp

Abstract

Objective

To assess the functional disability in Japanese patients with systemic sclerosis (SSc) using the EuroQol-5-Domain-5-Level health questionnaire (EQ-5D-5L), which was developed in Europe to demonstrate the cost utility of treatments for non-specific diseases.

Methods

The EQ-5D-5L and Disability Index of the Health Assessment Questionnaire (HAQ-DI), which is a questionnaire for the quality of life for rheumatic diseases, were completed by 109 Japanese patients with SSc, and the clinical findings and laboratory data were collected at the same time.

Results

There was a correlation between the EQ-5D-5L score and HAQ-DI score. The EQ-5D-5L index score was affected by the % of predicted vital capacity (%VC), pulmonary arterial hypertension, and renal crisis. The %VC and renal crisis were also indicated as factors reducing the quality of life in the HAQ-DI. There was no difference in the EQ-5D-5L score between the SSc subtypes or among autoantibodies.

Conclusion

Our single-center study demonstrated the EQ-5D-5L to be a valuable assessment tool for functional disability in Japanese SSc patients, similarly to the disease specific HAQ-DI.

Introduction

Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by excessive fibrosis of the skin and internal organs, and microvascular damage with an autoimmune background[1)]. Moreover, SSc is a heterogeneous and progressive disorder of unknown origin with no effective treatment or cure, resulting in disability and reduced life expectancy or health-related quality of life (HRQOL). Among the clinical manifestations, interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), scleroderma renal crisis, etc. are considered to lead to a poor life prognosis, and progression of the symptoms lowers the QOL[2,3)]. QOL assessment is important for outcome assessment of the quality of medical technology and the efficacy of pharmaceuticals in general medical care[4,5)].

The EuroQol-5-Dimensions (EQ-5D) is a representative questionnaire for HRQOL whose scores are expected to change after medical care. The content of the questionnaires was developed by the EuroQol group established in 1987 and is offered in more than 170 countries[6)]. The Japanese version was introduced in 2015[7,8)].There are two answering methods, 3 Level (EQ-5D-3L) and 5 Level (EQ-5D-5L), and 5 Level is known to be more sensitive than 3 Level, thereby reducing the ceiling effect observed with 3 Level[9,10)]. EQ-5D-5L utilizes the quality-adjusted life year (QALY) as a unified index to evaluate the cost-effectiveness of medical technology and medicines for different diseases[5,11-13)]. EQ-5D has been used for cancer, Alzheimer's disease, cerebrovascular disease, amyotrophic lateral sclerosis, and rheumatoid arthritis, with healthy subjects as controls[14-19)].

In SSc patients, social perspectives, such as medical expenses and nursing care expenses, were examined using EQ-5D in Europe[20)], and EQ-5D scores were correlated with the Center for Epidemiologic Studies Depression Scale and Fatigue scale[21-23)], whereas the QOL depends on life style. Therefore, the results of EQ-5D evaluation for Japanese SSc patients are important. In general, the Disability Index of the Health Assessment Questionnaire (HAQ-DI) is recommended as a disease-specific rating scale to demonstrate disability in SSc patients[24-26)]. The HAQ-DI is also used for assessing the effects of therapy[27,28)]. In addition, Japanese SSc patients evaluated by the HAQ-DI demonstrated disability in grip and eating, as in American studies[24-26,29)]. Moreover, the Short Form 36 (SF-36) is a popular questionnaire to evaluate HRQOL, but it is a profile-type QOL evaluation, not assessing the medical economics[30)]. We evaluated the QOL of Japanese SSc patients using the EQ-5D-5L in comparison with the HAQ-DI and clinical findings in order to evaluate the availability of EQ-5D for assessing cost-utility for Japanese SSc patients.

Materials and methods

Subjects

This was a single-center, prospective cross-sectional study. One hundred and nine consecutive Japanese patients with SSc (95 females and 14 males, with a median age of 57.7 years [range 16–82 years]) who visited Kanazawa University Hospital between March 1, 2017 and December 31, 2017 were included in this study (Table 1). The median disease duration of SSc was 10.3 years (range 0.4–33 years). The disease duration was calculated from the time of the first clinical event of a manifestation of SSc other than Raynaud's phenomenon. All patients fulfilled the 1980 American College of Rheumatology preliminary classification criteria[31].

Clinical evaluation

All subjects were evaluated for HRQOL using the EQ-5D-5L and HAQ-DI. Clinical data for disease duration, including autoantibodies, SSc subtype according to the classification system proposed by LeRoy et al.[32] (diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc (lcSSc)), modified-Rodnan total skin thickness score (MRSS), nailfold videocapillaroscopy (NVC) pattern, ILD, PAH, digital ulcer, irrecoverable finger contractures, scleroderma renal crisis, upper gastrointestinal tract (GI) involvement, lower GI involvement, % of predicted vital capacity (%VC), % of predicted diffusing capacity of lung carbon monoxide (%DLco), sialylated carbohydrate antigen KL-6, corticosteroid usage, and cyclophosphamide usage were collected from the patients' records. The NVC pattern was classified into four patterns: normal NVC pattern, early NVC pattern, active NVC pattern, and late NVC pattern[33-35]. ILD was diagnosed by a respiratory physician by HRCT. PAH was confirmed when the pulmonary artery pressure was 25 mmHg or higher by cardiac catheter test and/or the RVSP was 50 mmHg or higher by echocardiography before treatment.

Ethics committee approval for this study was received from Kanazawa University Hospital (No. 2397). All subjects gave written informed consent according to the Declaration of Helsinki.

Assessment questionnaires

The EQ-5D-5L has am index score as the first component, and patients select outcomes from no problems, slight problems, moderate problems, severe problems, or being unable to do/extreme problems (scored 1–5) for five domains (mobility, self-care, activity, pain/discomfort, and anxiety/depression)[4,5,9]. A total score of 3125 can be calculated as 'health state'. As a set of values has been obtained from a large sample of the Japanese population aged 16 and older, a time trade-off procedure elicits utility weights for these health states with scores ranging from

−0.59 to 1.00 (a lower time trade-off is indicative of poorer health)[36]. Full health is indicated by a score, and values below zero are regarded as a state worse than death. The second component of the EQ-5D is a patient global assessment measured from 0 to 100 on a vertical 20-cm visual analogue scale (VAS), where 100 is indicative of the best subjective imaginable health state.

The 20-item HAQ-DI is an arthritis-specific instrument used to assess disability. It is divided into eight domains: dressing and grooming, arising, eating, hygiene, reach, grip, and activity. Patients rate their ability to perform these activities of daily living on a scale from 0 (without difficulty) to 3 (unable to do). The use of aids or devices to assist with these activities is also recorded. The HAQ-DI score is calculated by dividing the summed component scores by the number of components answered, and yields a score between 0 (no disability) to 3 (severe disability)[24-26].

Statistical analysis

All numerical data are shown as the mean ± standard deviation. Correlations were examined between the index score and VAS score of the EQ-5D-5L, and HAQ-DI scores using Pearson's correlation. MRSS, disease duration, %VC, %DLco, and KL-6 were analyzed for their relationship with the index score and VAS score of the EQ-5D-5L, and HAQ-DI scores using Pearson's correlation test. Patients were separated into four autoantibody groups, which were anti-centromere antibody (Ab), anti-topoisomerase I Ab, anti-RNA polymerase Ab, and other anti-nuclear Abs. Each index score and the VAS score of the EQ-5D-5L, and HAQ-DI scores were compared among the four autoantibody groups or four NVC patterns using the Tukey-Kramer HSD test, and compared between SSc subtypes, presence of ILD, PAH, digital ulcer, finger contractures, scleroderma renal crisis, upper and lower GI involvement, corticosteroid usage, and cyclophosphamide usage by the Student's t-test. The significant variables were selected for subsequent stepwise multiple regression analysis. P-values of <0.05 were considered significant. Statistical analyses were performed using JMP version 10 statistical software (Cary, NC).

Results

The mean MRSS was 10.4±7.8 (Table 1). When the patients were divided by subtypes, 43 patients were lcSSc and 66 patients were dcSSc. Anti-topoisomerase I antibody Ab was positive in 47, anti-centromere Ab was positive in 19, and anti-RNA polymerase Ab was positive in 17. The remaining 26 patients were positive for other antinuclear Abs or negative. Based on microvascular lesions, 20 patients had the early NVC pattern, 62 had the active NVC pattern, and 18 had the late NVC pattern. The remaining 9 patients had a normal NVC pattern. Clinical

symptoms included 62 cases of ILD, 13 cases of PAH, 27 cases of digital ulcer, 25 cases of finger contractures, 10 cases of scleroderma renal crisis, 66 cases of upper GI involvement, and 4 cases of lower GI involvement. Seventy-four patients were treated using corticosteroids and 28 patients were treated using cyclophosphamide.

The index score of the EQ-5D-5L was 0.73±0.19, the VAS score was 69.2±19.0, and the HAQ-DI was 0.70±0.71 (Table 2). Of HAQ-DI components, eating, grip, and reach had slightly higher scores. Correlations were found between the index score and HAQ-DI ($r=-0.79$, $p<0.0001$), between the VAS score and the HAQ-DI ($r=-0.51$, $p<0.0001$), and between the index score and VAS score ($r=0.59$, $p<0.0001$).

The relationships between each QOL score and clinical findings are shown in Table 3. There was a significant decrease in the index score in patients with ILD, PAH, digital ulcer, finger contractures, scleroderma renal crisis, upper GI involvement, impaired %VC, %DLco, or late NVC pattern compared with those with the early NVC pattern.

There was a significant decrease in the VAS score in patients with scleroderma renal crisis, or upper and lower GI involvement. The HAQ-DI score was significantly affected by dcSSc subtype, ILD, digital ulcer, finger contractures, scleroderma renal crisis, impaired %VC, and late NVC pattern compared with the early NVC pattern.

Multiple regression analysis revealed that %VC, PAH, and renal crisis were significant factors negatively affecting the QOL in the index score ($r^2 = 0.26$) (Table 4). In the HAQ-DI, %VC and renal crisis were found to be significant negative factors ($r^2 = 0.25$). The VAS score was not related to any of the clinical factors ($r^2 = 0.06$).

Discussion

In a previous cross-sectional study of SSc regarding economic burden, the index score of the EQ-5D-5L ranged from 0.49 to 0.75 and the VAS score ranged from 58.7 to 65.9 in Spain, UK, France, Hungary, Germany, Sweden, and Italy[20]. The scores in this study were similar, suggesting that SSc patients in Japan have the same QOL as those in other countries. Furthermore, the effects of treatments, such as drug therapy and rehabilitation, were able to be evaluated in the same manner even in Japan, although no systematic study has been conducted for Japanese patients except a case report on Japanese SSc using EQ-5D-5L. For example, the EQ-5D was applied in a pilot study to measure the therapeutic effects of low-output external shock wave therapy for digital ulcers[37]. To confirm the availability of EQ-5D-5L for Japanese SSc, further studies are needed in terms of evaluation of the effects of intervention.

The correlations between the index score and the VAS score of the EQ-5D-5L, and the HAQ-DI were also reported in previous studies in Europe[21,22], which support that the EQ-5D-5L can be used to evaluate the HRQOL

instead of the HAQ-DI for Japanese SSc patients. Moreover, the affected items in the HAQ-DI, eating and gripping, were the same as in previous reports.[24-26, 29)] The HAQ-DI is generally used as an indicator of the HRQOL in SSc patients before and after treatments, the outcome of SSc patients with interstitial pneumonia, or the long-term outcomes of hand function[38,39)]. Therefore, EQ-5D-5L may be used to evaluate Japanese SSc patients regarding many social fields.

Most patients in this study had dcSSc with anti-topoisomerase I Ab, and ILD was a common complication. The index score of the EQ-5D-5L and HAQ-DI score were related to the %VC and presence of ILD. On the other hand, the UK survey reported that the index score in SSc patients was only related to upper GI involvement because the patients had lcSSc with anti-centromere Ab[22)]. Additionally, in a study on SF-36, the Health Value Measures and Dermatology Life Quality Index demonstrated QOL involvement in patients with dcSSc[40,41)], whereas the QOL was not associated with the SSc subtype in this study. The differences in patients, clinical findings of SSc, and assessment method of QOL were considered to have affected the results.

Of note, the %VC was more closely related to the HRQOL than the presence of ILD based on the multiple regression analysis. The %VC may reflect the physical condition rather than the presence of ILD. However, ILD, PAH, and renal crises increase the risk of death in SSc patients [2,3)], and these factors were found to negatively affect the index score of the EQ-5D-5L in this study. Recently, the prognosis of PAH and renal crises has improved by advances in treatments[42-46)]; therefore, the index score of the EQ-5D-5L may be useful for future cost-effectiveness studies on Japanese SSc patients. The VAS score of the EQ-5D-5L, albeit a simple evaluation, was insufficient to demonstrate the relevance of clinical findings. Indeed, the VAS score does not reflect the overall QOL of the target group, but is instead used to track changes in individuals[47)].

In addition, the raw QOL scores in patients with lower GI disease were the lowest among the clinical findings examined (Table 3), and the HR-QOL score by SF-36 was also reported to be low in SSc patients with lower GI symptoms[48)]. However, only 4 out of 109 patients had lower GI disease in this study, and a significant difference based on lower GI disease was not observed by multiple regression analysis as a factor affecting QOL.

There are some limitations in this study. First, this study included a relatively small number of SSc patients at a single center, which limited the generalizability of the findings. Second, as this study was performed at the rehabilitation department, outpatients during the survey period were more likely to be anti-topoisomerase I Ab-positive dcSSc patients undergoing rehabilitation of finger function. Consequently, the SSc patients in this study had been transferred from dermatologists except for one patient from a rheumatologist, and the study design was unable to exclude the bias in the patient distribution regarding autoantibodies. Further studies are needed to

confirm the results in a larger population.

Conclusion

EQ-5D-5L and HAQ-DI were used to evaluate the HRQOL of Japanese SSc patients. Both the index score and VAS score of the EQ-5D–5L were correlated with the HAQ-DI. Moreover, the index score was related to the %VC, PAH, and renal crisis. This suggested that the EQ-5D-5L is useful as a QOL evaluation for SSc patients regardless of ethnic background or social customs. The EQ-5D–5L may be used as an indicator of therapeutic effect in the future.

Conflict of interest

None.

Funding

This study was supported by a grant for Research on Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan (to Naoki Mugii).

References

1. Medsger TA Jr. Systemic sclerosis (scleroderma): clinical aspects. In: Koopman WJ, editor. Arthritis and Allied Conditions. 13th ed. Baltimore: Williams & Wilkins; 1997.p. 1433-64.
2. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis. 2007, 66: 940-4.
3. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010, 69: 1809-15.
4. EuroQol Group: EuroQol. A new facility for the measurement of health-related quality of life. Health Policy. 1990, 16: 199-208.
5. Brooks R with the EuroQoL Group. EuroQol: the current state of play. Health Policy. 1966, 37:53-72.
6. Brauer CA, Rosen AB, Greenberg D, Neumann PJ. Trends in the measurement of health utilities in published cost-utility analyses. Value Health. 2006, 9: 213-218.
7. Ikeda S, Shiroiwa T, Igarashi, A, Noto S, Fukuda T, Saito S et al. Developing a Japanese version of the

EQ-5D-5L value set. Journal of the National Institute of Public Health. 2015, 64: 47-55.

8. Tsuchiya A, Ikeda S, Ikegami N, Nishimura S, Sakai I, Fukuda T, et al. Estimating an EQ-5D population Value set. The case of Japan. Health Econ. 2002, 11: 341-353.
9. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011, 20: 1727-36.
10. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the Eq-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012, 15: 708-15.
11. Gold M.R, Siegel J.E, Russell L.B, Weinstein M.C.(eds.): Cost-effectiveness in health and medicine, Oxford University Press, New York, 1996.
12. Azuma MK, Ikeda S. Investigation of evidence sources for health-related quality of life in cost-utility analysis of pharmaceuticals in Japan. Value in Health Regional Issue. 2014, 3C: 190-196.
13. Devin N. and Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Econ. 2004, 13: 437-452.
14. Sang M P, Myung H P, Joo H W, Wha SC, Dae SH, Si-Young K, et al.: EuroQol and survival prediction in terminal cancer patients: a multicenter prospective study in hospice-palliative care units. Support Care Cancer. 2006, 14: 329–333.
15. Mahmood Y, Safa N, Shahram G, Alireza M-A, Hossein G. Comparison of SF-6D and EQ-5D Scores in Patients With Breast Cancer. Iran Red Crescent Med J. 2016, 18: e23556.
16. Montgomery W, Goren A, Kahle-Wrobleski K, Nakamura T, Ueda K. Alzheimer's disease severity and its association with patient and caregiver quality of life in Japan: results of a community-based survey. BMC Geriatr. 2018, doi: 10.1186/s12877-018-0831-2.
17. Rodgers H, Shaw L, Bosomworth H, Aird L, Alvarado N, Andole S, et al. Robot Assisted Training for the Upper Limb after Stroke (RATULS): study protocol for a randomised controlled trial. Trials. 2017, doi 10.1186/s13063-017-2083-4.
18. Kiebert GM, Green C, Murphy C, Mitchell JD, O'Brien M, Burrell A, Leigh PN.: Patients' health-related quality of life and utilities associated with different stages of amyotrophic lateral sclerosis. J Neurol Sci. 2001, 191: 87-93.
19. Jørgensen T.S, Turesson C, Kapetanovic M, Englund M, Turkiewicz A, Christensen1 R, et al. EQ-5D utility, response and drug survival in rheumatoid arthritis patients on biologic monotherapy: A prospective observational study of patients registered in the south Swedish SSATG registry. PLOS one. 2017,

doi:10.1371/journal.pone.0169946.

20. Lopez-Bastida J, Linertova´ R, Oliva-Moreno J, Serrano-Aguilar P, Posada-de-la-Paz M, Kanavos P, et al. Social/economic costs and heaith-related quality of life in patients with scleroderma in Europe. Eur J Health Econ. 2016, 17 Suppl 1: 109-117.
21. Müller H, Rehberger P, Günther C, Schmitt J. Determinants of disability, quality of life and depression in dermatological patients with systemic scleroderma. Br J Dermatol. 2012, 166: 343-53.
22. Strickland G, Pauling J, Cavill C, McHugh N. Predictors of health-related quality of life and fatigue in systemic sclerosis: evaluation of the EuroQol-5D and FACIT-F assessment tools. Clin Rheumatol. 2012, 31: 1215-22.
23. Rehberger P, Müller H, Günther C, Schmitt J. Treatment satisfaction and health status in patients with systemic sclerosis. J Dtsch Dermatol Ges. 2012, 10: 905-12.
24. Steen VD, Medsger TA Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum. 1997, 40: 1984–91.
25. Poole JL, Steen VD. The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. Arthritis Care Res. 1991, 4: 27–31.
26. Clements PJ, Wong WK, Hurwitz EL, Furst DE, Mayes M, White B, et al. Correlates of the disability index of the Health Assessment questionnaire A measure of functional impairment in systemic sclerosis. Arthritis Rheum. 1999, 42: 2372-80.
27. Khanna D. Clements PJ, Furst DE, Chon Y, Elashoff R, Roth MD, et al. ; Scleroderma Lung Study Group. Correlation of the degree of dyspnea with Health-Related Quality of Life, functional abilities, and diffusing capacity for carbon monoxide in patients with systemic sclerosis and active alveolitis. Arthritis Rheum. 2005, 52: 592-600.
28. Merkel PA, Silliman NP, Clements PJ, Denton CP, Furst DE, Mayes MD, et al.; Scleroderma Clinical Trials Consortium. Patterns and predictors of change in outcome measures in clinical trials in scleroderma. Arthritis Rheum. 2012, 64: 3420-29.
29. Kuwana M, Sato S, Kikuchi K, Kawaguchi Y, Fujisaku A, Takehara K. et al. Evaluation of functional disability using the Health Assessment Questionnaire in Japanese patients with systemic sclerosis. J Rheumatol. 2003, 30: 1253－58.
30. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ. 1993. 306(6890): 1437-40.

31. Anonymous. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980, 23: 581–90.
32. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988, 15: 202-5.
33. Cutolo M, Sulli A, Pizzorni C, Accardo S. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J Rheumatol. 2000, 27: 155-60.
34. Cutolo M, Pizzorni C, Secchi ME, Sulli A. Capillaroscopy. Best Pract Res Clin Rheumatol. 2008, 22: 1093-108. doi: 10.1016/j.berh.2008.09.001.
35. Cutolo M, Pizzorni C, Tuccio M, Burroni A, Craviotto C, Basso M, et al. Nailfold videocapillaroscopic patterns and serum autoantibodies in systemic sclerosis. Rheumatology (Oxford). 2004, 43: 719-726.
36. Macran S, Weatherly H, Kind P. Measuring population health: A comparison of three generic health status measures. Med Care. 2003, 41: 218-231.
37. Saito S, Ishii T, Kamogawa Y, Watanabe R, Kawaguchi Y, Harigae H, et al. Extracorporeal Shock Wave Therapy for Digital Ulcers of Systemic Sclerosis: A Phase 2 Pilot Study. Tohoku J Exp Med. 2016, 238: 39-47.
38. Hasegawa M, Fujimoto M, Ihn H, Kuwana M, Sato S, Takehara K, et al. Serum adhesion molecule levels as prognostic markers in patients with early systemic sclerosis: a multicentre, prospective, observational study. PLoS One. 2014, 6; 9: e88150. doi: 10.1371/journal.pone.0088150. eCollection 2014.
39. Mugii N, Matsushita T, Oohata S, Someya F, Takehara K, Hamaguchi Y, et al. Long-term follow-up of finger passive range of motion in Japanese systemic sclerosis patients treated with self-administered stretching. Mod Rheumatol. 2018, 15: 1-7.
40. Khanna D, Ahmed M, Furst DE, Ginsburg SS, Park GS, Hornung R, et al. Health values of patients with systemic sclerosis. Arthritis Rheum. 2007, 57: 86–93.
41. Chularojanamontri L, Sethabutra P, Kulthanan K, Manapajon A. Dermatology life quality index in Thai patients with systemic sclerosis: a cross-sectional study. Indian J Dermatol Venereol Leprol. 2011, 77: 683–7.
42. Woodworth TG, Suliman YA, Li W, Furst DE, Clements P. Scleroderma renal crisis and renal involvement in systemic sclerosis. Nat Rev Nephrol. 2016, 12: 678-691.

43. Volkmann ER, Tashkin DP, Li N, Roth MD, Khanna D, Hoffmann-Vold AM, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. Arthritis Rheumatol. 2017, 69: 1451-1460.
44. Shenoy PD, Bavaliya M, Sashidharan S, Nalianda K, Sreenath S. Cyclophosphamide versus mycophenolate mofetil in scleroderma interstitial lung disease (SSc-ILD) as induction therapy: a single-centre, retrospective analysis. Arthritis Res Ther. 2016, 18: 123. doi: 10.1186/s13075-016-1015-0.
45. Kabunga P, Coghlan G. Endothelin receptor antagonism: role in the treatment of pulmonary arterial hypertension related to scleroderma. Drugs. 2008, 68: 1635-45.
46. Johnson SR, Brode SK, Mielniczuk LM, Granton JT. Dual therapy in IPAH and SSc-PAH. A qualitative systematic review. Respir Med. 2012, 106: 730-9.
47. EuroQol Group: EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument; Rotterdam, 2015. p. 22-23.
48. Franck-Larsson K, Graf W, Rönnblom A. Lower gastrointestinal symptoms and quality of life in patients with systemic sclerosis: a population-based study. Eur J Gastroenterol Hepatol. 2009, 21: 176-82.

Table 1 Clinical profile of 109 systemic sclerosis patients.

Clinical features	
MRSS (mean ± SD)	10.4±7.8
Disease duration in years (mean ± SD)	10.3±8.1
SSc subtype (dcSSc/lcSSc)	66/43
Autoantibodies (Topo1/RNAP/ACA/other)	47/17/19/26
Nailfold capillaroscopy (normal/early/active/late)	9/20/62/18
Organ involvement (number of positive patients, %)	
Interstitial lung disease	62, 56.9%
Pulmonary hypertension	13, 11.9%
Digital ulcer	27, 24.8%
Finger contractures	25, 22.9%
Scleroderma renal crisis	10, 9.2%
Upper GI disease	66, 60.6%
Lower GI disease	4, 3.7%
%VC (% of predicted value)*, (mean ± SD)	92.2±23.6
%DLco (% of predicted value)**, (mean ± SD)	51.9±19.4
KL-6 (U/mL), (mean ± SD)	749.0±750.4
Corticosteroid usage (number of patients, %)	74, 67.9%
Cyclophosphamide usage (number of patients, %)	28, 25.7%

*: Data available for 95 patients, **: Data available for 92 patients,
MRSS: modified-Rodnan total skin thickness score, %VC: % of predicted vital capacity,
%DLco: % of predicted diffusing capacity of lung carbon monoxide,
KL-6: sialylated carbohydrate antigen.

Table 2 HAQ scores and EQ-5D-5L scores for 109 systemic sclerosis patients

EQ-5D-5L	
Index score	0.73±0.19
VAS score	69.2±19.0
HAQ	
Overall HAQ-DI score	0.70±0.71
Dressing	0.57±0.69
Rising	0.39±0.66
Eating	1.00±0.95
Walking	0.61±0.92
Hygiene	0.40±0.84
Reach	0.87±1.07
Grip	0.89±0.98
Activity	0.79±1.04

Table 3 Associations of HAQ scores and EQ-5D-5L scores with clinical features of 109 patients

Clinical features	EQ-5D-5L Index score	p-value	EQ-5D-5L VAS score	p-value	HAQ	p-value
MRSS	r= 0.02	ns	r= -0.12	ns	r= 0.14	ns
Disease duration	r= -0.17	ns	r= -0.01	ns	r= 0.11	ns
SSc subtype (dcSSc/lcSSc)	0.72±0.19/ 0.75±0.19	ns	68.3±/17.6 70.6±21.1	ns	0.80±0.09/ 0.56±0.65	<0.05
Autoantibodies (Topo1/RNAP/ACA/other)	0.73±0.19/ 0.67±0.19/ 0.74±0.20/ 0.76±0.20	ns	72.2±15.0/ 61.9±21.5/ 66.8±23.5/ 70.2±19.6	ns	0.72±0.69/ 0.85±0.75/ 0.53±0.69/ 0.71±0.73	ns
Nailfold capillaroscopy (normal/early/active/late)	0.68±0.15/ 0.81±0.17/ 0.74±0.19/ 0.65±0.20	<0.05*	67.2±18.6/ 70.3±19.4/ 69.3±19.4/ 68.5±18.7	ns	0.81±0.20/ 0.47±0.67/ 0.66±0.68/ 1.06±0.80	<0.05*
Interstitial lung disease (yes/no)	0.69±0.21/0.78±0.16	<0.05	68.4±17.8/70.3±20.6	ns	0.84±0.77/0.52±0.57	<0.05
Pulmonary hypertension (yes/no)	0.62±0.25/0.75±0.18	<0.05	68.5±23.8/69.3±18.4	ns	0.88±0.76/0.68±0.70	ns
Digital ulcer (yes/no)	0.62±0.19/0.77±0.18	<0.05	65.0±19.1/70.6±18.9	ns	1.09±0.74/0.57±0.65	<0.05
Finger contractures (yes/no)	0.64±0.20/0.76±0.18	<0.05	62.9±19.1/71.1±18.7	ns	1.10±0.70/0.58±0.67	<0.05
Scleroderma renal crisis (yes/no)	0.60±0.23/0.74±0.18	<0.05	55.5±19.6/70.6±18.5	<0.05	1.19±1.02/0.65±0.65	<0.05
Upper GI disease (yes/no)	0.70±0.20/0.78±0.17	<0.05	66.0±18.3/74.0±74.0	<0.05	0.80±0.70/0.55±0.69	ns
Lower GI disease (yes/no)	0.59±0.27/0.74±0.19	ns	0.50±31.6/69.9±18.2	<0.05	0.91±1.27/0.70±0.69	ns
%VC	r= 0.40	<0.0001	r= 0.24	0.02	r= -0.46	<0.0001
%DLco	r= 0.40	<0.0001	r= 0.15	ns	r= -0.29	<0.005
KL-6	r= -0.04	ns	r= 0.04	ns	r= -0.06	ns
Corticosteroid usage (yes/no)	0.72±0.20/0.75±0.18	ns	70.4±17.4/66.7±21.9	ns	0.79±0.75/0.53±0.56	ns
cyclophosphamide usage (yes/no)	0.73±0.19/0.73±0.20	ns	72.8±14.9/67.9±20.1	ns	0.62±0.63/0.73±0.73	ns

* Late NVC pattern compared with the early NVC pattern. In the other comparisons, there was no significant difference.

Table 4. Associations of index score of the EQ-5D-5L and HAQ-DI scores with clinical features by multiple regression analysis (n=109)

	Unstandardized coefficient		Standardized Coefficient	p-value	95%CI	Adjusted R^2
	B	SE	β			
(Index score of the EQ-5D-5L)						
%VC	0.00276	0.00071	0.355	0.0002	0.0014 - 0.0042	0.24
PAH	-0.0746	0.02606	-0.261	0.0052	-0.126 - -0.023	
RC	-0.0660	0.03153	-0.188	0.0391	-0.129 - -0.003	
(HAQ-DI scores)						
%VC	-0.01286	0.00257	-0.453	<0.0001	-0.018 - -0.008	0.23
RC	0.25524	0.11558	0.200	0.0297	0.0257 - 0.4848	

RC: Scleroderma renal crisis