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Health State Utilities and Disease Duration in Systemic Sclerosis: Is There an Association? Results from the UCLA Scleroderma Quality of Life Study

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Abstract

Objective—Health state utility values (HSUVs) are used as weightings to calculate quality-adjusted life years (QALYs) in economic evaluations. Evidence suggests that patients' perceptions of a new diagnosis for a chronic disease, while initially poor, may improve over time. The objective of this study was to examine the association between disease duration and direct HSUV scores in patients with systemic sclerosis (SSc).

Methods—Our study included patients with SSc from a US Scleroderma center. An interviewer administered direct HSUV techniques including the Visual Analogue Scale (VAS), Time Trade-Off (TTO), and Standard Gamble (SG). We calculated the Short Form 6D HSUVs from the SF-36. Additional clinical and demographic variables were collected.

Results—The mean age of the SSc sample (n=223) was 51 years (SD: 15) with the majority being female (84%). Median disease duration was 5 years (IQR: 7.38). Mean (SD) HSUVs were 0.67 (0.19) for the VAS, 0.76 (0.28) for the TTO, 0.84 (0.22) for the SG, and 0.65 (0.13) for the SF-6D. In patients with early disease (defined as <2 years (n=77), the mean HSUV values were 0.64 (VAS), 0.70 (TTO), 0.80 (SG), and 0.63 (SF-6D), versus for those with longer disease duration 0.69, 0.79, 0.87, 0.67, respectively. In multivariate analysis, the SG measure showed a significant and positive association with disease duration measured as a continuous variable and using a threshold of 2 years (p=0.047 and p=0.023, respectively).

Conclusions—Greater disease duration showed a positive association with a direct measure (SG) of utility elicitation after a period of two years.

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Introduction

Systemic sclerosis (SSc; scleroderma) is a rare connective tissue disease that has a prevalence of between 286-659 cases per million people in the United States (1). Patients are typically classified as having limited cutaneous (lcSSc) or diffuse cutaneous systemic sclerosis (dcSSc). In general, the sub-classification is based on skin involvement and is a surrogate for internal organ involvement. Typically, patients with dcSSc have higher morbidity and mortality. There is no effective treatment for this disease meaning that most treatment offered is symptom-dependent (2). It is well established that SSc patients have a decreased health-related quality of life (HRQOL) compared to the general population (3).

Preference-based measures of health assess the desirability of particular health state and summarize HRQOL as a single number, the health state utility value (HSUV) (4). HSUVs can be measured directly using methods such as the visual analogue scale (VAS), the time-trade off method (TTO), or the standard gamble method (SG). Multidimensional measures, such as the Short-Form 6D (SF-6D), can also be used to estimate utilities indirectly (5). The advantage of these measures is that they are easy to administer, easy to understand, and have low respondent burden. HSUVs can also be derived using algorithms for general health questionnaires such as the Short-Form 12 (SF-12) or SF-36 (5). It has been well-established that values estimated from these different measures do not align perfectly (6). HSUVs estimated using such measures are an important component to the economic evaluation of health interventions, specifically cost-utility analyses. These values are used as a weight to incorporate quality and length of life into a single metric (the quality-adjusted life-year or QALY) in order to facilitate comparison among competing health care options (7). Results of cost-utility analyses are often used to inform reimbursement decisions of new health interventions so it is essential that methods for capturing patients' utility are well-understood.

Patients often perceive higher HRQOL for their health states than the general population perceives the same health states (3,8). Part of this difference has been attributed to the influence of adaptation over time, a phenomenon whereby either the values or preferences associated with one's own health state or choices made between alternative health states may change as a result of experiencing that state (9). 'Response shift' may also occur when patients' internally alter their ideas about their own HRQOL (10). This study sought to explore whether the patients' duration of disease were associated specifically with their direct HSUVs (SG and TTO). In particular, we sought to explore the idea that SSc patients' would be initially have strong preferences for other health states over their own; more recently diagnosed patients might be more willing to 'trade-off' or 'gamble' for another health state. Therefore, our *a priori* hypothesis is that patients with shorter disease duration would have lower utility estimates with these direct measures than patients with longer disease duration.

Methods

Patients were recruited at the University of California at Los Angeles (UCLA) with rheumatologist confirmed SSc in the UCLA Scleroderma Quality of Life study (11,12). This

study is a single-center, longitudinal, observational study where consecutive patients with SSc were invited to participate during their clinic visits and completed written consent and Health Insurance Portability and Accountability Act (HIPAA) forms. The study was approved by UCLA Institutional Review Board (IRB).

Inclusion criteria include adult patients (18 years) with diagnosis of SSc by scleroderma clinicians (Drs Clements and Khanna). The exclusion criterion included inability to read and write English. Patients with SSc were further stratified into lcSSc, dcSSc, and overlap syndrome. Limited SSc (lcSSc) is defined as skin thickening distal, but not proximal, to the knees and elbows, with or without facial involvement; dcSSc is defined as skin thickening distal and proximal to the knees and elbows with or without facial involvement; and overlap syndrome is defined as patients with SSc and another rheumatic disease (such as inflammatory myositis or rheumatoid arthritis). All patients signed a UCLA Institutional Review Board-approved written consent and Health Insurance Portability and Accountability Act (HIPAA) forms.

Physician assessment of skin severity

The Modified Rodnan Skin Score (MRSS) is the most widely used measure to assess skin thickening. The examiner palpates the skin in 17 areas (face, chest, and abdomen; fingers, hands, forearms, arms, feet, legs, and thighs for both sides of the body) and scores the level of thickening from 0-3 (from 'uninvolved' to 'severe thickening'). The total skin score is the sum of the skin scores of the individual areas with the maximum possible score being 51 (13). MRSS is a measure of severity of skin thickness and in dcSSc, higher MRSS is associated with internal organ involvement and is considered as a surrogate for overall disease severity (14).

Questionnaires

Patient-reported outcome measures: The Health Assessment Questionnaire-Disability Index (HAQ-DI) assesses a patient's ability to function (15). There are a total of 20 questions in 8 categories that asks the patient about their ability to carry out daily tasks in order to determine the detrimental effect to their health (15). The HAQ-DI has been validated for use in a number of diseases including SSc (16). The HAQ-DI has a range of 0 to 3.0, with higher scores being worse than lower. The CES-D Scale (Center for Epidemiologic Studies Depression Scale) is a patient-reported measure that is designed to capture symptoms of depression in the general population (17). The FACIT-Fatigue scale (the Functional Assessment of Chronic Illness Therapy Fatigue Scale) is a brief measure (13 items) to capture patients' level of fatigue; it has been validated in patients with rheumatic diseases (18).

Direct HSUV instruments: Direct utility elicitation tasks were performed using the software package UMaker (19). For all HSUV measures, a higher score indicates better health with a score of '1' indicating perfect health. Patients were first asked to complete a VAS that asked them to mark a point on a scale (0-100mm) which best described their health in daily life over the past week.

Patients were then directed to complete a TTO exercise. This exercise asks patients their willingness to accept a shorter life in a state of perfect health. The TTO was presented as two bars, one longer (the current health state) and a bar representing shorter length of life in better health. The patients were asked a series of these questions until an indifference point was reached between the length of life in their current health state and the time the patient would spend in perfect health.

A SG exercise was then completed by the patients. This HSUV elicitation method forces the participant to choose between their life expectancy in their current health state versus a period of perfect health with a probability of immediate death. This probability was represented as a pie chart (or wheel) and users could alter the probability until a point of indifference was achieved between this possibility and their current health state. The associated utility was simply 1 minus this probability. Further details of this process are available in Khanna et al. (20).

Indirect HSUV instruments: Patients were asked to answer the SF-36 Health survey which is commonly used to asses patients' health. Using an established algorithm, the SF-36 was converted into the SF-6D to obtain a HSUV score (5). The SF-6D has six domains (physical functioning, role limitations, bodily pain, vitality, social functioning, and mental health) and 18 000 possible health states.

Analysis: Descriptive statistics were calculated for the study population. Parametric and non-parametric (Wilcoxon Mann Whitney) tests were used where appropriate, based on the variable distributions, to compare differences in HSUV values between measures. Chi-square tests were used for evaluating associations between categorical variables. A series of univariate and multivariate linear regression models were constructed to examine the effect of disease duration on each of the HSUV measures adjusting for potential demographic confounders including age (continuous), sex (categorical, 2 levels), income (categorical, 6 levels), and education level (categorical, 6 levels). Covariates were considered for the multivariate model if they met a threshold in univariate analysis ($p<0.2$) and were added stepwise by comparing AIC (Akaike information criterion) of each specification. Spearman correlation coefficients were compared for explanatory variables to be included in the model to identify the presence of multicollinearity. Heteroskedasticity was tested for using the White test and normality among the regression residuals was assessed by kernel density plots. We explored disease duration as a continuous variable and then using a categorical variable at 1 and 2 years based on our *a priori* hypothesis. These thresholds were based on clinical observation (DK) that patients generally accept living with a chronic disease over a period of 2 years. The primary analyses focused on using the SG and TTO as dependent variables. Secondary analyses used the SF-6D and VAS as dependent variables. Statistical significance was achieved for p-values (two-tailed) less than of 0.05 (α). All analyses were done in SAS version 9.3 (Cary, North Carolina).

Results

A total of 223 patients were recruited into this study. The mean age in this patient population was 50.9 years (SD: 15.5) and 84.3% of patients were female. More than 80% of patients

had at least some college education and approximately three quarters of patients had an annual income greater than $50,000 (USD). The median time since patients were diagnosed with SSc was 5 (IQR: 1.5-9) years and 44% of patients had dcSSc. Twenty-six percent (n=58) of patients reported not having worked in the past 5 years due to their disease; less than 1% of patients reported being hospitalized in the previous 12 months.

Mean HSUV estimates in the patient population ranged from 0.654 (SF-6D) to 0.844 (SG) (Figure 1). Seventy-three patients (33%) reported being in perfect health (HSUV=1) with at least one of the HSUV measures. Thirty-five patients (16%) reported perfect health with two or more measures. No patients reported perfect health in all four HSUV measures. More patients reported perfect health (=1) with the TTO and SG (48 [22%] and 59 [27%]) than the VAS and the SF-6D, respectively. The number of patients reporting perfect health using the VAS and SF-6D were 8 (4%) and 3 (1%), respectively. To discern whether or not HSUV measures were different by disease type (lcSSc versus dcSSc), we conducted pairwise tests to examine significant differences in HSUV scores between these two patient groups. HSUV scores from the VAS, TTO, SG and SF-6D were all significantly higher in the lcSSc group than the dcSSC group indicating that they do distinguish well between the two disease types (all $p < 0.05$).

A priori, the study hypothesis was that disease duration would have a positive association with HSUV scores, particularly with the SG method of utility elicitation. To test this hypothesis, 3 different measures of disease duration were used: continuous disease duration, duration greater than 1 year, and duration greater than 2 years (Table 2). The univariate results for disease duration as a continuous variable and the threshold at 2 years disease duration (n=145, 70%) were in accordance with this hypothesis ($p<0.05$) (see Table 2). Results using the one-year (n=161, 78%) threshold showed trends for both the SG and TTO measures but were not statistically significant (p-values: 0.70 and 0.29, respectively). The TTO and SG were found to be significantly and positively associated with disease duration greater than 2 years compared to disease duration less than 2 years, with coefficients of 0.084 and 0.076, respectively ($p < 0.05$). Regression coefficients for disease duration (for both specifications) with the VAS and SF-6D as outcomes were not significant ($p>0.05$). A clinical measure of SSc skin severity (MRSS) and patient reported measures (FACIT Fatigue Scale, CES-D, HAQ-DI) were also significantly associated with all HSUV measures in the expected direction (Table 2). Patient characteristics such as age, sex, and income were not significantly associated with TTO and SG values and results were mixed for the VAS and SF-6D (Table 2).

In the main multivariate analysis, there was a significant association between SG and disease duration as a continuous variable (p=0.047) and disease duration as a categorical variable using a threshold of two years (p=0.023). Disease duration greater than two years was associated with a seven point increase in SG score which reflects the *a priori* hypothesis of this study. For the TTO, multivariate analyses did not produce significant associations for disease duration when included as a continuous variable nor as a categorical value (using a two-year threshold) (p-values: 0.762 and 0.081, respectively) but the regression coefficients were in the expected direction (0.001 and 0.072, respectively).

In order to see if there were differences between SSc types, a subgroup analysis was done for each of these diagnoses. In patients with dcSSc (n=90), no significant associations were found for disease duration greater than two years (all p-values > 0.1). However, in patients with lcSSc (n=118), disease duration greater than two years was positively associated with the SG, TTO, and the SF-6D measures after controlling for covariates (coefficients: 0.109, 0.118, and 0.061, respectively; p<0.05 for all).

Discussion

To our knowledge, this is the first study to elicit direct and indirect HSUVs and examine associations with disease duration in SSc patients. We found that disease duration had a significantly positive association with the SG scores suggesting that after a period of time post-SSc diagnosis, patients may adapt to their health state and are less willing to 'trade' for a better health state. However, the results of this study also suggest that disease severity, as assessed by MRSS, appears to be more important in determining the association with HSUV in the multivariate models, particularly in patients with dcSSc. In sub-group analyses, patients with lcSSc showed a positive association between disease duration greater than 2 years and HSUV scores (SG, TTO, SF-6D).

Adaptation is a phenomenon where values or preferences associated with the evaluation of one's own health state or 'trade-offs' made between alternative health states may change as a result of experiencing that state (9). It has been observed in studies evaluating the HRQOL of individuals sustaining serious accidents leading to paraplegia or quadriplegia (21), as well as individuals sustaining limb loss (22) or burn injuries (23). Response shift, a similar phenomenon, includes changes in the meaning of one's self-evaluation of QoL resulting from changes in internal standards, values, or conceptualization of their health (10).

Several elements of adaptation can render patients' ratings of HRQOL higher, which likely contributes to the fact that typically patients perceive higher HRQOL in their health states than perceived by the general population (8). This has been observed in SSc and corroborated here with our study. The general public reported mean (SD) HSUV scores of 25.3-69.7 (15.2-16.3) for the VAS, 0.36-0.80 (0.25-0.31) for the TTO, and 0.50-0.81 (0.26-0.32) for the SG, depending on disease severity (3); compared to the mean scores from SSc patients in the current study of 0.67 (0.19), 0.76 (0.28), and 0.84 (0.22), respectively, scores that fell in the least severe SSc categories in the previous study by Khanna et al. (3). For context, Marra et al. (6) reported on minimally important differences (MIDs) for several utility measures in patients with rheumatoid arthritis. While the analysis did not report on the SG measure, the MID for the SF-6D measure (Table 3) was found to be 0.03 to 0.05, depending on the methodology employed, similar to results from earlier studies (24). These MID values are comparable to the result from this study of 0.037 (95% CI: 0.014-0.068) for effect of disease duration greater than 2 years on SF-6D score (Table 3).

Of particular interest based on our *a priori* hypothesis was the association between the SG utility score and disease duration. We anticipated that patients with shorter disease duration would be willing to 'gamble' more substantially than those with longer disease duration due to the real or perceived desirability of other health states. This desirability reflects that

treatment for SSc involves a marked amount of risk with no certainty of improvement. Univariate analysis (Table 2) using a categorical variable for disease duration over 2 years yielded results that were consistent with our hypothesis. In multivariate analysis, the SG measure showed positive and statistically significant associations with disease duration greater than 2 years. MRSS appeared to be the most consistently significant correlate of HSUV scores suggesting that the progressive nature of SSc may outweigh the effect of adaptation over time. This idea was confirmed when we performed sub-group analysis of lcSSc versus dcSSc. While patients may adapt somewhat to their disease state, for those patients with concurrent disease progression (and associated pain) the net effect may be a decrease in HSUV scores. However, in patients with lcSSc, a disease subtype with milder SSc, disease duration greater than 2 years was positively associated with HSUV.

The results of this study have practical implications for cost-utility analyses involving SSc patients. Utility estimates obtained immediately after SSc diagnosis may not be stable over time. Cost-utility analyses should therefore appreciate this phenomenon and ensure that analyses that span a patient's lifetime incorporate changing HSUVs. Failure to do so may mean that the results of cost-utility analyses may be prone to error. Previous studies have shown that the choice of utility elicitation method may generate different results (25) and this study adds that, for SSc patients, there are nuances within specific measures that must be well understood.

Limitations

There are several limitations to this study. First, the study was not designed specifically to answer the question of adaptation. The non-significant results in the subgroup analyses, for example, especially with dcSSc, may be due to lack of power to show such effects. Second, patients were required to respond to a survey that was of considerable length. While most questions were quite easily answered, it is possible that this proved to be burdensome. However, response rates, particularly to HSUV measures were high, with the lowest observed with the SF-6D (95%). Third, the cross-sectional nature of our investigation does not allow us to view changes in HSUVs and clinical measures of disease severity in individual patients over time. It also does not allow for us to investigate whether or not the changes in direct and indirect utility measures are similar and if these changes are reflected in the clinical measures of disease severity (and vice-versa). We recognize that this type of study design has the potential for bias (i.e. the healthy-worker effect) but because recruitment was done exclusively from an SSc clinic, this should be minimized. Fourth, we did not systematically capture which patients declined to participate in the study and also acknowledge that the method and location of recruitment might mean that these results are not generalizable to all SSc patients. Finally, information on treatments that patients may have been receiving for comorbid diseases may have been beneficial in order to know what effect, if any, these treatments were having on patients' quality of life.

In conclusion, this study showed that certain methods of obtaining HSUVs appreciate patients' perceptions of their disease, particularly in the period immediately after diagnosis. For the primary analyses, both univariate and multivariate analyses showed that disease duration greater than 2 years was positively associated with the TTO and SG HSUV

measures in accordance with our hypothesis. This analysis also showed, however, disease severity, as measured by skin severity, was consistently and significantly negatively associated with all HSUV measures suggesting that while disease duration may influence patients' HSUV scores, patients' disease severity may mitigate this effect.

Acknowledgments

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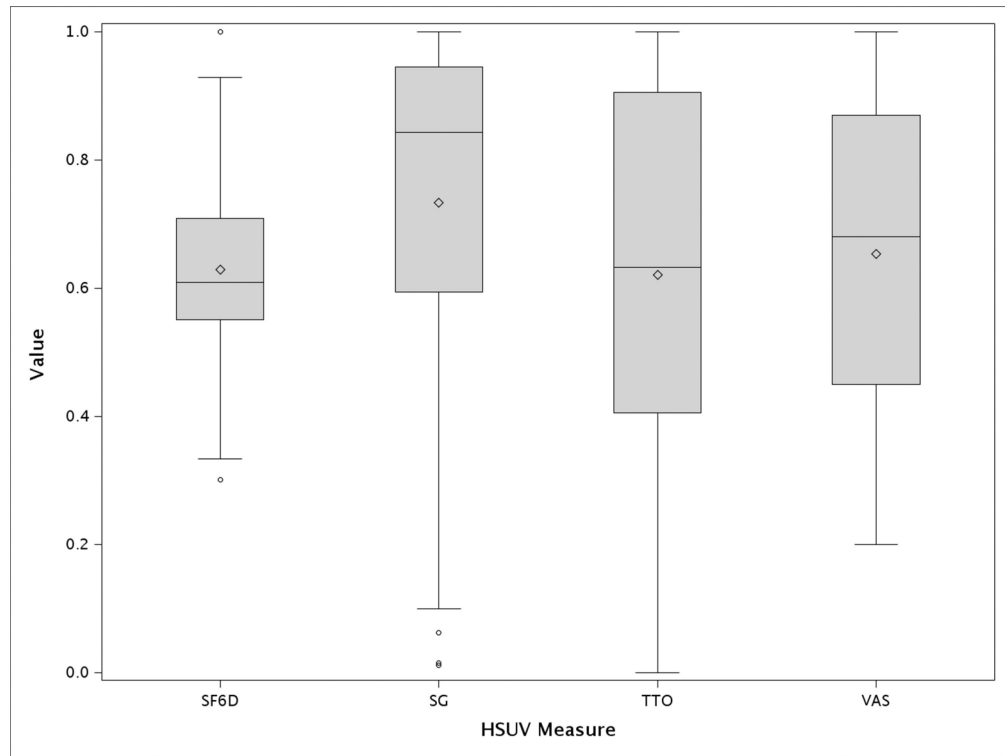
Figure 1.
Boxplot of HSUV scores by measure. (SF6D n= 211; SG n = 222; TTO n = 222; VAS n= 222)

Table 1

Study participant characteristics (n=223).

Parameter	Mean (SD)
Age (years)	50.9 (15.5)
Sex (% female)	84.30%
Disease Duration	7.37 (7.85)
Alcohol Use	48%
Marital Status (% married)	58.80%
Education	
Less than High School Graduate	4.10%
High School Graduate	12.70%
Post-Secondary Education	83.20%
Income	
<25000	19.90%
25000 to <50000	16.80%
50000 to <75000	14.90%
>75000	48.40%
Insurance Type	
Private	56.70%
Medicare/MediCal	24.30%
Medicare + Private	12.40%
None	1.40%
Ethnicity	
White	71.70%
Black/African American	6.30%
Asian	12.10%
More than one	2.20%
Unknown	6.30%
Scleroderma Type	
Localized Scleroderma	1 (0.46%)
Diffuse Scleroderma	90 (41.29%)
Limited Scleroderma	112 (51.38%)
Sine Scleroderma	4 (2.29%)
Overlap	10 (4.59%)

Table 2

Regression coefficients and 95% confidence intervals of univariate analyses with each HSUV measure as the outcome.

Variable	SG Coeff (95% CI)	TTO Coeff (95% CI)	SF-6D Coeff (95% CI)	VAS Coeff (95% CI)
Duration (cont)	**0.004 (0.0001, 0.008)**	0.004 (−0.001, 0.009)	0.002 (−0.001, 0.004)	−0.001 (−0.005, 0.002)
Duration (>1) [*]	0.015 (−0.06, 0.089)	0.051 (−0.043, 0.144)	**0.056 (0.012, 0.101)**	0.008 (−0.058, 0.075)
Duration (>2) [*]	**0.076 (0.009, 0.142)**	**0.084 (0, 0.167)**	0.036 (−0.005, 0.076)	0.033 (−0.027, 0.092)
Age	−0.001 (−0.003, 0.001)	−0.001 (−0.003, 0.002)	0.0002 (−0.001, 0.001)	−0.002 (−0.004, −0.0001)
Sex	−0.037 (−0.121, 0.046)	0.028 (−0.077, 0.133)	−0.009 (−0.058, 0.040)	0.014 (−0.059, 0.087)
Income	0.014 (−0.013, 0.042)	0.012 (−0.022, 0.047)	**0.031 (0.016, 0.046)**	**0.028 (0.005, 0.052)**
Education	0.022 (−0.003, −0.046)	0.028 (−0.003, 0.059)	**0.018 (0.003, 0.032)**	0.008 (−0.015, 0.030)
SSc Type [†]	**−0.089 (−0.152, −0.026)**	**−0.120 (−0.199, −0.041)**	**−0.04 (−0.076, −0.004)**	−0.035 (−0.091, 0.021)
MRSS (cont)	**−0.005 (−0.009, −0.002)**	**−0.007 (−0.011, −0.003)**	**−0.003 (−0.005, −0.001)**	**−0.004 (−0.007, 0)**
HAQ-DI	**−0.092 (−0.133, −0.049)**	**−0.161 (−0.212, −0.111)**	**−0.106 (−0.127, −0.086)**	**−0.106 (−0.141, −0.070)**
CESD	**−0.001 (−0.015,−0.005)**	**−0.014 (−0.020, −0.008)**	**−0.015 (−0.017, 0.013)**	**−0.015 (−0.019, −0.011)**
Facit Fatigue Scale	**−0.005 (−0.007, −0.003)**	**−0.009 (−0.011, −0.006)**	**−0.008 (−0.009, −0.007)**	**−0.007 (−0.009, −0.005)**
Ethnicity	−0.033 (−0.103, 0.037)	−0.038 (−0.126, 0.050)	**−0.068 (−0.108, −0.028)**	−0.037 (−0.099, 0.024)
Marital Status [**]	0.019 (−0.043, 0.081)	−0.014 (−0.092, 0.064)	0.018 (−0.018, 0.054)	0.004 (−0.050, 0.059)

MRSS: Modified Rodnan Skin Score; HAQ-DI: Health Assessment Questionnaire Disability Index; CI: Confidence Interval; Cont: Continuous variable; SG: Standard Gamble; TTO: Time Trade-Off; SF-6D: Short-Form 6D; VAS: Visual Analogue Scale. Numbers in bold text are statistically significant (p<0.05).

[*] For these variables the parameter is equal to one if the condition is met.

[†] SSc type is equal to 0 for lSSc and equal to 1 for dSSc

[**] Marital status is equal to '1' if married, '0' if otherwise.

Table 3

Regression coefficients for primary and sub-group analyses with 95% confidence intervals for disease duration in multivariate analyses with each HSUV measure as the outcome.

	SG		TTO		SF6D		VAS	
	Coeff	95% CI	Coeff	95% CI	Coeff	95% CI	Coeff	95% CI
Primary Analysis								
Duration *	**0.004**	**(0.00004, 0.007)**	0.0007	(−0.004, 0.005)	0.001	(−0.0002, 0.003)	0.002	(−0.005, 0.0009)
Duration>2 Years **	**0.072**	**(0.010, 0.138)**	0.072	(−0.009, 0.153)	**0.037**	**(0.014, 0.068)**	0.061	(−0.017, 0.089)
Sub-Group Analysis								
dcSSc Patients Only								
Duration *	0.005	(−0.004, 0.014)	−0.006	(−0.017,0.004)	0.002	(−0.002, 0.006)	0.001	(−0.005, 0.006)
Duration>2 Years **	0.062	(−0.056, 0.180)	0.039	(−0.105, 0.183)	0.033	(−0.007, 0.073)	0.056	(−0.021, 0.133)
lcSSc Patients Only								
Duration *	0.030	(−0.001, 0.007)	0.003	(−0.002, 0.008)	0.002	(−0.00002, 0.004)	−0.003	(−0.007, 0.0003)
Duration>2 Years **	**0.109**	**(0.029, 0.188)**	**0.118**	**(0.015, 0.220)**	**0.061**	**(0.018, 0.104)**	0.038	(−0.046, 0.123)

Adjusted for: age, sex, MRSS, education, CES-D, HAQ-DI. SG: Standard Gamble; TTO: Time Trade-off; SF6D: Short Form 6-D; VAS: Visual Analogue Scale; Coeff: Regression Coefficient. Numbers in bold text are statistically significant (p<0.05).

*
Disease duration modeled as continuous variable.

**
Disease duration modeled as categorical variable (equal to 1 if greater than 2 years).