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Does hand involvement in Systemic Sclerosis limit Completion of Patient Reported Outcome Measures?

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Abstract

Introduction / objectives —The objective of this analysis is to examine whether the severity of systemic sclerosis (SSc)-hand involvement influences patient reported outcome measure (PROM) completion rate in a United States cohort of early disease.

Method—Participants included SSc patients with less than 5 years disease duration consented and enrolled in the Collaborative, National, Quality and Efficacy Registry (CONQUER) between June 2018 and December 2019. Participants' socio-demographics, hand clinical features (severe modified Rodnan Skin Score, presence of small joint contractures, acro-osteolysis, calcinosis, and digital ulcers), and completion rates of seven PROMs including a Resource Use Questionnaire were analyzed. Cohort characteristics and baseline PROM completion were evaluated. Multivariable logistic regression assessed the relationship between hand limitations and PROM incompleteness at several time points using generalized estimating equations.

Results —At the time of data lock, 339 CONQUER subjects had a total of 600 visits available for analysis. Calcinosis (odds ratio [OR] 6.35, confidence interval [CI] 2.41-16.73 and acro-osteolysis OR 3.88 (1.57-9.55) were significantly associated with incomplete PROM. The Resource Use Questionnaire was the PROM most commonly not completed. Increasing age was correlated with resource use questionnaire incompleteness rate.

Conclusions —Acro-osteolysis and calcinosis were associated with lower PROM completion rates in a US SSc cohort, independent of the length of the questionnaires or the modality of administration (electronic or paper). Resource Use Questionnaires are important for understanding the economic impact and burden of chronic disease; however, in this study it had lower completion rates than PROMs devoted to clinical variables.

Introduction:

Patient reported outcome measures (PROM) are critical in understanding the effect of disease progression as well as overall disease burden on patients. Patient questionnaires provide valuable structured data on the impact of a medical condition from the patient's perspective. In general, a resource utilization questionnaire can be particularly useful for understanding the individual economic and human costs resulting from chronic diseases [1]. However, it is well recognized that studies requiring extensive questionnaire completion assessing every health domain can be burdensome and result in PROM fatigue and missing data [2]. While guidelines exist for PROM development [3], the most effective modality for implementing PROM longitudinally in systemic sclerosis (SSc, scleroderma), a disease characterized by Raynaud's phenomenon and possible limitations in hand mobility and function, has not been well studied.

The Collaborative National Quality and Efficacy Registry (CONQUER) for SSc is a longitudinal cohort of patients with less than 5 years disease duration from first non-Raynaud's phenomenon, that focuses on minimizing missing data, prioritizing bio-specimen

collection, as well as longitudinal correlative PROM data [4]. The CONQUER database has 748 data fields that includes a complete physical exam by the same treating physician every visit. The CONQUER registry also collects PROM that are routinely used in SSc research [5, 6], including: participant global assessment (PGA), scleroderma health assessment questionnaire (SHAQ), Scleroderma Clinical Trials Consortium Gastrointestinal Tract questionnaire (GIT 2.0), Patient Reported Outcome Measurement Information System (PROMIS)-29, a patient skin assessment, the modified medical research council (mMRC) dyspnea scale, Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnea questionnaire, and a Resource Use Questionnaire.

Clinical features of scleroderma, which may influence completion of PROM, include the extent of hand involvement such as skin thickening, joint contractures, digital ulcerations (DU--defined as loss of epithelial surface), digital amputations, calcinosis, and resorption of the digital tufts and distal phalanges (acro-osteolysis) determined by physical exam or radiograph. In the CONQUER registry, physicians assess these features every six months. The purpose of this study was to investigate whether there is a correlation between SSc-specific hand manifestations and PROM completion rates. This is important since any such correlation may introduce bias into PROM collection.

Methods:

The CONQUER registry includes 14 SSc centers across the United States (US). After informed consent, the treating physician collects patient clinical outcome data at the time of clinical appointments at baseline and then every 6 months thereafter. During the consent process patients indicate whether they prefer to complete PROM electronically or on paper.

PROM:

The CONQUER PROM forms are uploaded into the CONQUER research electronic data capture (REDCap) database. The dyspnea PROM is an assessment that includes a single mMRC dyspnea scale to describe shortness of breath on a 5-point scale, and an 11-item two-part FACIT-dyspnea assessing shortness of breath for activities and function over the previous seven days. The PGA is a 0-10 scale for rating overall health related to SSc in the past week, followed by a 4-item patient skin assessment of overall skin disease and perceived tightness, pain, redness, hardening, and hard/itchy skin over the past week as well as in comparison to 6-months ago. The PROMIS-29 (v2.1) assesses physical function, anxiety, depression, fatigue, sleep, ability to participate in social roles and activities, pain interference, and pain intensity over the past 7 days. The SHAQ has 8 measures of dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activity; 2 items assess the need for help from another person and use of aids/devices; and 5 activity related issues related to intestinal problems, breathing problems, Raynaud's attacks, finger ulcers, and disease severity. The 34-item GIT 2.0 has domains for reflux, distention/bloating, diarrhea, social functioning, emotional wellbeing, and constipation is included on PROM. The final PROM is the Resource Use Questionnaire, which asks the patient to report on the number of health professionals visited, tests and diagnostic procedures, alternative treatments, aid and devices, outpatient procedures, hospitalizations, rehabilitation, and time spent seeing health

professionals over the past twelve months. The Resource Use Questionnaire can have a minimum of 53 items, but can expand to 195 questions that is dependent on responses. Since the Resource Use Questionnaire can thus be lengthy, our team has been concerned that patients may elect not to complete this form annually after completing once at baseline.

PROM Data collection:

Depending on patient request at the time of the consent (prior to seeing the length of the questionnaire), the CONQUER PROM may either be emailed to the patient prior to the scheduled clinical visit with reminders sent every three days until the visit, or if the patient prefers the PROM may be administered on paper at the time of the visit. If the PROM is incomplete at the clinical visit, the care provider is notified. If the institution has a tablet device, then this is used for in person PROM completion. Alternatively, paper forms may be provided to the patient during the visit and data is entered manually. All patients are asked to complete the PROM prior to them leaving the office.

Clinical Data Collection:

During the clinical visit, the treating physician completes a sociodemographic assessment and physical exam that includes an assessment of modified Rodnan skin score (mRSS), DU, finger joint contractures, calcinosis, digital amputations, tendon friction rubs, and acro-osteolysis. For this analysis, physical findings were reported individually and also categorized as the presence or absence of “hand limitation”. Hand limitation was considered present if there was any of the following: either hand mRSS scored as a three (severe), a finger contracture present, acro-osteolysis present, or an active DU defined by loss of epithelium was present. No patients had digital amputations, thus this variable was excluded from the analysis.

Data Analysis:

Cohort characteristics and PROM completion at baseline and 12 month visits were described using summary statistics (Table 1). Categorical variables were described with counts and percentages and continuous variables were described with median and Interquartile Ranges [IQR]. We categorized each individual subject visit as PROM completion (completed all 6 PROMs [Participant Global, Scleroderma Health, GIT, PROMIS, Patient Skin and Dyspnea Assessments]) or non-completion (did not complete at least one of the PROMs at that visit). We predicted PROM non-completion at each visit using generalized estimating equations (GEE). GEE accounts for the correlation between repeated measures for the same subject at multiple time points. A compound symmetry correlation structure was used. Five sets of univariate analyses were performed predicting PRO non-completion for each of the five hand limitations: calcinosis, mRSS, small joint contracture, acro-osteolysis and active digital ulcer (Table 2). Five separate multivariable GEE models were also performed predicting PRO non-completion for the five hand limitations adjusting for age at baseline, gender, race, ethnicity, employment status, marital status, and preferred method of completion (email or in-person) (Table 2). To analyze the association of patient demographics and hand limitations with RUQ completion within the first year (baseline or 6-month visit), univariate and multivariate logistic regression were performed (Table 3). Thirteen separate univariate logistic regressions were run, one for each patient characteristic. The multivariate model

contained all thirteen predictors. The expectation of patients is that the RUQ is completed once per year. Individuals were categorized as having completed it (either at the baseline or six-months) or did not complete it. The logistic model predicts non-completion of RUQ within the first year, where higher odds ratios indicate a larger likelihood of not completing the RUQ assessment.

Results:

Between June 2018 and December 2019, 339 CONQUER subjects had 600 total visits available for analysis. Eighty-six patients had both a baseline and a 12-month follow-up visit. The RUQ was administered to patients at both time periods. The completion rates of the RUQ and 6 PROMs at baseline and 12-months are shown in Table 1. The PROM completion rates for the RUQ and 6 PROMS are similar at baseline (between 85% and 90%); however, the first 6 PROMS were each completed at least 82% of the time at the 12-month visit, while the RUQ was completed only 62.8% of the time. In the univariate GEE models, calcinosis and acro-osteolysis features were significantly associated with non-completion of the 6 PROMs (calcinosis: odd ratio (OR) 2.89 confidence interval (CI) 1.33-6.29, $p=0.007$, acro-osteolysis: OR 2.95 CI 1.41-6.20 $p=0.004$). The five multivariate GEE models predicting non-completion of any PROM at a visit had the same conclusions. Calcinosis (OR 3.97 CI 1.36-11.54, $p=0.012$) and acro-osteolysis (OR 3.57 CI 1.37-9.32, $p=0.001$) are associated with non-completion of the PROMs (Table 2) when adjusting for those confounders (within their respective models). In the univariate logistic regressions, age was significantly associated with non-completion of RUQ within the first year of baseline, with older subjects having lower odds of completing the questionnaire (OR 0.97 CI 0.95-0.99, $p=0.009$, Table 3). Patients who indicated preference of emailed surveys had higher odds of non-completion compared to those who did not prefer email (OR 3.13 CI 1.49-7.4 $p=0.002$, Table 3). Presence of acro-osteolysis at baseline was significantly associated with RUQ non-completion (OR 3.31 CI 1.09 - 9.19, $p=0.035$, Table 3). In the multivariable analysis, email interest remained significant where patients who requested email instead of paper surveys were 3.34 times more likely to not complete the RUQ within the first year compared to those who did not prefer email ($p=0.007$, Table 5). Presence of acro-osteolysis was associated with non-completion of RUQ within the first year, but did not reach statistical significance ($p=0.075$).

Discussion:

Longitudinal multi-center research is critical for the identification of disease features that may be barriers for capturing the patient's perspective. The CONQUER database integrates user-friendly formats to allow patients to complete PROM online prior to, during or after their clinical visit, thus is an excellent platform to explore possible barriers. Hand involvement in SSc is an important consideration for questionnaire completion.

Acro-osteolysis and calcinosis were significantly associated with PROM non-completion in this longitudinal US based cohort of patients with early SSc. The presence of DU, contractures, or severe hand mRSS were not associated with PROM non-completion. This finding is important since ongoing efforts to develop PROM specific to these domains is

thus, still feasible [7, 8]. This report also highlights the importance of understanding the morbidity of acro-osteolysis and calcinosis on hand function in systemic sclerosis. These features impact PROM completion and have limited management options [9, 10], thus it will be important to consider this during future clinical trial design. Acro-osteolysis and calcinosis clearly affect how SSc patients feel and function, however, these features are not currently adequately captured in CONQUER clinical research using guideline based PROM [11, 12]. The differential distribution of PROM completion in different age groups also merits further consideration since younger patients may need to be reminded of the importance of completion of PROM in order to minimize missing data.

In order to improve allocation of resources [13] in SSc it is important that we are able to adequately collect PROM data. In the CONQUER study the Resource Use Questionnaire was the PROM that was most commonly incomplete, especially in younger patients. While the Resource Use Questionnaire is helpful for understanding the economic impact and burden of disease, alternative strategies for administering this survey at a different time point than other PROMs may reduce patient fatigue and minimize missing data.

Our study is not without limitations. The results reported are from observational research not a randomized trial. As such, the clinical data collection is completed at the time of clinical care not a structured research visit, which adds time limitations to the extent of data collected. For example, while tendon friction rubs are captured, only the number not the specific location is reported. Similarly, small and large joint contractures are not reported by which specific joint is involved and degree of range of motion loss is not recorded. While we recognize that other severe disease features captured by the database, such as interstitial lung disease and pulmonary hypertension, may influence a patient's willingness to complete a PRO, this analysis is specifically looking at hand limitations. Nonetheless, CONQUER is a valuable resource developed by physicians, patients, and researchers with a goal to provide a platform for studying PROM in SSc [4]. This report supports the concept of measuring not only severity of disease, but also assessing the burden of participation in observational research is critical to maximize response rate. Specifically, efforts to identify the characteristics of the completers versus non-completers of the Resource Use Questionnaire compared to the other PROMs can be used to focus on ensuring the patient population is well represented in CONQUER. Specifically, unbundling the Resource Use Questionnaire from the other PROM may well be a strategy that would result in higher completion rates, and this is something we intend to investigate as the CONQUER cohort continues to expand.

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Key Points:

- Multiple strategies are needed to ensure optimal completion of PROM in longitudinal cohort studies. Even if patients request electronic surveys, we have found it is important to follow up incomplete surveys with paper forms provided at the time of a clinical visit.
- The Resource Utilization Questionnaire was lengthy and prone to non-completion in the younger population.
- Acro-osteolysis and calcinosis were associated with reduced PROM completion rates.

Table 1.

Patient Characteristics

	Overall (N = 339)
Age at baseline visit: Median (Q1, Q3)	53.7 (42.3, 62.8)
Age at baseline visit category	
18-30 years	25 (7.4%)
30-60 years	210 (61.9%)
60+ years	104 (30.7%)
Gender	
Female	275 (81.1%)
Male	64 (18.9%)
Race	
White	259 (76.4%)
Black or African American	41 (12.1%)
Other	30 (8.8%)
Missing	9 (2.7%)
Ethnicity	
Not Hispanic or Latino	294 (86.7%)
Hispanic or Latino	37 (10.9%)
Missing	8 (2.4%)
Employment status	
Full-time	156 (46.0%)
Other	163 (48.1%)
Missing	20 (5.9%)
Marital status	
Married	225 (66.4%)
Not Married	108 (31.9%)
Missing	6 (1.8%)
Patient indicated interest in receiving emailed surveys and provided an email address	
Yes	225 (66.4%)
No	114 (33.6%)
Tendon friction rubs (anywhere on active palpation of ankles, knees, wrists or elbows)	
Yes	39 (11.5%)
No	291 (85.8%)
Missing	9 (2.7%)
Calcinosis	
Severe; functionally impairing or large/multiple lesions on exam	3 (0.9%)
Mild (palpable on exam)	14 (4.1%)
Asymptomatic or only radiographic	2 (0.6%)
None	317 (93.5%)
Missing	3 (0.9%)
Hand Modified Rodnan Skin Score	

	Overall (N = 339)
Severe	51 (15.0%)
Mild/Moderate	270 (79.6%)
Negative	17 (5.0%)
Missing	1 (0.3%)
Small Joint Contracture	
Present	151 (44.5%)
Absent	173 (51.0%)
Missing	15 (4.4%)
Acro-osteolysis	
Present	17 (5.0%)
Absent	304 (89.7%)
Missing	18 (5.3%)
Active Digital Ulcer (including Gangrene)	
Present	44 (13.0%)
Absent	295 (87.0%)
Hand Limitation¹	
Yes	178 (52.5%)
No	161 (47.5%)
Baseline PROM Completion	
Participant Global Assessment Complete	304 (89.7%)
Scleroderma Health Assessment Complete	305 (90.0%)
GIT Assessment Complete	304 (89.7%)
PROMIS Assessment Complete	300 (88.5%)
Patient Skin Assessment Complete	301 (88.8%)
Dyspnea Assessment Complete	297 (87.6%)
Resource Utilization Assessment Complete	288 (85.0%)
Subject had twelve month visit	86 (25.4%)
12 Month PROM Completion	
Participant Global Assessment Complete	71 (82.6%)
Scleroderma Health Assessment Complete	72 (83.7%)
GIT Assessment Complete	72 (83.7%)
PROMIS Assessment Complete	72 (83.7%)
Patient Skin Assessment Complete	71 (82.6%)
Dyspnea Assessment Complete	71 (82.6%)
Resource Utilization Assessment Complete	54 (62.8%)

¹Hand Limitation: if Hand Rodnan is severe, Small Joint Contracture is present, Acro-osteolysis is present or Active Digital Ulcer is present.

Table 2.

GEE models predicting PROM¹ non-completion across all observed visits

	<u>Univariate analysis²</u>		<u>Multivariate analysis³</u>	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Calcinosis = Severe or Mild⁴	2.89 (1.33, 6.29)	0.007	3.97 (1.36, 11.54)	0.012
Hand Modified Rodnan Skin Score = Severe⁵	0.91 (0.46, 1.79)	0.781	0.49 (0.19, 1.24)	0.132
Small Joint Contracture⁶	1.06 (0.67, 1.66)	0.805	1.06 (0.61, 1.85)	0.826
Acro-osteolysis⁷	2.95 (1.41, 6.20)	0.004	3.57 (1.37, 9.32)	0.001
Active Digital Ulcer (including Gangrene)⁸	1.20 (0.64, 2.24)	0.564	0.86 (0.39, 1.88)	0.700

¹ Patient reported outcome measures (PROMs): Participant Global, Scleroderma Health, Gastrointestinal Tract (GIT), Patient Reported Outcome Measurement Information System (PROMIS), Patient Skin and Dyspnea Assessments (does not include Resource Utilization Questionnaire).

² Results are 5 different univariate (unadjusted) generalized estimating equations (GEE) models.

³ Results are 5 different multivariate GEE models adjusting for age, gender, race, ethnicity, employment status, marital status, email interest and tendon friction rubs.

⁴ Number of events analyzed (N) for univariate and multivariate analyses is 581 and 489 respectively.

⁵ N for univariate and multivariate analyses is 593 and 495, respectively.

⁶ N for univariate and multivariate analyses is 572 and 485, respectively.

⁷ N for univariate and multivariate analyses is 568 and 481, respectively.

⁸ N for univariate and multivariate analyses is 596 and 497, respectively.

Table 3.

Logistic regression models predicting RUQ¹ non-completion

	Univariate analysis ²		Multivariate analysis ³	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age at baseline visit	0.97 (0.95, 0.99)	0.009	0.99 (0.96, 1.02)	0.403
Gender		0.806		0.494
Male	Reference		Reference	
Female	1.10 (0.53, 2.54)		1.41 (0.55, 4.22)	
Race		0.205		0.641
White	Reference		Reference	
Black or African American	1.10 (0.39, 2.64)		1.41 (0.36, 4.65)	
Other	2.33 (0.91, 5.46)		1.67 (0.48, 5.09)	
Ethnicity		0.855		0.722
Hispanic or Latino	0.91 (0.30, 2.29)		0.80 (0.20, 2.55)	
Not Hispanic or Latino	Reference		Reference	
Employment status		0.424		0.456
Full-time	1.29 (0.69, 2.43)		1.33 (0.63, 2.84)	
Other	Reference		Reference	
Marital status		0.637		0.713
Married	0.86 (0.46, 1.63)		1.17 (0.52, 2.81)	
Not Married	Reference		Reference	
Patient indicated interest in receiving emailed surveys and provided an email address		0.002		0.007
No	Reference		Reference	
Yes	3.13 (1.49, 7.41)		3.34 (1.37, 9.49)	
Tendon friction rubs (anywhere on active palpation of ankles, knees, wrists or elbows)		0.316		0.780
No	Reference		Reference	
Yes	0.59 (0.17, 1.57)		0.84 (0.22, 2.64)	
Calcinosis = Severe or Mild		0.775		0.118
No	Reference		Reference	
Yes	1.21 (0.27, 3.88)		3.65 (0.69, 15.82)	
Hand Modified Rodnan Skin Score		0.945		0.489
Negative	Reference		Reference	
Mild/Moderate	0.81 (0.25, 3.63)		0.38 (0.08, 2.83)	
Severe	0.87 (0.22, 4.37)		0.28 (0.04, 2.52)	
Small Joint Contracture		0.814		0.315
Absent	Reference		Reference	
Present	0.93 (0.51, 1.69)		1.50 (0.68, 3.31)	
Acro-osteolysis		0.035		0.075
Absent	Reference		Reference	
Present	3.31 (1.09, 9.19)		4.08 (0.86, 19.17)	

	<u>Univariate analysis²</u>		<u>Multivariate analysis³</u>	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Active Digital Ulcer (including Gangrene)		0.542		0.998
Absent	Reference		Reference	
Present	1.30 (0.53, 2.87)		1.00 (0.27, 3.12)	

¹Resource Utilization Questionnaire (RUQ): completed once every year so this outcome is whether the subject completed it at baseline or 6 months.

²Results are 13 different univariate (unadjusted) logistic models. The number of subjects in each model (N) is as follows: Age =339, Gender=339, Race=330, Ethnicity=331, Employment status=319, Marital status=333, Email =339, Tendon rubs=330, Calcinosis =336, Hand rodnan=338, Small joint contracture=324, Acro-osteolysis=321, Digital ulcers=339.

³Results are 1 multivariate logistic model with all listed predictors. N=270 with 40 having completed RUQ in the first year.

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