The development and preliminary validation of the CTCL-PRO-20: a novel quality of life survey for patients with cutaneous T-cell lymphoma

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Abstract

Cutaneous T-cell lymphoma (CTCL) is a rare disease with a high symptom burden, negatively impacting patients' quality of life (QoL). There is no agreed-upon CTCL-specific metric to measure QoL in CTCL. Thus, we created a novel questionnaire to fill this gap. Eighty CTCL patients participated in this cross-sectional survey study. An iterative process of principal components analysis (PCA) yielded a 5-component solution with 20 items; this patient-reported outcomes (PRO) questionnaire, the CTCL-PRO-20, had high internal-consistency reliability (Cronbach's α=0.93). Components measured self-consciousness (α=0.94), treatment burden (α=0.92), lack of CTCL resources (α=0.74), sleep/fatigue (α=0.87), and skin (α=0.88) concerns. High Pearson correlations were observed between the CTCL-PRO-20 and QoL measures more relevant to patients' experiences (e.g., MF/SS-CTCL QoL and Skindex-29); lower correlations were observed with the generic-QoL (SF-36) and single-focused (e.g., sleep-disturbance) measures. Patients with stable/no active disease (*vs.* progressive disease) reported significantly lower treatment-burden scores (i.e., better QoL). Patients who received systemic and topical treatments (*vs.* no treatment) reported significantly higher CTCL-PRO-20 scores (i.e., poorer QoL). This single-center study provides preliminary evidence of construct and convergent validity of the CTCL-PRO-20 and its components, warranting further validation in a well-powered study to examine its sensitivity to change after treatment intervention.

Introduction

Cutaneous T-cell lymphoma (CTCL) is a rare form of T-cell non-Hodgkin lymphoma that presents in the skin; mycosis fungoides (MF) and its leukemic variant Sézary syndrome (SS) are the most common CTCL subtypes.[1] CTCL is treatable but not curable without an allogeneic transplant, and therefore therapy is largely palliative and symptom directed. Patients with advanced-stage disease (stage IIB-IVB) have a poor prognosis, and a median survival of <5 years.[2,3] In addition, CTCL carries unique disease-specific challenges, which have a significant negative impact on patient quality of life (QoL), partially due to the particularly debilitating symptom burden even when compared to other malignancies and skin diseases.[4,5] A prior study by Herbosa *et al.*[4] evaluating QoL in patients with CTCL showed significantly worse scores than patients with general dermatologic diseases on several QoL measures, including the Health Utilities Index-3 (HUI3),[6] RAND 36-item Health Survey 1.0 (SF-36),[7] Skindex-29,[8] Visual Analog Scale (VAS)-Itch (evaluating itching over the previous 24 hours),[9] and the 5-D Itch Scale.[10] The Herbosa *et al.*[4] study also showed that CTCL patients with advanced-stage disease had greater QoL impairment than patients with early-stage disease (stage IA-IIA).

While clinical trials in CTCL have incorporated tools to evaluate QoL, they have relied largely on measures used for other dermatologic conditions or more general oncology QoL metrics, as robust CTCL-specific measures that show sensitivity to change in disease status were not available at

the time these trials were conducted. In addition, several measures used to evaluate QoL in patients with CTCL are lacking critical information about CTCL-specific concerns important to this patient population. Using inductive thematic analysis of interviews with CTCL patients, Bhat *et al.*[11] identified several issues important to patients' QoL including itching, pain, fatigue, sleep, skin breaks, skin flaking, concerns about appearance, isolation, a sense of "otherness", depression, hopelessness, uncertainty, treatment burden, and a lack of resources about CTCL in the community; some of these particular patient concerns have not been captured in existing QoL measures. To our knowledge, there is no existing QoL measure that has been made using all of those concerns affecting QoL in CTCL patients.[11]

We, therefore, sought to develop a comprehensive, CTCL-specific PRO measure based on analysis of patient interview data, incorporating patient feedback on the development of items in the questionnaire, and validating this new measure in patients with early- and advanced-stage disease in a single-center, pilot study.

Methods

Patient population

A single-center, cross-sectional survey study was conducted at Washington University in St. Louis from 15th March to 10th August 2023. Eligibility criteria included patients who had a biopsy-confirmed diagnosis of CTCL, were ≥18 years old, able to read and speak English, and able to independently complete surveys. This study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Washington University School of Medicine Institutional Review Board (IRB). All enrolled patients provided informed consent.

Development of questionnaire items

Based on inductive thematic analysis of semi-structured interview data from 18 patients with early- and late-stage CTCL,[11] 54 items were developed for a new CTCL-focused QoL questionnaire. These items were reviewed for clinical relevance by a multidisciplinary panel including oncologists, dermatologists, and an expert in instrument development, after which 46 items remained. Next, one-on-one cognitive interviews were conducted with 9 CTCL patients (5 early-stage, 4 late-stage) to elicit feedback about the clarity of the wording of the items, their interpretation, response options, and survey length.[12,13] Participant feedback was examined by the multidisciplinary panel, who then revised or removed items identified as problematic (e.g., compound sentence construction or redundancy), leaving 41 items for pilot testing (*Online Supplementary Figure S1*).

Response options for each new CTCL-PRO item used a 5-point Likert scale ranging from Strongly disagree (1 point) to Strongly agree (5 points). Four CTCL-PRO items focused on the treatment burden that patients had experienced in the past month; for these four items, a sixth response option was offered for patients not receiving treatment: "Not applicable – I have not been on treatment in the last month." This option was given a score of 0, which would not adversely affect the total score a patient received. Lower total scores due to "not applicable" responses to these items (scored 0) would not be interpreted differently than a score of 1 on these items.[14] Item responses were summed, and higher total scores indicate greater CTCL-specific concerns (i.e., poorer QoL).

Data collection

In addition to the 41 newly developed items, participants completed six previously validated questionnaires, including the eight SF-36 subscales,[7] Mycosis Fungoides/Sézary Syndrome (MF/SS)-CTCL QoL,[14] VAS-Itch (past 24 hours),[9] Skindex-29,[15] Center for Epidemiologic Studies Depression (CES-D) Scale,[16] and the Patient Reported Outcomes Measurement Information System (PROMIS™) Sleep Disturbance.[17] Scoring of each measure followed the developer's published scoring guidelines. Patients could complete the survey either electronically using REDCap or on paper. Clinical data were collected from the electronic medical record and included initial stage at diagnosis, current stage and disease status at time of survey completion (stable/no active disease, active disease responding to current therapy, and progressive disease), type(s) of treatment received (light, topical, radiation, and systemic therapies), and number of lines of treatment received (from 0 to 4).

Statistical analysis

An iterative process of principal components analysis (PCA)[18] with the 41 newly developed, CTCL-focused PRO items was run for data reduction. PCA is a commonly used, efficient statistical process for data reduction to empirically identify multi-item components for analysis from item responses.[19,20] After dropping items that lacked variance in response, we ran the PCA using an oblique (oblimin) rotation to examine correlations among individual items and item loadings on specific components, and to determine if components were intercorrelated.[21] Component loadings are the regression co-efficients of each item on each component extracted. We retained items loading ≥0.600 on a single component and dropped items loading ≥0.400 on more than one component after rotation.[18,22] Cross-loading on more than one component indicates that an item does not discriminate between different constructs.[23] At this early stage of instrument development, we also considered retaining items that loaded ≥0.500 on a component if the item was especially relevant to CTCL topics identified during patient interviews,[11] without loading ≥0.400 on another component. We thus retained components using commonly accepted criteria: each component should have at least three items with moderate-to-high component loadings on one factor

after rotation[18] and an eigen¬value >1.000.[18] Cronbach's α was used to measure the internal-consistency reliability of items that loaded highly on each component and on the overall CTCL-PRO; Cronbach's α ≥0.70 was considered acceptable.[24,25] We examined the construct and convergent validity of the new measure using Pearson correlations between our new CTCL-PRO measure and each of the other questionnaires. We examined differences in each of the QoL continuous measures by patient demographics, disease status, stage, and treatments received using analyses of variance (ANOVA). We used χ^2 tests to measure associations among the categorical demographic and clinical variables. Two-tailed statistical significance was set at $P<0.05$. Statistical tests were performed using IBM SPSS version 28.0.0.0 (IBM Corp, Armonk, NY, USA).

Table 1. Characteristics of patients who gave their consent to participate in the study who completed and did not complete the survey (N=93).

	Completed the survey N=74 (%)	Did not complete the survey N=19 (%)	P[a]
Age, mean (SD), yr	64.1 (15.0)	64.6 (13.6)	0.90
Sex			0.20
Male	42 (56.8)	14 (73.7)	
Female	32 (43.2)	5 (26.3)	
Race/ethnicity			0.72
White	63 (85.1)	16 (84.2)	
Black	9 (12.2)	3 (15.8)	
Hispanic	2 (2.7)	0 (0.0)	
Initial stage			0.40
Early (IA, IB, IIA)	47 (63.5)	14 (73.7)	
Advanced (IIB-IVB)	27 (36.5)	5 (26.3)	
Current[b] stage			0.99
Early (IA, IB, IIA)	66 (89.2)	17 (89.5)	
Advanced (IIB-IVB)	8 (10.8)	2 (10.5)	
Current[b] disease status			0.86
Stable/no active disease	35 (47.3)	10 (52.6)	
Active disease responding to current therapy	28 (37.8)	7 (36.8)	
Progressive disease	11 (14.9)	2 (10.5)	
Current[b] treatment			
Systemic[c]			0.41
Yes	39 (52.7)	12 (63.2)	
No	35 (47.3)	7 (36.8)	
Light treatment			0.59
Yes	26 (35.1)	5 (26.3)	
No	48 (64.9)	14 (73.7)	
Topical			0.80
Yes	31 (41.9)	9 (47.4)	
No	43 (58.1)	10 (52.6)	
Radiation therapy			0.58
Yes	4 (5.4)	0 (0.0)	
No	70 (94.6)	19 (100.0)	
Combinations of treatment received			0.39
Untreated	6 (8.1)	0 (0.0)	
Only other types of treatment	29 (39.2)	7 (36.8)	
Systemic with or without other treatment	39 (52.7)	12 (63.2)	
Total N of types of treatment received			0.86
0	8 (10.8)	1 (5.3)	
1	40 (54.1)	12 (63.2)	
2	22 (29.7)	5 (26.3)	
3	4 (5.4)	1 (5.3)	

Results

Patients' characteristics

Ninety-three patients agreed to participate in this study, of whom 80 (88%) were included in the PCA. Seventy-four (80%) patients completed >75% of items on each measure and were included in the subsequent analyses to examine the construct and convergent validity of the new CTCL-PRO questionnaire following the PCA. There were no significant differences in demographic or clinical variables between participants and non-participants (Table 1). Among the 74 participants with complete data, 42 (57%) were men and 63 (85%) self-identified as white. Forty-seven (64%) participants were early-stage and 27 (36%) were advanced-stage CTCL at diagnosis. At time of survey completion, 19 of the 27 patients with initial advanced-stage disease were re-staged as early-stage disease due to response to treatment, all patients with initial early-stage disease remained early-stage. Thirty-five (47%) patients had stable/no active disease, 28 (38%) had active disease responding to current therapy, and 11 (15%) had progressive disease. Most patients received 1-2 types of treatment (84%). Specific systemic therapies patients had received most recently prior to survey completion are described in a footnote to Table 1.

Principal component analysis

An iterative process of PCA was run using (oblique) oblimin rotation, yielding a 5-component solution with 20 items. The 20 items comprising this novel measure, the CTCL-PRO-20, are shown in *Online Supplementary Figure S2*. The pattern matrix loadings after rotation are reported in Table 2. Items with loadings ≥0.600 on one component were retained,[22]

[a]χ^2 tests reported or Fisher's exact tests when cells for 2 x 2 tests included <10 cases. [b]"Current" refers to the time of survey completion (participants who gave their consent who completed the survey) or consent (participants who gave their consent but did not complete the survey). [c]Systemic treatment includes any cutaneous T-cell lymphoma (CTCL)-directed therapy that was given via an oral or intravenous route, including the following: bexarotene (N=19), mogamulizumab (N=5), lacutamab (N=3), brentuximab vedotin (N=3), methotrexate (N=1), gemcitabine (N=1), pembrolizumab (N=1), upadacitinib (N=1), liposomal doxorubicin (N=1), and mogamulizumab-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone; N=1). One patient had most recently received an allogeneic stem cell transplant as their CTCL-directed therapy. N: number; SD: standard deviation; yr: years.

as were two items loading ≥0.500 on their respective component measuring sleep problems and concern about sores, which were identified in patient interviews as being especially relevant to CTCL-related QoL.[11] Items with moderate-to-high loadings on each of the five CTCL-PRO-20 components demonstrated acceptably high internal-consistency reliabilities: Component 1, 6-item self-consciousness (Cronbach's α=0.94); Component 2, 4-item treatment burden (Cronbach's α=0.92); Component 3, 3-item lack of CTCL resources (Cronbach's α=0.74); Component 4, 4-item sleep/fatigue (Cronbach's α=0.87); and Component 5, 3-item concern about sores (Cronbach's α=0.88). Cronbach's α for the overall 20-item CTCL-PRO-20 measure was 0.93. We computed total scores for the overall CTCL-PRO-20 and each of the five subscales; higher total scores on the CTCL-PRO-20 and subscales indicate greater CTCL-related concerns and poorer QoL. In the component correlation matrix after oblimin rotation, the self-consciousness component and sleep/fatigue component were moderately correlated (r=0.543); however, correlations among other pairs of components were low (range: r=0.095 to r=0.363).

Construct and convergent validity

We assessed the construct and convergent validity of the overall CTCL-PRO-20 and its components using Pearson correlations between each of these CTCL-PRO-20 components and other previously validated metrics (Table 3).

Overall CTCL-PRO-20 - Low-to-moderate correlations were observed between the overall CTCL-PRO-20 and each of the measures less specific to CTCL. Low-to-moderate negative correlations were observed between the overall CTCL-PRO-20 and the SF-36 scales (higher scores on the SF-36 indicate better QoL and higher scores on the CTCL-PRO-20 indicate poorer QoL). The lowest significant correlation was between the overall CTCL-PRO-20 and SF-36 Physical functioning scale (r=-0.314). Correlations were moderate between the overall CTCL-PRO-20 and each of the VAS-Itch (r=0.665), CES-D Scale (r=0.617), and PROMIS™ Sleep Disturbance Scale (r=0.465). Correlations were highest between the overall CTCL-PRO-20 and the MF/SS-CTCL QoL (r=0.803) and Skindex-29 overall (r=0.809).

CTCL-PRO-20 self-consciousness component - The self-consciousness component showed moderate-to-high correlations with each of the other QoL measures except for the SF-36 Physical functioning (r=-0.205) and Role limitations due to physical health subscales (r=-0.366); this component also showed a low but significant correlation with patient age (r=-0.244).

CTCL-PRO-20 treatment-burden component - Moderate correlations were observed between the CTCL-PRO-20 treatment-burden component and the VAS Itch (r=0.434) and Skindex-29 Symptoms subscale (r=0.408). Overall, low correlations were observed between the CTCL-PRO-20 treatment-burden component and other variables. Low but significant correlations were seen between the treatment-burden component and the Skindex-29 overall (r=0.342) measure, the Skindex-29 Emotional (r=0.284) and Functioning (r=0.296) subscales, the SF-36 Social functioning subscale (r=-0.272), and the MF/SS-CTCL QoL (r=0.322). The remaining six variables were not significantly correlated with this component.

CTCL-PRO-20 lack of CTCL resources component - Moderate correlations were observed between the CTCL-PRO-20 lack-of-CTCL-resources component and the MF/SS-CTCL QoL, seven of eight SF-36 subscales, Skindex-29 overall and subscales, and CES-D. However, low, correlations between this lack-of-CTCL-resources component and the VAS Itch, PROMIS™ sleep disturbance, and SF-36 Physical functioning subscale were statistically significant.

CTCL-PRO-20 sleep/fatigue component - The CTCL-PRO-20 sleep/fatigue component demonstrated moderate-to-high correlations with each of the other measures, except for the SF-36 Role limitations due to the emotional problems subscale (r=-0.320). Of note, the sleep/fatigue component was only moderately correlated with PROMIS™ sleep disturbance, but highly correlated with VAS Itch, MF/SS CTCL QoL, and Skindex-29 overall and Symptoms and Functioning subscales.

CTCL-PRO-20 concerns about sores component - There were low correlations between the CTCL-PRO-20 concerns-about-sores component and each of the VAS-Itch (r=0.319) and eight SF-36 subscales, but moderate correlations were observed between this component and the other QoL measures.

Correlations among CTCL-PRO-20 overall and five component scores

The self-consciousness (r=0.872) and sleep/fatigue (r=0.820) components correlated more highly with the overall CTCL-PRO-20 than the other three components, which nevertheless showed moderate-to-high correlations (ranging from 0.601 to 0.765) with the overall CTCL-PRO-20 (Table 4). Each component also correlated more highly with the overall CTCL-PRO-20 than they correlated with each of the other CTCL-PRO-20 components.

Between-group differences in the overall CTCL-PRO-20 and components

Using ANOVA, we observed no significant differences according to sex or race/ethnicity in the CTCL-PRO-20 overall or its components (*data not shown*). Differences based on disease status, initial stage, and current stage are summarized in Table 5. The CTCL-PRO-20 treatment-burden

Table 2. Descriptive statistics for each item and pattern matrix from principal components analysis after oblimin rotation showing item loadings on each component of the Cutaneous T-Cell Lymphoma Patient-reported Outcomes 20-item Questionnaire (N=80).

	Mean (SD)[a]	Component co-efficients*				
		Self-consciousness	Treatment burden	Lack of CTCL resources	Sleep/fatigue problems	Concern about sores
Item 2. I refrain from going out in public because of my appearance.	1.9 (1.2)	0.890*	0.085	-0.068	0.078	-0.169
Item 6. I am embarrassed to be with other people due to skin flaking.	2.1 (1.2)	0.842*	0.015	-0.117	0.023	0.076
Item 23. I am concerned about my appearance due to MF/SS.	2.8 (1.3)	0.746*	-0.081	0.158	0.009	0.172
Item 24. I feel self-conscious about my appearance due to MF/SS.	2.9 (1.4)	0.822*	-0.037	0.106	-0.051	0.163
Item 35. I feel socially isolated because of my MF/SS.	2.2 (1.2)	0.758*	0.137	0.102	0.026	0.009
Item 37. I am embarrassed about the way I look.	2.6 (1.3)	0.809	0.014	0.082	0.017	0.110
Item 38. The frequency of my treatment(s) interferes with my daily activities.	2.1 (1.4)	-0.029	0.968*	0.031	0.009	-0.100
Item 39. The frequency of my treatment(s) interferes with my social life.	1.9 (1.3)	0.026	0.897*	0.012	0.097	-0.034
Item 40. The time I have spent receiving treatment for MF/SS has been a burden.	2.0 (1.3)	0.061	0.942*	-0.035	-0.127	0.042
Item 41. The side effects of MF/SS treatments have been burdensome.	2.1 (1.3)	-0.040	0.693*	0.013	0.088	0.273
Item 17. In the general population, there is a lack of understanding about MF/SS.	4.1 (0.9)	-0.111	-0.009	0.876*	-0.077	0.060
Item 21. It is frustrating that more people do not know about MF/SS.	3.2 (1.1)	0.225	0.085	0.643*	0.123	-0.034
Item 22. There is a lack of available resources for me to share with friends and family to help them better understand MF/SS.	3.1 (1.0)	0.073	-0.012	0.752*	0.105	-0.073
Item 1. Worrying about MF/SS prevents me from falling asleep.	2.1 (1.2)	0.397	0.000	0.098	0.548*	-0.201
Item 7. Symptoms of MF/SS, including itch, impact my ability to fall asleep.	2.7 (1.4)	0.087	0.097	0.042	0.837*	-0.072
Item 20. Fatigue due to MF/SS or its treatment prevents me from completing daily tasks.	2.5 (1.2)	0.140	0.024	0.093	0.646*	0.086
Item 31. My MF/SS symptoms, including itch, cause me to wake up during the night.	2.8 (1.4)	-0.183	-0.007	-0.006	0.943*	0.190
Item 8. I have experienced broken skin (sores or cuts) due to MF/SS or its treatment.	3.2 (1.4)	0.057	0.119	-0.029	0.025	0.853*
Item 10. I am concerned about the sores and/or cuts on my skin.	3.0 (1.3)	0.124	0.092	0.115	0.105	0.767*
Item 19. Skin flaking due to MF/SS is bothersome.	3.1 (1.4)	0.330	-0.081	-0.079	0.266	0.586*

[a]Response options for each item used a 5-point Likert scale ranging from 1=Strongly disagree to 5=Strongly agree, with higher scores indicating poorer quality of life. *Co-efficients indicating items with moderate-to-high correlations on each component. CTCL-PRO-20: Cutaneous T-cell Lymphoma Patient-reported Outcomes 20-item Questionnaire; MFSS/CTCL: Mycosis Fungoides/Sézary syndrome.

component differed significantly by disease status (*P*=0.02); in Bonferroni post-hoc pairwise comparisons, patients with stable/no active disease reported significantly lower treatment-burden scores (i.e., better QoL) than patients with progressive disease (6.9 [SD 4.9] *vs*. 11.1 [SD 5.1]; *P*=0.02). Patients with active disease responding to current therapy scored between these two groups. There were no statistical differences observed between other CTCL-PRO-20 components and overall score according to disease status. In addition, there were no significant differences in the CTCL-PRO-20 overall score or its component scores according to initial or current stage.

In ANOVA of the CTCL-PRO-20 overall or component scores according to types of treatment received by time of survey (Table 6), patients receiving (*vs*. not receiving) systemic therapies reported significantly higher scores indicating greater agreement with self-consciousness and concern about sores. Patients receiving topical treatments reported higher scores for the CTCL-PRO-20 overall measure, self-consciousness, and a lack of CTCL resources. CTCL-PRO-20 Overall and

Table 3. Pearson correlations among each of the Cutaneous T-Cell Lymphoma Patient-reported Outcomes 20-item Questionnaire's overall and component scores and other variables of interest (N=74).

Variables	Overall	Self-consciousness	Treatment burden	Lack of CTCL resources	Sleep/fatigue problems	Concern about sores
Age	-0.182	-0.244[c]	-0.016	-0.092	-0.216	-0.054
VAS Itch	0.665[a]	0.538[a]	0.434[a]	0.315[b]	0.638[a]	0.535[a]
MFSS/CTCL QoL	0.803[a]	0.777[a]	0.322[b]	0.507[a]	0.766[a]	0.603[a]
PROMIS Sleep disturbance	0.465[a]	0.440[a]	0.079	0.361[b]	0.564[a]	0.319[b]
SF36 Physical functioning	-0.314b	-0.205	-0.138	-0.364[b]	-0.407[a]	-0.159
SF36 Role limitations-physical health	-0.504[a]	-0.366[b]	-0.300[b]	-0.437[a]	-0.491[a]	-0.371[b]
SF36 Role limitations-emotional problems	-0.439[a]	-0.478[a]	-0.186	-0.384[a]	-0.320[b]	-0.265[c]
SF36 Vitality	-0.521[a]	-0.464[a]	-0.175	-0.499[a]	-0.552[a]	-0.326[b]
SF36 Emotional well-being	-0.587[a]	-0.642[a]	-0.141	-0.429[a]	-0.555[a]	-0.397[a]
SF36 Social functioning	-0.611[a]	-0.556[a]	-0.272[c]	-0.518[a]	-0.616[a]	-0.359[b]
SF36 Pain	-0.505[a]	-0.428[a]	-0.194	-0.438[a]	-0.579[a]	-0.302[b]
SF36 General health	-0.531[a]	-0.425[a]	-0.291[c]	-0.464[a]	-0.520[a]	-0.351[b]
Skindex-29 Symptoms	0.760[a]	0.574[a]	0.408[a]	0.406[a]	0.743[a]	0.748[a]
Skindex-29 Emotional	0.756[a]	0.767[a]	0.284[c]	0.499[a]	0.677[a]	0.567[a]
Skindex-29 Functioning	0.754[a]	0.736[a]	0.296[c]	0.486[a]	0.716[a]	0.556[a]
Skindex-29 Overall	0.809[a]	0.757[a]	0.342[b]	0.504[a]	0.758[a]	0.649[a]
CES-D	0.617[a]	0.632[a]	0.184	0.503[a]	0.552[a]	0.450[a]

CES-D: Center for Epidemiologic Studies-Depression; CTCL-PRO-20: Cutaneous T-Cell Lymphoma Patient-reported Outcomes 20-item; MFSS/CTCL QoL: Mycosis Fungoides/Sézary Syndrome Cutaneous T-Cell Lymphoma Quality of Life; PROMIS™: Patient Reported Outcomes Measurement Information System; SF-36: RAND 36-Item Health Survey (Short Form); VAS: Visual Analog Scale. [a]*P*<0.001. [b]*P*<0.01. [c]*P*<0.05.

Table 4. Pearson correlations among each of the Cutaneous T-Cell Lymphoma Patient-reported Outcomes 20-item Questionnaire's overall and component scores (N=74).

CTCL-PRO-20 components	Overall	Self-consciousness	Treatment burden	Lack of CTCL resources	Sleep/fatigue problems	Concern about sores
Self-consciousness	0.872[a]	1.00	-	-	-	-
Treatment burden	0.657[a]	0.384[a]	1.00	-	-	-
Lack of CTCL resources	0.601[a]	0.467[a]	0.258[c]	1.00	-	-
Sleep/fatigue problems	0.820[a]	0.632[a]	0.396[a]	0.486[a]	1.00	-
Concern about sores	0.765[a]	0.623[a]	0.363[b]	0.313[b]	0.577[a]	1.00

CTCL-PRO-20: Cutaneous T-Cell Lymphoma Patient-reported Outcomes 20-item Questionnaire. [a] *P*<0.001. [b]*P*<0.01. [c]*P*<0.05.

component scores did not differ significantly between patients receiving and not receiving light or radiation therapy, though sample sizes were small for these groups, especially radiation (received by 4 patients).

Discussion

The CTCL-PRO-20 is a novel 20-item CTCL-specific questionnaire reflecting concerns affecting CTCL patient QoL. It is one of very few CTCL-specific QoL surveys created with input from both early- and advanced-stage patients, and was developed for use in clinical practice and clinical research studies. The MF/SS-CTCL-QoL questionnaire[14] and Functional Assessment of Cancer (FACT)-CTCL[26] were also developed to measure QoL in CTCL patients; however, these two measures use different item wording and have a single factor structure. The FACT-CTCL, which includes both the well-validated, 27-item FACT-General (FACT-G)[27] and the newer CTCL-S asks patients to indicate their responses "as it applies to the past 7 days"[26] without mention of MF/SS, whereas the MF/SS-CTCL-QoL[14] and CTCL-PRO-20 ask patients to consider their response over the "past 4 weeks" or "past month," respectively, with explicit mention of MF/SS. Although we compute a CTCL-PRO-20 total score, the five distinct, multi-item subscales can each be used as separate CTCL-specific QoL measures, setting this measure apart from the MF/SS-CTCL-QoL and CTCL-S, which are both single-score measures of QoL. Moreover, the CTCL-PRO-20 component addressing the lack of knowledge and resources about CTCL is unique to this measure. Importantly, all three of these CTCL-specific QoL questionnaires require further validation to show sensitivity to change in response to treatment in clinical trials. Up to now, none of these CTCL-specific measures have been adequately validated for use in clinical practice.

Table 5. Analysis of variance of the Cutaneous T-Cell Lymphoma Patient-reported Outcomes 20-item questionnaire's overall and component mean (SD) total scores, by current disease status and initial and current stage (N=74).

CTCL-PRO-20 components	Current disease status				Initial stage			Current stage		
	Stable/no active disease N=35	Active disease responding to therapy N=28	Progressive disease N=11	*P*	Early N=47	Advanced N=27	*P*	Early N=66	Advanced N=8	*P*
Overall	49.5 (17.3)	52.3 (16.0)	61.2 (14.9)	0.13	50.2 (16.3)	55.9 (17.2)	0.16	51.6 (16.7)	58.0 (17.6)	0.31
Self-consciousness	13.6 (7.2)	14.0 (5.7)	17.4 (5.9)	0.24	13.6 (6.2)	15.6 (7.0)	0.20	14.0 (6.5)	16.9 (6.8)	0.24
Treatment burden	6.9 (4.9)	8.8 (4.0)	11.1 (5.1)	0.02	8.0 (5.4)	8.6 (3.6)	0.59	8.2 (5.0)	8.3 (3.0)	0.98
Lack of CTCL resources	10.2 (2.7)	10.1 (2.5)	10.5 (2.0)	0.94	10.0 (2.6)	10.7 (2.3)	0.22	10.2 (2.5)	10.4 (2.3)	0.86
Sleep/fatigue	9.9 (4.8)	9.9 (4.1)	11.0 (3.9)	0.76	9.6 (4.4)	10.9 (4.2)	0.25	9.8 (4.4)	12.0 (4.0)	0.19
Concern about sores	8.9 (3.7)	9.4 (3.9)	11.3 (3.2)	0.18	9.0 (3.4)	10.1 (4.2)	0.20	9.3 (3.7)	10.5 (4.1)	0.39

CTCL-PRO-20: Cutaneous T-Cell Lymphoma Patient-reported Outcomes 20-item Questionnaire. N: number; SD: standard deviation.

Table 6. Analysis of variance of the Cutaneous T-Cell Lymphoma Patient-reported Outcomes 20-item questionnaire's overall and component mean total scores, by each type of treatment received (N=74).

CTCL-PRO-20 components	Systemic therapy N (SD)		*P*	Light therapy N (SD)		*P*	Topical therapy N (SD)		*P*	Radiation therapy N (SD)		*P*
	No N=35	Yes N=39		No N=48	Yes N=26		No N=43	Yes N=31		No N=70	Yes N=4	
Overall	48.5 (15.0)	55.7 (17.7)	0.06	54.6 (17.0)	48.0 (15.9)	0.11	56.5 (17.5)	46.4 (14.0)	0.009	52.0 (16.7)	57.8 (19.1)	0.50
Self-consciousness	12.7 (5.4)	15.8 (7.2)	0.04	15.4 (6.7)	12.3 (5.9)	0.06	16.3 (7.0)	11.5 (4.6)	0.002	14.3 (6.5)	14.8 (7.9)	0.89
Burden of treatment	7.6 (5.3)	8.8 (4.3)	0.26	8.0 (4.5)	8.5 (5.4)	0.69	8.9 (4.7)	7.4 (4.8)	0.18	8.2 (4.8)	9.5 (4.4)	0.59
Lack of CTCL resources	10.2 (2.3)	10.2 (2.7)	0.99	10.4 (2.6)	9.8 (2.2)	0.34	10.9 (2.3)	9.3 (2.5)	0.007	10.2 (2.5)	11.0 (2.2)	0.53
Sleep/fatigue	9.5 (4.3)	10.6 (4.4)	0.27	10.7 (4.5)	8.9 (3.9)	0.08	10.7 (4.4)	9.2 (4.1)	0.12	10.1 (4.4)	10.2 (4.4)	0.94
Concern about sores	8.5 (3.5)	10.2 (3.8)	0.047	10.0 (3.8)	8.4 (3.5)	0.08	9.7 (3.8)	9.0 (3.6)	0.42	9.3 (3.7)	12.2 (2.5)	0.12

CTCL-PRO-20: Cutaneous T-Cell Lymphoma Patient-reported Outcomes 20-item Questionnaire. N: number; SD: standard deviation (component mean).

In this preliminary assessment of the psychometric properties of the CTCL-PRO-20, items on each of the five components and the overall CTCL-PRO-20 demonstrated high internal-consistency reliability.[25] The MF/SS-CTCL-QoL and overall Skindex-29, which predominantly measure issues that affect CTCL patient QoL, were highly correlated with the overall CTCL-PRO-20, supporting its convergent validity. The significant low-to-moderate correlations between the CTCL-PRO-20 and other QoL questionnaires indicate the CTCL-PRO-20 measures constructs that may be related to but are different from the other questionnaires, supporting discriminant validity. Additionally, each of the CTCL-PRO-20 components correlated more highly with the overall measure than with each other, indicating that each component contributes differentially to this measure. The CTCL-PRO-20 treatment-burden component scores were significantly higher in patients with progressive disease and patients receiving systemic therapy scored significantly higher on the self-consciousness and concern about sores components, providing preliminary evidence that the CTCL-PRO-20 captures treatment effects on QoL. To our knowledge, the association between lack of CTCL resources and QoL is a novel finding, indicating a need for more patient-directed resources and information to better prepare them for living with this rare disease. In contrast to our previous findings using other QoL measures,[4] we observed no significant differences in CTCL-PRO-20 scores based on stage. This finding may be due to the small sample of patients with advanced-stage CTCL or the efficacy of some well-tolerated modern therapies, and warrants further study.

Other studies reported that women with CTCL have worse QoL than men,[27-29] and Black patients are more likely to develop CTCL and have worse overall survival compared to white patients.[30,31] However, CTCL-PRO-20 scores did not differ significantly according to sex or race/ethnicity. This could be due to the CTCL-specific focus of this measure, suggesting that, among patients in our sample, the effects of CTCL on QoL may not be differentially experienced according to sex or race/ethnicity. Similar results were reported using the MF/SS CTCL QoL.[14]

As noted, there are already two existing surveys intended to measure QoL in CTCL patients: the MF/SS-CTCL-QoL and FACT-CTCL. However, these have received only preliminary validation. The MF/SS-CTCL-QoL study included mostly patients with early-stage disease, and stage was self-reported,[14] introducing potential inaccuracies, as staging CTCL can be complex. While the CTCL-PRO-20 overall was highly correlated with the MF/SS-CTCL-QoL, some CTCL-PRO-20 components had low or moderate correlations with the MF/SS-CTCL-QoL, indicating that these components are measuring different constructs. A subscale of the FACT-CTCL questionnaire, the CTCL-S,[26] was published after our study was initiated and was not, therefore, included in our preliminary validatory assessments. The CTCL-PRO-20 provides unique insights into PRO that are either not captured, or not captured in as much depth, by these existing questionnaires as they are in the multi-item self-consciousness and lack the CTCL resource components of the CTCL-PRO-20. The extent to which the CTCL-PRO-20 and CTCL-S are correlated will be examined in future validation studies using both measures. Importantly, further research is needed to examine the sensitivity of each of these new CTCL-specific measures to change in response to therapy.[14,26]

The CTCL-PRO-20 covers additional CTCL-specific domains compared to other validated measures used in clinical trials including FACT-G and Skindex-29. Skindex-29 measures skin-related symptoms, which is only one component of the many important domains affecting CTCL patient QoL. Importantly it lacks questions about skin breaks/sores and lack of understanding in the community, which we found to be important components of CTCL patient QoL. FACT-G, developed to measure health-related QoL in patients with cancer, does not include questions about itching, skin breaks/flaking, concern about appearance/self-consciousness, and lack of understanding in the community. The items developed for the CTCL-PRO-20 initially included all domains we found important specifically to CTCL patient QoL, and the domains retained after the PCA included nearly all of these important domains, representing a unique combination not provided by existing measures (*Online Supplementary Table S1*). Items regarding pain, depression, hopelessness, and uncertainty, while noted as important to CTCL patient QoL[11] and, therefore, included in the initial PCA, either cross-loaded on two or more components with loadings >0.400 or did not load highly (≥0.600) on a single component measuring affect as intended.[22] Such items were either complex or otherwise unable to distinguish between constructs; therefore, they were dropped from further analysis.[23]

Quality of life metrics have become an important endpoint in registrational trials in CTCL. The phase III ALCANZA[32] and MAVORIC trials[33] evaluating the efficacy of brentuximab vedotin and mogamulizumab, respectively, used Skindex-29, FACT-G, and EQ-5D (ALCANZA only) to measure QoL and showed improved QoL in the experimental arms.[32,34] However, none of these trials included a CTCL-specific measure of PRO. After additional validation, we hope the CTCL-PRO-20 can be used to measure PRO for patients with CTCL in clinical trials and could also be applied to disease assessment in the clinic. In other rare diseases, such as myelofibrosis, disease-specific QoL tools have become a primary endpoint of registrational trials,[35] and such PRO measures are needed in CTCL. Development of the CTCL-PRO-20 was driven by the need for a CTCL-focused measure of QoL, which continues to be a critical focus of our future work to assess this new measure's sensitivity to change after therapeutic intervention.

Limitations include the fact that this study was carried out at a single center with a relatively small sample

size. Based on prior work, larger samples of 150-200 participants and moderate component saturation (i.e., loadings ≥0.600) provide more stable estimates and can approximate a good fit to the population pattern across varying conditions.[22] We purposefully retained items with moderate-to-high component loadings that did not load >0.400 on any other component; thus, the component saturation was adequate for each of the five components and the overall measure. Few patients had advanced-stage disease at time of survey completion, limiting our ability to observe significant differences according to stage, and while representative of our patient population, few non-White patients participated, limiting the generalizability of our findings. Validation studies with larger samples are needed to further substantiate the stability of the component structure,[22] the convergent and discriminant validity of the CTCL-PRO-20, and establish the external validity of the new measure in a more diverse population. Thus, we are carrying out a large multicenter study (N=250) to evaluate the CTCL-PRO-20 measure's test:re-test reliability and sensitivity to change in response to treatment. We then plan to carry out a prospective assessment of CTCL-PRO-20 scores in a cohort undergoing a therapeutic intervention in a clinical trial with uniform response assessment, which will enable us to evaluate the survey's sensitivity to change in response to treatment. The CTCL-PRO-20 has already been incorporated into an ongoing investigator-initiated CTCL clinical trial. If validated in multi-center studies, we expect the CTCL-PRO-20 will prove useful as a CTCL-specific QoL tool that can be used as an endpoint for clinical trials and a simple aid to clinical decision-making.

Disclosures

NMS has served as a consultant for Kyoka Hakka Kirin, Ono Pharmaceutcials, Secura Bio, Daiichi Sankyo, Genentech, Janssen, Pfizer, AstraZeneca, Acrotech, and Autolous; and has institutional research support from Institutional Research Funding: Bristol Myers Squibb, Celgene, Verastem Pharmaceuticals, Innate Pharmaceuticals, Roche/Genentech, Corvus Pharmaceuticals, AstraZeneca, Daiichi Sankyo, C4 Pharmaceuticals, and Morphosys. All the other authors have no conflicts of interest to disclose.

Contributions

NAA is responsible for study concept, methodology and funding acquisition, wrote the original draft, and reviewed and edited the manuscript. DBJ is responsible for study concept, methodology and funding acquisition, statistical data analysis and management, wrote, critically reviewed and edited the manuscript, and supervised the study. NA is responsible for statistical data analysis and management. AM and NMS are responsible for study concept, methodology and funding acquisition, wrote, critically reviewed and edited the manuscript, and supervised the study. AK is responsible for data curation, project administration, data acquisition, and editing the manuscript. MW is responsible for project administration, data acquisition, and editing the manuscript. All authors approved the final version of the manuscript for publication.

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Data-sharing statement

De-identified data may be shared upon reasonable request to the corresponding author.

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