Development and initial validation of a disease-specific instrument to measure health-related quality of life in hypersensitivity pneumonitis

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The HP-HRQOL has strong validity and reliability characteristics for measuring disease-specific health-related quality of life in patients with hypersensitivity pneumonitis https://bit.ly/49M2Pvo

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Abstract

Rationale and objective Disease-specific health-related quality of life (HRQOL) instruments enable us to capture domains that are most relevant to specific patient populations and are useful when a more individualised approach to patient assessment is desired. In this study, we assessed the validity and reliability of the first instrument specifically developed to measure HRQOL in hypersensitivity pneumonitis (HP).

Methods A 39-item HP-HRQOL instrument and several anchors were collected from a cohort of patients with HP. Exploratory factor analysis and item reduction were utilised to construct a shortened version of the instrument. Several validity and reliability analyses were conducted on this version of the HP-HRQOL.

Measurements and main results 59 patients with HP completed the study. The revised HP-HRQOL instrument comprises 15 items composing two factors (domains): 1) impacts on daily life; and 2) mental wellbeing. Internal consistency reliability was strong for Factor 1 (Cronbach's α=0.94, 95% CI 0.92–0.96) and Factor 2 (Cronbach's α=0.89, 95% CI 0.85–0.94). Test–retest reliability was strong (ICC 0.94, 95% CI 0.89–0.97). The HP-HRQOL strongly correlated with other validated patient-reported outcome measures and moderately correlated with % predicted forced vital capacity. The HP-HRQOL distinguished between those with different severities of HP as determined by lung function and supplemental oxygen use.

Conclusions The HP-HRQOL, the first patient-reported outcome instrument specific to adults with HP, possesses strong validity and reliability characteristics for measuring disease-specific HRQOL and distinguishes among patients with different severities of disease.

Introduction

Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) that occurs in a susceptible individual when there is injury to the lung parenchyma resulting from an immune reaction to an inhaled environmental antigen, such as bird feathers or mould [1, 2]. Aside from primary treatment by exposure avoidance, which is often difficult to achieve [3, 4], there are limited well-studied pharmacological treatment options. Patients who live with HP experience poor health-related quality of life (HRQOL) [5, 6]. Physiological measures of disease severity, such as pulmonary function tests (PFTs), only depict a fraction of how HP impacts any individual. Furthermore, PFTs do not necessarily correlate well with the outcomes that patients with ILD value most in their day-to-day lives [7–9]. Owing to this disconnect, it is often difficult for clinicians to monitor disease status and make individualised treatment recommendations.

Patient-reported outcome measures (PROMs) offer a patient-centred perspective on severity of disease and treatment effectiveness. PROMs are also known to enhance shared decision making by facilitating patient–physician conversations [10]. In a prior investigation, we discovered that currently available HRQOL measures used in ILD do not capture some of the quality-of-life impacts that patients with HP have expressed as important [11], thus identifying a crucial gap in patient-centred care in HP. For example, in addition to more common ILD experiences of dyspnoea and cough, patients with HP grapple with complex psychosocial issues and hypervigilance related to antigen exposure and avoidance, significant uncertainty about the disease and future, and debilitating fatigue. These concepts are not captured comprehensively by other HRQOL instruments historically administered in ILD.

Disease-specific HRQOL instruments enable us to capture information about (and change in) domains that are most relevant to specific patient populations, allowing for a more individualised approach to patient assessment. To our knowledge, there are no existing HRQOL instruments specifically for people living with HP. As pharmacological and non-pharmacological interventions are implemented in HP, we need instruments that can capture their impact on HRQOL. To address this gap, we developed the HP-HRQOL pilot instrument. The objective of this study is to finalise item content, formally evaluate the internal structure and assess the psychometric properties of the HP-HRQOL in a cohort of patients living with HP.

Methods

PROM development pathway

The development of the HP-HRQOL instrument followed the steps outlined in the Food and Drug Administration (FDA) guidelines for development of a new PROM in a target population [12] (figure 1). Briefly, in our prior work, we developed a conceptual framework of living with HP using data from 18 qualitative interviews where we identified six major themes representing impacts on HRQOL [11]. Guided by the major themes, we created an initial set of 39 items that represented each theme. We performed cognitive debriefing interviews where we revised the items, refined the overall instrument and evaluated readability statistics with patient input [13]. The current study describes the next steps in the pathway of PROM development by assessing the validity and reliability statistics of the HP-HRQOL in a cohort of patients with HP.

Study design, setting and participants

This was an observational study that recruited participants living with HP who were ⩾18 years of age at Weill Cornell Medicine (WCM) in New York City, NY, and The University of Virginia in Charlottesville,

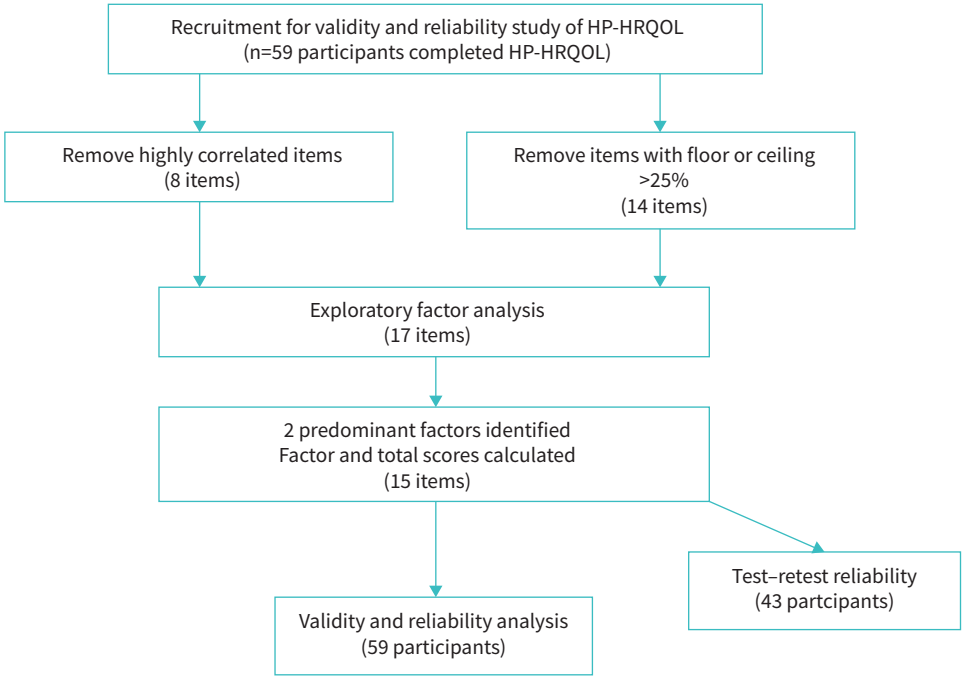

FIGURE 1 Study flow diagram. HP-HRQOL: hypersensitivity pneumonitis health-related quality of life.

VA, between July 2020 and February 2023. All patients with a confirmed diagnosis of HP were eligible for screening. HP was the primary pulmonary diagnosis, and the diagnosis of HP was made *via* expert multidisciplinary consensus based on the combination of clinical history, high-resolution computed tomography scan, lung function and pathology where applicable. Patients were required to be English speaking and were excluded if they were unable to complete questionnaires due to cognitive impairment as determined by their treating clinician. All data collection and study visits were conducted by the WCM site, using remote methods (*e.g.*, telephone contact and electronic completion of surveys) most frequently. All sites obtained institutional review board approval (WCM IRB# 1905020233, UVA IRB HSR# 23633).

Measures and data collection

The 39-item HP-HRQOL was administered at the first study visit and 2 weeks later. Two additional PROMs were administered at enrolment to be used as anchors. The King's Brief ILD (KBILD) questionnaire has been developed and validated in ILD [14]. It consists of 15 items across three domains: breathlessness and activity, chest symptoms and psychological. It has been administered in both paper and electronic format [15]. The 12-item Short-Form Health Survey (SF-12) is a self-report instrument that assesses eight domains of health and wellbeing that comprise two different summary scores: the physical component score (PCS) and mental component score (MCS). The SF-12 has been validated for use in both paper and electronic format [16]. Enrolled participants personally completed questionnaires (electronically or on paper) on two separate occasions, ∼2 weeks apart. Additional medical data (including PFTs, 6-min walk distance, computer tomography scans, medications) and demographic data were abstracted from patient's medical charts by a member of the research team.

Response scale and scoring

A 5-point Likert scale was used for all response options throughout the development of the HP-HRQOL (online supplementary material B). Each item was scored out of 5 points and, for items surviving item reduction steps, summation scoring was used to derive domain scores. The overall score was calculated by adding individual domain scores for the items that were part of the final factor solution. Lower scores indicated worse quality of life and higher scores indicated better quality of life. The means for each domain and the total score were reported separately.

Structural validity: domain refinement and item reduction

To minimise respondent burden, we evaluated the initial list of 39 items for redundancy using a correlation matrix. For items with a correlation >0.8, the weaker item (as determined by prior content and face validity testing) was eliminated [17]. We evaluated the remaining items individually for floor (minimum) and ceiling (maximum) effects using a conservative threshold of 25% [18]. Items with "1" or "5" responses above the pre-specified threshold were considered for elimination, and exceptions were discussed at length among the research team and a final determination was made based on clinical judgement. Surviving items were subjected to an exploratory factor analysis (EFA) to determine the number of dimensions underlying the item set and how each item related to the dimensions. We used a principal axis method and orthogonal varimax rotation to extract factors that were uncorrelated. Orthogonal rotation was used to maximise the association of each item with a single factor [19]. Individual items with dominant factor loadings >0.6 on a single factor were retained and summed to create the total factor (domain) score. Any exceptions were made in discussion with the research team and based on clinical judgement [20].

Reliability

Internal consistency reliability was assessed on the individual domains using Cronbach's coefficient α [21]. We considered α>0.7 as representing a high degree of internal consistency. Test–retest reliability (TRT) was calculated using intraclass correlation coefficients (ICC) on scores from participants who completed the baseline and 2-week follow-up survey. Participants who were documented to have a respiratory illness, hospitalisation or change in respiratory medication between the time of the first and second survey administration were excluded from the TRT. A value >0.7 was used as the accepted cut-off for TRT [22].

Validity

Concurrent validity (how well the scores of the HP-HRQOL compare with a measure that has validity data available in HP) was assessed using a Spearman correlation coefficient between the HP-HRQOL scores and several anchors collected at baseline. Physiological anchors included % predicted forced vital capacity (FVC) and % predicted diffusing capacity of the lungs for carbon monoxide (D_{LCO}). Owing to restrictions in performing lung function tests as a part of clinical research during the early COVID-19 pandemic, the FVC and D_{LCO} values were collected from most recent values documented as a part of routine clinical care. PROM anchors included: the SF-12 [23, 24] and the KBILD instruments [14]. We evaluated each

domain of the HP-HRQOL and the sum score with each domain and total score of the KBILD and SF-12. We considered r<0.4 to indicate a weak correlation, r⩾0.4<0.7 to indicate moderate correlation and r>0.7 to indicate a strong correlation [25, 26].

Known groups validity was assessed using analysis of variance (ANOVA) in which we compared the mean HP-HRQOL score as a dependent variable across categories of several variables: 1) known/unknown antigen; 2) use of supplemental oxygen; 3) % predicted FVC (<50%, 50–80%, >80%); 4) % predicted D_{LCO} (moderate to severe ⩽59%, mild and normal ⩾60%); 5) use of systemic steroids, immunosuppressants, neither, or both; and 6) use of antifibrotic drugs. We hypothesised that participants with worse lung function and those using supplemental oxygen would have worse HP-HRQOL scores than those with better lung function and not using supplemental oxygen. We hypothesised that those taking immunosuppressants and antifibrotics would have higher HP-HRQOL scores than those not taking those medications. We hypothesised that there would be no difference in scores between patients with known and those with unknown antigen.

Results

59 participants completed the baseline surveys and were included in the analysis. Most questionnaires were administered electronically (54, 92%) using REDCap and a few were completed by paper and pen for a small number of participants who requested this mode of completion (5, 8%). The mean age of participants was 71 years, of which 63% were female, 38% were using supplemental oxygen and 56% had a known antigen exposure. All additional relevant baseline characteristics are shown in table 1.

Structural validity

Of the initial 39 items, 8 (21%) items were dropped due to high item–item correlation (>0.8). An additional 14 (36%) items with floor/ceiling effects >25% were dropped. One item asking about cough was retained in the survey despite a floor effect of 33%, due to the clinical significance and impact of cough on quality of life. The 17 remaining items were subjected to EFA revealing two factors encompassing 15 out of the 17 questions (figure 2). Two additional questions on supplemental oxygen did not fall into either of the main factors and were kept for exploratory analyses (online supplementary material C and D). The main factors (domains) were given the following names: Factor 1: Impacts on daily life (11 items), Factor 2: Mental wellbeing (four items). Each question was multiplied by 5, allotting 55 points for Factor 1 and 20 points for Factor 2. For the total score, Factors 1 and 2 were summed together to equal 75 points.

Reliability

Cronbach's α was 0.94 (95% CI 0.92–0.96) for Factor 1, and 0.89 (95% CI 0.85–0.94) for Factor 2. TRT was calculated in 43 of the 59 respondents and suggested good repeatability for all individual factors (ICC Factor 1: 0.93, p<0.0001; ICC Factor 2: 0.91, p<0.0001) and the total (ICC 0.95, p<0.0001). A Bland–Altman plot of HP-HRQOL total score repeatability is shown in figure 3.

Concurrent validity

There were strong correlations in the hypothesised direction between Factors 1 and 2 and the total score with the KBILD total score (0.818, 0.776 and 0.874, respectively; p<0.0001). There were strong correlations between Factor 1 and the total score with the SF-12 PCS (0.729 and 0.651, respectively, p<0.0001). There was a strong correlation in the hypothesised direction between Factor 2 and the total score with the KBILD psychological score (0.765 and 0.736, respectively, p<0.0001) and a moderate correlation of Factor 2 with the SF-12 MCS (0.552, p<0.0001). There were moderate correlations in the hypothesised direction between Factor 1 and the total score with the % predicted FVC (0.509 and 0.471, respectively, p<0.0001) and with Factor 1 and the % predicted D_{LCO} (0.400, p<0.005) (figure 4).

Known groups validity

Patients using supplemental oxygen had a statistically significantly lower (worse) HP-HRQOL total score than those not using supplemental oxygen (35.8 *versus* 50.3) (p=0.0002) (Figure 5a). Individuals with FVC <50% predicted had a significantly lower mean HP-HRQOL total score (32.3) than those in higher FVC subgroups (FVC 50–80%, mean=43.6; FVC >80%, mean=52.3) (p=0.0006) (figure 5b). Individuals in the group with D_{LCO} ⩽59% predicted had a significantly lower mean HP-HRQOL total score (40.9) than those with D_{LCO} ⩾60% (52.91) (p=0.004) (figure 5c). There was no statistically significant difference in HP-HRQOL score between people who identified as having known *versus* unknown antigen exposure (47.3 *versus* 49.8) (p=0.53) (figure 5d). Patients taking antifibrotics had a close to 10-point higher score than those not (46.4 *versus* 36.8) (p=0.07); however, this did not reach statistical significance (figure 5e). Those patients taking immunosuppressants alone had scores that trended lower (mean 38.9) than those

TABLE 1 Participant characteristics (n=59)

Age years	71 (62–76)
Female	37 (63)
Race and ethnicity	
Asian	3 (5)
Black or African American	2 (3)
White	49 (83)
Other[#]	5 (9)
Hispanic or Latino	5 (9)
Education[¶]	
Some high school	4 (7)
High school graduate, or some college	15 (26)
Technical/vocational school or associate degree	3 (5)
Bachelor's degree	20 (35)
Master's, professional or doctoral degree	16 (28)
Use of supplemental oxygen	22 (38)
Fibrotic HP	47 (78)
Antigen known	33 (56)
Type of lung exposure (n=33)	
Avian/down	9 (27)
Mould	18 (55)
Occupational/organic dust exposure	4 (12)
Medication	2 (6)
Duration of disease[¶]	
3 months to 1 year	13 (23)
13 months to 5 years	24 (41)
Over 5 years	21 (36)
Survey and health measures	
KBILD questionnaire	
Total score	54.80 (46.50–61.00)
Psychological score	53.50 (46.40–65.50)
Breathlessness and activity score	41.90 (30.30–52.50)
Chest symptoms score	73.40 (54.30–85.20)
SF-12 survey	
PCS	41.18 (33.81–47.55)
MCS	46.45 (38.99–54.13)
FVC % predicted	0.74 (0.55–0.88)
D_{LCO} % predicted[+]	0.59 (0.46–0.73)

Data are presented as n (%) or median (IQR). HP: hypersensitivity pneumonitis; KBILD: King's Brief Interstitial Lung Disease; SF-12: 12-item Short Form Survey; MCS: mental health component score; PCS: physical health component score; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. [#]: includes American Indian or Alaska Native, mixed race and other races; [¶]: data available for 58 participants; [+]: data available for 48 participants.

taking corticosteroids alone (mean 48.5) or neither medication (mean 47.9); however, this did not reach statistical significance (figure 5f).

Discussion

We present the results of the first validation of an instrument developed to measure HRQOL in patients with HP. Items in this instrument are based on a thematic framework generated from qualitative interviews asking people living with HP about how the disease affects their HRQOL. Using standard procedures for item reduction and a robust factor analysis, we developed an instrument comprising 15 items that measures two distinct domains of HRQOL in people living with HP: impacts on daily life and mental wellbeing. We found that the 15-item instrument possesses strong reliability and validity for assessing HRQOL in a cohort of patients with HP. HP-HRQOL scores were strongly correlated with relevant anchors that measure HRQOL and moderately correlated with FVC. HP-HRQOL scores satisfactorily discriminate between patients living with HP who are hypothesised to have different severities of disease based on lung function and use of supplemental oxygen.

There was significant attention paid to the environmental and psychological impact of HP in this questionnaire. These items were of particular importance to people living with HP throughout the initial

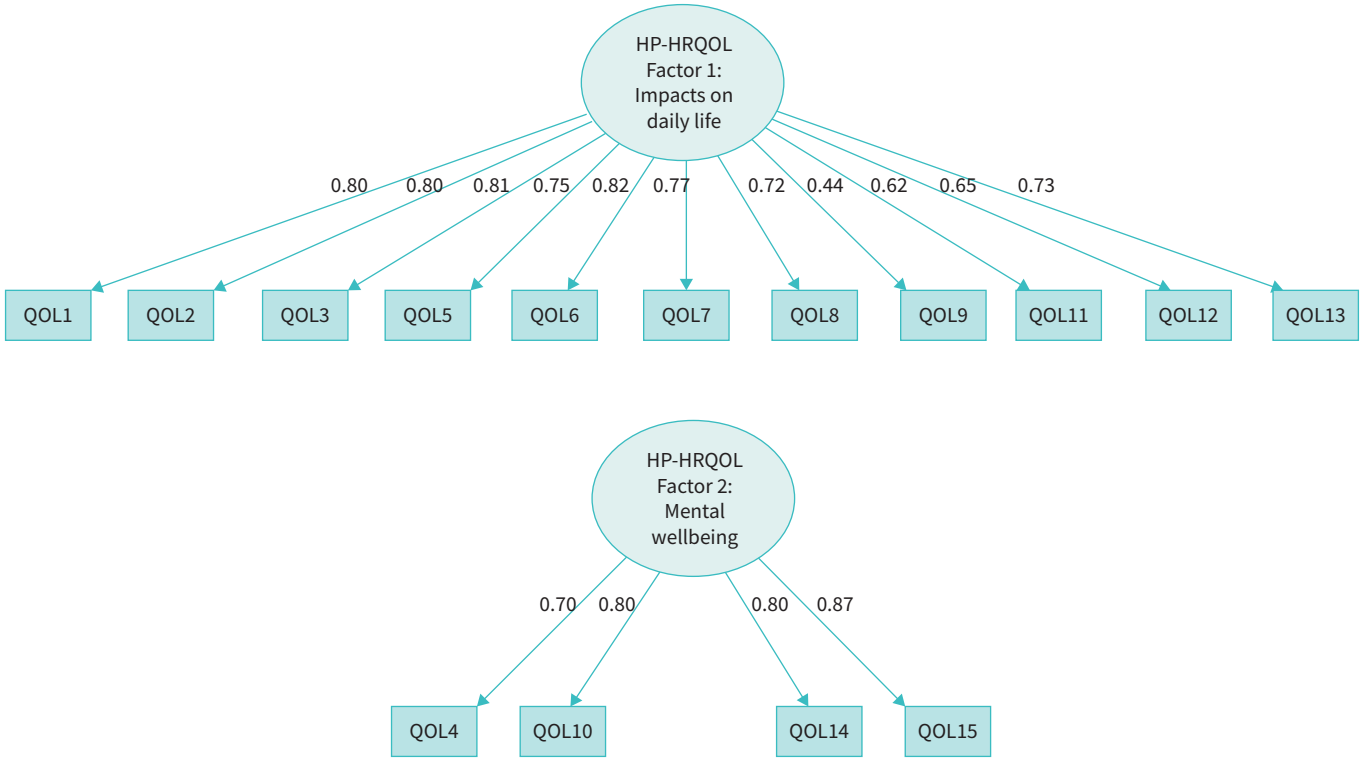

FIGURE 2 Exploratory factor analysis. Factor loadings for the exploratory factor analysis are shown. Numbers adjacent to the one-way arrows represent factor loadings for the individual items. QOL1–QOL15 are the short names for the questions; the actual item text and response options associated with each can be found in the online supplementary material A and B. HP-HRQOL: hypersensitivity pneumonitis health-related quality of life.

qualitative study and remained so during the cognitive interview phase, with wording as suggested by patients themselves [11, 13]. It is therefore not surprising that these items performed exceptionally well during this phase of validation.

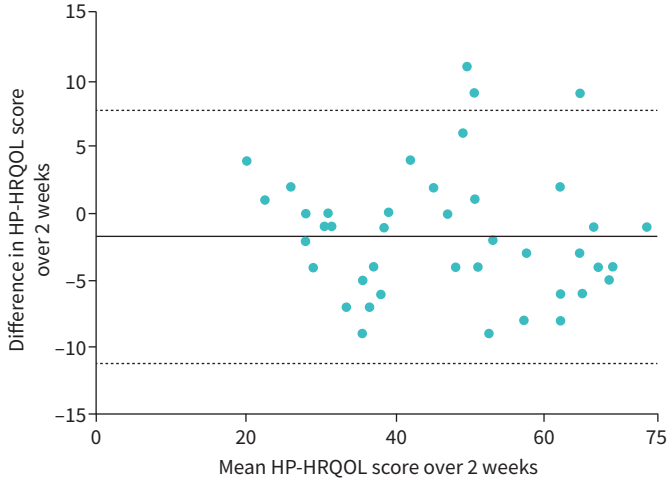

FIGURE 3 Bland–Altman plot of test–retest reliability. Repeatability based upon the total score of the hypersensitivity pneumonitis health-related quality of life (HP-HRQOL). The solid line represents mean difference and the dashed lines represent 95% limits of agreement.

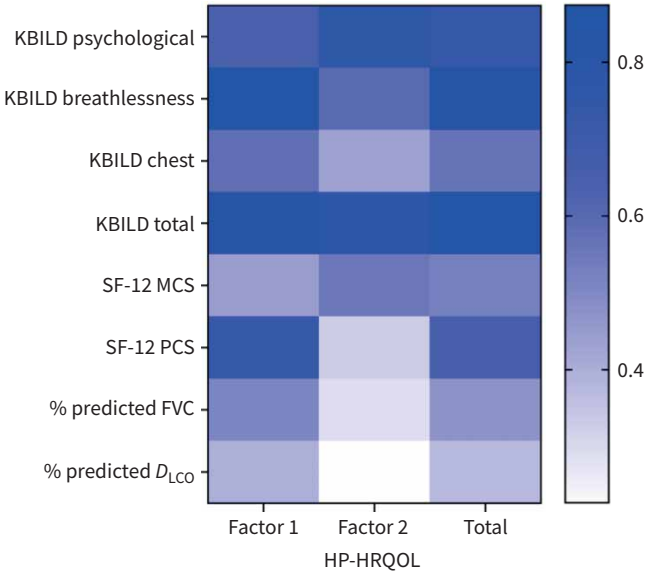

FIGURE 4 Hypersensitivity pneumonitis health-related quality of life (HP-HRQOL) concurrent validity with anchors. KBILD: King's Brief Interstitial Lung Disease; SF-12: 12-item Short Form Survey; MCS: mental health component score; PCS: physical health component score; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

This instrument was developed prior to the publication of the American Thoracic Society Guidelines (ATS) that recommended changing nomenclature from "acute", "subacute" and "chronic" to "fibrotic" and "non-fibrotic" HP [27]. All participants in this study had HP for at least 3 months, and 22% of participants were classified as having non-fibrotic HP. This study has shown that the HP-HRQOL instrument has strong validity and reliability characteristics in patients who have fibrotic HP, but also those who live chronically with non-fibrotic HP, allowing for it to be useful for a broader population of those living with HP.

As we hypothesised, the instrument did not distinguish between participants who self-identified as knowing their antigen *versus* those who did not know their antigen. Prior observational studies have shown that knowing one's inciting antigen is associated with improved FVC and survival [28, 29]; however, the impact that this knowledge has on a person's HRQOL has not been previously explored. We hypothesised that the HP-HRQOL instrument may not be able to distinguish between people who know their inciting antigen and those who do not. This hypothesis was based on our prior studies, where we identified several psychosocial complexities and consequences of antigen identification and avoidance that all patients (regardless of knowing or not knowing their exposure) experience [6, 30]. We hypothesised that there would be no difference due in part to the significant barriers associated with antigen avoidance, the significant uncertainty that an antigen has been successfully avoided even after identification and the impact of ridding of the source of the antigen on one's lifestyle. Using the HP-HRQOL and the individual questions associated with it may allow clinicians to explore how living with HP impacts HRQOL aside from just development of symptoms, with a focus on the psychosocial impact of antigen identification and avoidance. Considering this will be important as we work to develop interventions to target HRQOL in patients with HP, where approaches that include targeting the drivers of poor mental wellbeing for the individualised patient (including those related to coping with an exposure-related lung disease) may be considered.

Though there was no statistical significance, there was a trend towards the ability to distinguish whether individuals were prescribed antifibrotic drugs, with those taking antifibrotic drugs having lower (worse) HP-HRQOL scores. We may consider this another reflection of disease severity in HP, as guidelines suggest antifibrotic drugs be prescribed when disease progression (specifically progressive fibrosis) has occurred [31]. In the future, studies to investigate this instrument property in a larger cohort of patients with HP on antifibrotic drugs may be warranted.

In the past two decades other disease-specific instruments have been developed to measure HRQOL in ILD. The most utilised instruments with published validity data include the KBILD [14] and the Living with

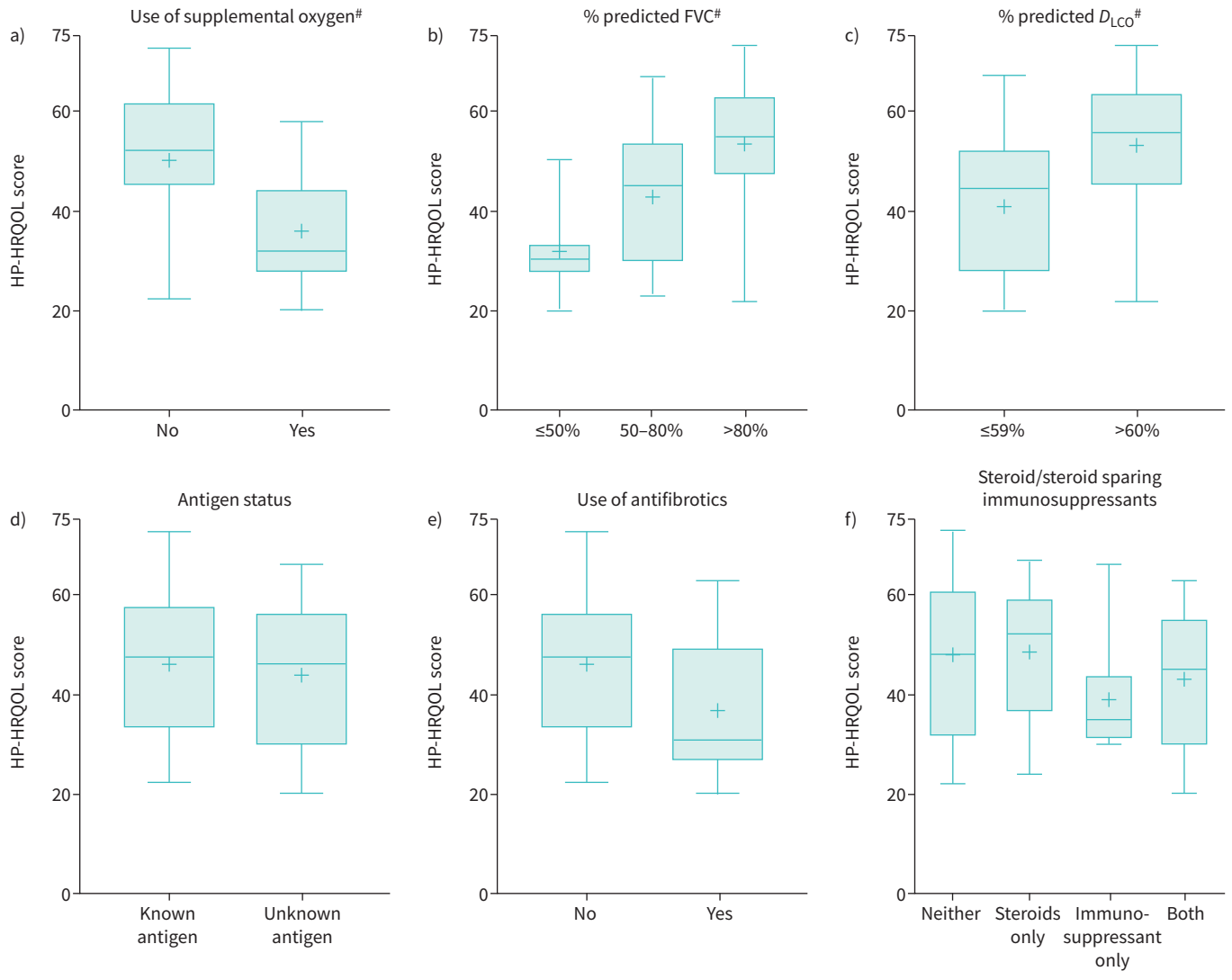

FIGURE 5 a–f) Known groups validity of HP-HRQOL. HP-HRQOL: hypersensitivity pneumonitis health-related quality of life; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. #: p<0.005.

Pulmonary Fibrosis Questionnaire (LPF) [32]. Though patients with HP were included in validity analyses of both instruments, neither was initially developed in a group of people with HP or includes specific items that address unique aspects of living with HP – such as the impacts of poor knowledge about HP, exposure identification (or not) and avoidance. When interpreting this study in the context of what is known about existing HRQOL instruments in ILD, it is important to keep in mind that there is no one "ideal" instrument to use to measure HRQOL. The choice of what instrument to use as an outcome measure in a study will depend on the interest of the investigators, the research question to be answered and the proposed mechanism of the intervention [33]. Further studies are needed to examine responsiveness of the HP-HRQOL in the setting of an intervention that targets the domains of interest, and to study its utility as an additional piece of patient-centred data to be used in clinical practice [34, 35].

The strengths of our study include the adherence to FDA PROM instrument development guidelines beginning with development of a conceptual framework from interviews with the target population of patients with HP [12, 36]. We included participants from two academic centres in different geographical locations and from all educational backgrounds in the study. We also included participants with a variety of known antigen exposures as well as a substantial number with unknown exposure.

There are several limitations to our study. This cohort comprises 59 patients; however, this is a recognised limitation when developing instruments in rare diseases such as HP, and the low amount of missing survey data adds strength to the analysis [37, 38]. This initial validation analysis is cross-sectional in nature; however, development and validation of instruments is a continuous process and data on responsiveness will be collected in future study that includes an intervention. Owing to limitations resulting from the COVID-19 pandemic, we were unable to collect PFTs in real-time as a part of the study and therefore were limited to collecting the most recently collected spirometry and D_{LCO} as a part of clinical care (median of 3.8 months between PFTs and HP-HRQOL completion). Though there was a mix of educational backgrounds in the study, there was underrepresentation of participants with less education. Lastly, this initial validation study included only English-speaking patients, and future studies will test the linguistic and cross-cultural validity of the instrument.

Conclusions

We present the first short and easily administered instrument that measures HRQOL in patients living with HP. The internal consistency, reliability and validity analyses support the patient-identified domains and the instruments' ability to measure these concepts as compared to other well-validated anchors. We also demonstrated the instrument's ability to discriminate between people with different severities of disease, which has important clinical implications. This instrument provides an additional tool for collecting a more comprehensive understanding of a patient's disease severity in HP aside from standard physiological testing.

Provenance: Submitted article, peer reviewed.

Ethics approval: All sites obtained institutional review board (IRB) approval (Weill Cornell Medicine IRB 1905020233 and University of Virginia IRB HSR 23633).

Author contributions: The authors confirm contribution to the manuscript as follows. Study conception and design: K.I. Aronson, L.C. Pinheiro, M.M. Safford, F.J. Martinez and R.J. Kaner; data collection: K.I. Aronson, J. Varadarajan and T.K. Paul; analysis and interpretation of results: K.I. Aronson, M. Rajan, J. Varadarajan, J.K. Krishnan, J.J. Swigris and L.C. Pinheiro; draft manuscript preparation: K.I. Aronson and J. Varadarajan. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest: K.I. Aronson reports funding from the NHLBI, Scleroderma Foundation and American Lung Association; medical writing from Genentech for a different manuscript; and sits on the scientific review committee for the Pulmonary Fibrosis Foundation. M. Rajan reports funding from the American Lung Association and Weill Cornell Medicine Department of Medicine Fund for the Future Award. J.K. Krishnan reports funding from the American Thoracic Society, Weill Cornell Medicine Research Assistant for Primary Parents Award, Deans Diversity Award, Fund for the Future Award, NIH T32HL134629 and COMMUNITY Center Investigator Development Core; consulting fees for advisory board of Verona Pharma; and medical writing/receipt of gifts from Novartis, Boehringer Ingelheim, GSK, Donna Redel Research Fund and Thomas King Fellowship. R.J. Kaner reports funding from the NIH, Boehringer Ingelheim, Cheisi, CSL Behring, Genentech, Respivant, Toray, Bellerophon and the US Department of Defense; royalties or licences from UptoDate; payment or honoraria from Boehringer Ingelheim, Genentech, Vindico and the France Foundation; support for travel from United Therapeutics and Boehringer Ingelheim; participation on a data safety monitoring board with Puretech, Pliant, Boehringer Ingelheim, Genentech, United Therapeutics, Verona Pharma, Galapagos and AstraZeneca; leadership roles in the Pulmonary Wellness Foundation and Stony-Wold Foundation; stock in Doximity and Air Cycle Systems; and receipt of medical writing or gifts from Boehringer Ingelheim, Genentech, Galapagos and AstraZeneca. F.J. Martinez reports funding from Afferent/Merck/Boehringer Ingelheim, Biogen, Bristol Myers Squibb, Devpro, Nitto, Patara/Respivant and NHLBI; consulting fees from Boehringer Ingelheim, Bristol Myers Squibb, Hoffman/Laroche, IQVIA, Lung Therapeutics, Novartis, Sanofi, Shionogi, Two XR, Veracyte and GSK; honoraria and support for meetings/travel from Boehringer Ingelheim; and participation in data safety monitoring board for Boehringer Ingelheim and Biogen. M.M. Safford is a member of the MESA OSMB, and is the Chief Scientific Officer of MedExplain and owns stock in MedExplain. J. Varadarajan, T.K. Paul, J.J. Swigris and L.C. Pinheiro report no conflicts related to this work.

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