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ORIGINAL RESEARCH ARTICLE

Observational study of health utilities in adult primary ciliary dyskinesia patients: preliminary data on associations with molecular diagnosis, clinical phenotype and HRQOL measures

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ABSTRACT

Background: Primary ciliary dyskinesia (PCD) is a congenital disorder characterized by chronic respiratory morbidity. To date, there is no information on PCD-specific preference-based quality of life measures such as health utilities (HU). We cross-sectionally assessed HU in adult PCD patients and explored relationships with genotype, phenotype and quality of life (QOL)-PCD scales.

Methods: Diagnostic testing was performed according to international guidelines, while participants completed the visual analog scale (VAS), time trade off (TTO), standard gamble (SG), and EuroQol 5 dimensions (EQ5D) HU instruments, as well as the QOL-PCD questionnaire. Hierarchical regression was used to identify the QOL-PCD scales that are most predictive of HU.

Results: Among 31 patients, median HU are 0.75 (VAS), 0.86 (EQ5D), 0.91 (TTO) and 0.99 (SG). The underlying genotype is not associated with HU measures. VAS and EQ5D are associated with lung function, while TTO and SG values are not sensitive to any of the examined factors. Among the QOL-PCD scales, physical functioning and lower respiratory symptoms explained much of VAS (R^2= 0.419) and EQ5D (R^2= 0.538) variability.

Conclusions: Our study demonstrates that HU elicitation in PCD is feasible using both direct and indirect methods. Overall, HU scores are relatively high among adult patients, with higher scores observed in SG and TTO, followed by EQ5D and VAS. VAS and EQ5D HU values are sensitive to lung function as well as to QOL-PCD physical functioning and lower respiratory symptom scores.

Key words: Primary ciliary dyskinesia; health utilities; quality of life; rare disease.

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Introduction

Primary ciliary dyskinesia (PCD) is a rare, hereditary disease characterized by structural and functional abnormalities of motile cilia. PCD patients usually suffer from recurrent airway infections, development of bronchiectasis, and progressive loss of lung function. Common manifestations of PCD also include chronic wet cough and rhinorrhea, situs laterality defects, nasal polyps and infertility [1]. To date, treatment outcomes or disease severity in PCD have been primarily evaluated by clinical parameters such as lung function [2-5], high resolution chest tomography [6,7] or sputum microbiology [4,8]. Some studies assessed disease impact on the overall health status of patients through the use of generic patient reported outcomes tools such as the short form 36 Health Survey (SF36) or through general respiratory questionnaires such as the St. George's respiratory questionnaire [9-11]. More recently, a specific health-related quality of life (HRQOL) measure for PCD (QOL-PCD) has been developed and is currently undergoing translation, cross-cultural adaptation and validation in Europe and elsewhere [12-17].

QOL-PCD questionnaire and other respiratory health status instruments assess the disease impact across different HRQOL domains, such as physical, emotional and social functioning, using a set of non-preference-based questions to calculate an overall score [15]. However, the health impact of a disease can also be evaluated in a preference-based approach using health utility (HU) instruments that allow for the direct or indirect reflection of the patient's perception of his or her health state. A utility score usually ranges from 0 (indicating a preference for death) and 1 (indicating a perception of perfect health) and has been traditionally estimated based on the patient's willingness to accept dangerous treatments or to sacrifice longevity in order to achieve perfect health [18]. As opposed to non-preference based HRQoL metrics that are primarily used as outcomes in observational and randomized clinical studies [19], HU values are usually used to estimate quality of life in the context of cost-effectiveness analyses that use the ratio of cost per quality-adjusted life-year (QALY) as the main outcome [20]. Despite recent advancements in the study of HRQoL in PCD, the HU of PCD patients has not yet been investigated and the understanding of the disease impact on quality of life remains limited. In addition, information on HU in PCD will allow comparisons with other diseases and will better inform the evaluation of health interventions and decision making.

The aims of this study were to: i) evaluate preference-based HRQOL (health utilities-HU) in adult PCD patients for the first time; ii) investigate the relationship between HU and genotypic, demographic and phenotypic characteristics; and iii) assess the relationship and predictive ability of QOL-PCD morbidity scales for HU in PCD.

Methods

Study participants

A total of 31 adult PCD patients, followed-up at the Hospital 'Archbishop Makarios III' in Nicosia, Cyprus between January 2017 to December 2018, participated in the study. Following a clinic appointment, patients responded to all administered questionnaires in a single interview session. The interview was always performed by the same researcher and the order of questionnaire administration was randomized across individuals. Prior questionnaire completion, the patients were explained the procedure and received information on the methodology of HU assessment. The study was approved by the Cyprus National Bioethics Committee (ΕΕΒΚ/ΕΠ/2013/21). All subjects gave written informed consent prior to participation in the study.

Molecular testing

All participants provided peripheral blood sample and DNA was extracted for molecular testing. Molecular diagnosis was achieved using a custom, targeted next generation sequencing (NGS) panel for 39 known PCD genes. Sequencing was performed on Illumina MiSeq® platform and data analysis and variant filtering was carried out as described previously [21].

Diagnostic, clinical and lung function data

Diagnostic results, clinical data and lung function outcomes were extracted from the patients' medical records. Diagnostic testing included performance of nasal nitric oxide (nNO) measurement, ciliary motility assessment using high speed video microscopy (HSVM) and ciliary ultrastructural assessment using transmission electron microscopy (TEM), as described previously [22]. A diagnosis of PCD was confirmed in accordance with the European Respiratory Society (ERS) guidelines for the diagnosis of PCD [23]. Data on forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) from the same visit, were also used and were converted to age-, sex- and height-specific z-scores [24].

Elicitation of health utilities

For the direct elicitation of HU, we used three different methods, namely the visual analog scale (VAS), the time trade off (TTO) and standard gamble (SG) approach. The VAS elicits the patient's own assessment of his/hers overall (global) HRQOL using a 0 to 100 rating scale where 0 represents the worst imaginable health state (death) and 100 represents the best imaginable health state (perfect health) [25]. On the other hand, the TTO approach relies on the assumption that the disease health burden can be expressed by the number of life-years the patient is willing to sacrifice (trade) in exchange for perfect health. Based on this approach, the number of life-years the patient is willing to trade is proportional to the burden of the disease and inversely proportional to his/hers overall (global) HRQOL [26]. The SG approach assesses the utility of a particular health state by asking the patient to choose between living with the disease and a gamble between the best imaginable health state (perfect health) and immediate death. As a result, the greater the disease burden (worse HRQOL) experienced by the patient, the higher risk of death he/she will be willing to accept in order to be free of disease. Higher SG values represent acceptance of lower risk of dying and thus correspond to lower disease burden and higher overall (global) HRQOL [27]. Both TTO and SG are also scored in 0-100 scale where 0 corresponds to the worst imaginable health state (death) and 100 corresponds to the best imaginable health state (perfect health).

In addition to the direct methods, we also performed an indirect elicitation of HU using the validated Greek version of the Euro Qol-5D-5L (EQ-5D-5L) scale [28], which is a hybrid between the traditional measurement of HRQOL and the TTO approach. More specifically, the EQ-5D-5L is comprised by 5 sub-scales (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), and the patient responds to each sub-scale with one of the following levels (no problems, limited problems, moderate problems, severe problems and extreme problems), similar to a traditional HRQOL measurement. However, the different health states described have pre-assigned preferences obtained by general population polling using the TTO approach [29].

Assessment of health-related quality of life

Assessment of HRQOL was carried out using the validated Greek version of the adult QOL-PCD questionnaire [17]. The QOL-PCD questionnaire is self-administered and is composed by 40 questions, divided into ten scales: physical functioning, vitality, emotional functioning, health perception, treatment burden, upper respiratory symptoms, lower respiratory symptoms, role, social functioning and hearing symptoms. Each scale is scored from 0-100 and higher scores indicate higher quality of life.

Statistical analysis

Participants' genetic, demographic, clinical and diagnostic characteristics are summarized using frequencies for categorical variables and medians with interquartile ranges (IQR) for continuous variables. All utility measures were normalized to 0.0-1.0 scales to facilitate comparisons and ceiling and floor effects were evaluated. The Kruscal Wallis test was used to assess differences in HU measures across different genetic defects, while the Mann Whitney U test was used to assess differences in HU measures across binary categories of demographic (gender, age) and clinical (FVC, FEV_1) characteristics. To assess the relationship between scales of QOL-PCD and HU, Spearman rank correlations were calculated. QOL-PCD scales that were found to be significantly correlated with at least one HU measure were included in a hierarchical multiple linear regression analysis to identify the scale that is the most predictive for each HU (has the highest impact on the variance of each HU). All statistical tests reported are two-sided and statistical significance was set at $p<0.05$. All the analyses were performed with the SPSS 25 for Windows (SPSS Inc, Chicago, IL).

Results

Participants' characteristics

A total of 31 adult PCD patients were recruited and responded to all study questionnaires. The main demographic, genotypic, clinical and diagnostic characteristics of the participants are summarised in Table 1. The median age was 33.6 (IQR: 22.2-50.9) while the majority were women (58.1%). The most frequently mutated PCD gene among the participants was *RSPH9* (22.6%) followed by *CFAP300* (16.1%) and *DNAH11* (12.9%). Pathogenic mutations were also identified in *DNAH5* (6.5%), *TTC25* (6.5%) as well as in various other known PCD genes at lower frequencies (12.9%). In the remaining 22.6% of the participants, we did not identify biallelic pathogenic mutations in any of the 39 known PCD genes tested.

Health related quality of life (QOL-PCD) and health utility scores

The distributions of QOL-PCD and HU scores are presented in Table 2. PCD patients reported an overall good HRQOL with most QOL-PCD scales being characterised by median values greater than 60. The most highly rated scale was emotional functioning (86.67, IQR:66.67-193.33) and the lowest was social functioning (33.30, IQR: 0.00-66.70). Notable ceiling and floor effects were observed only in the hearing symptoms and social functioning scales, respectively. HU scores were generally high, although some variation was observed depending on the methodology used for utility elicitation. More specifically, the lowest HU score was obtained using the VAS method (0.75, IQR=0.67-0.85) followed by EQ5D (0.86, IQR=0.73-0.92), TTO (0.91, IQR=0.84-0.98) and SG (0.99, IQR=0.95-1.00). A notable ceiling effect was only observed using the SG approach. The utilities derived by the VAS and EQ5D methods were well correlated with each other (r= 0.67, $p<0.001$) but not with TTO (r=0.195, p=0.292) or SG (r: 0.111, p=0.553). A moderate correlation was observed between TTO and SG (r=0.328, p=0.072)

Association of health utilities with demographic and clinical characteristics

Irrespective of the elicitation methodology used, HU were found to be similar among male and female and among younger and older patients. However, significant differences were observed across levels of lung function (both for FVC and FEV_1), with patients characterized by higher lung function reporting higher scores for HU, especially when VAS and EQ5D were used as the elicitation methods (Table 3).

Association of health utilities with molecular diagnosis

The underlying genetic defect was not found to be associated with HU scores among patients with a confirmed molecular diagnosis. This finding was consistent across all elicitation methodolo-

Table 1. Descriptive demographic, genotypic, diagnostic and clinical characteristics of included patients.

Parameter	Adult PCD patients (n=31)	
Demographic information		
Current age*	33.6 (22.2-50.9)	
Gender (female)	18/31	58.1%
Age at presentation*	23.79 (17.8-45.1)	
Situs abnormalities	14/31	45.2%
Diagnostic characteristics		
Nasal nitric oxide (nL/min)*	24.9 (13.0-48.0)	
TEM result		
Normal TEM	8/31	25.8%
ODA+IDA	9/31	29.0%
ODA only	6/31	19.4%
CP/ IDA+MD	8/31	25.8%
Other	0/31	0.0%
HSVM result		
Normal HSVM	0/31	0.0%
Immotile/almost immotile	13/31	41.9%
Extremely stiff due to reduced ciliary bending	8/31	25.8%
Stiff beating pattern	3/31	9.7%
Circular pattern	7/31	22.6%
Molecular diagnosis (gene with defect)		
RSPH9	7/31	22.6%
CFAP300	5/31	16.1%
DNAH11	4/31	12.9%
DNAH5	2/31	6.5%
TTC25	2/31	6.5%
Other	4/31	12.9%
Unknown	7/31	22.6%
Clinical characteristics		
Chronic rhinorrhoea	31/31	100%
Chronic wet cough	31/31	100%
History of NRDS	14/31	45.2%
History of nasal polyps	8/30	26.7%
History of pneumonia	12/29	41.4%
History of haemoptysis	3/31	9.7%
History of lung resection	5/31	16.1%

*Median and interquartile range; TEM, transmission electron microscopy; HSVM, high speed video microscopy; ODA+IDA, combined outer dynein arm defect and inner dynein arm defect; ODA, isolated outer dynein arm defect; CP, central pair defect; IDA + MD, inner dynein arm and microtubular disorganisation defect; NRDS, neonatal respiratory distress syndrome.

gies. However, statistically significant lower HU scores were recorded for VAS (0.55, IQR=0.48-0.75 *vs* 0.75, IQR=0.70-0.85, p=0.045) in patients without molecular diagnosis compared to the rest of the cohort but not so much for EQ5D (0.70, IQR=0.63-0.85 *vs* 0.86, IQR=0.80-0.92, p=0.094). In contrast, patients without molecular diagnosis did not differ significantly in terms of lung function when compared to the rest of the cohort. Interestingly, patients with an *RSPH9* molecular diagnosis exhibited higher FVC (-0.98, IQR= -1.29, -0.53 *vs* -1.94, IQR= -3.28, -1.07, p=0.014) and FEV_1 (-1.32, IQR= -1.49, -0.59 *vs* -2.66, IQR= -4.09, -1.47, p=0.005) when compared to the rest of the cohort, although this was not reflected in the comparison of their HU metrics (Table 4).

Association between QOL-PCD scales and health utilities

Significant correlations between some of the QOL-PCD scales and HU scores were observed. More specifically, a moderate to strong positive correlation was observed for both VAS and EQ5D and physical functioning (VAS: r=0.58, p=0.001; EQ5D: r=0.64, p<0.001), vitality (VAS: r=0.37, p=0.039; EQ5D: r=0.49, p=0.005), emotional functioning (VAS: r=0.43, p=0.016; EQ5D: r=0.58, p=0.001), upper respiratory symptoms (VAS: r=0.38, p=0.035; EQ5D: r=0.49, p=0.005) and lower respiratory symptoms (VAS: r=0.58, p=0.001; EQ5D: r=0.72, p<0.001). TTO was significantly correlated with physical functioning (r: 0.37, p: 0.038), while SG only with hearing symptoms (r= 0.376, p=0.037). The results of all examined bivariate correlations are presented in Table 5. Hierarchical multiple linear regression analysis for the predictive relationship between the most important QOL-PCD scales and VAS or EQ5D provided consistent results and revealed that the amount of variance (R^2) in the dependent variable was largely explained by only two QOL-PCD scales: physical functioning (VAS ΔR^2: 0.316, p=0.001; EQ5D ΔR^2: 0.414, p<0.001)

Table 2. Health related quality of life (QOL-PCD) and health utility scores in adult PCD patients.

Variable	Median	IQR	Range	Floor, %	Ceiling, %
QOL-PCD*					
Emotional functioning	86.67	66.67-93.33	40.00-100.00	0.00	6.45
Health perspective	50.00	25.00-66.70	8.30-91.70	0.00	0.00
Hearing symptoms	66.70	66.70-100.00	0.00-100.00	3.23	35.48
Lower resp.	61.10	44.40-72.20	11.10-88.90	0.00	0.00
Upper resp.	58.30	41.70-83.30	0.00-91.70	3.23	0.00
Physical functioning	80.00	46.67-93.33	6.67-100.00	0.00	6.45
Role	66.70	58.30-91.70	0.00-100.00	3.23	16.13
Social functioning	33.30	0.00-66.70	0.00-100.00	25.81	3.23
Treatment burden	66.70	41.70-83.33	8.30-100.00	0.00	13.04
Vitality	66.67	44.44-77.78	22.22-88.89	0.00	0.00
Health utilities#					
VAS	0.75	0.67-0.85	0.45-0.95	0.00	0.00
TTO utility	0.91	0.84-0.98	0.50-1.00	0.00	9.68
SG utility	0.99	0.95-1.00	0.83-1.00	0.00	35.48
EQ5D score	0.86	0.73-0.92	0.49-1.00	0.00	16.13

*Higher scores represent higher quality of life/less pain or discomfort; #visual analog scale (VAS) asks the patient to rate his or her current health on a continuum from 0 to 100, anchored by death (0) and perfect health (100) - results were normalized to a 0.0 to 1.0.scale; the time trade off (TTO), scaled from 0.0 (death) to 1.0 (perfect health), asks how much, if any, life expectancy the patient is willing to give up to have perfect health; the standard gamble (SG), scaled from 0.0 (death) to 1.0 (perfect health), asks how great a risk of death one is willing to accept in order to have perfect health; the European quality of life five-dimensions questionnaire (EQ5D) is a set of responses on 5 dimensions, as completed by a representative sample of people from the general population on how they value their health in a standardized valuation experiment using TTO.

Table 3. Association of demographic and clinical characteristics with health utilities in PCD.

Predictors	VAS	p	TTO utility	p	SG utility	p	EQ5D score	p
Gender								
Male	0.85 (0.70-0.90)	0.060	0.90 (0.84-0.96)	0.399	0.96 (0.95-1.00)	0.193	0.86 (0.81-0.92)	0.236
Female	0.75 (0.67-0.75)		0.92 (0.89-0.98)		0.99 (0.98-1.00)		0.83 (0.70-0.92)	
Age								
>33.7 years old	0.75 (0.63-0.80)	0.263	0.90 (0.83-0.96)	0.143	0.99 (0.95-1.00)	0.714	0.81 (0.73-0.92)	0.552
<33.7 years old	0.76 (0.73-0.85)		0.94 (0.90-0.98)		0.99 (0.98-1.00)		0.86 (0.75-0.94)	
FVC								
<–1.47 z-score	0.67 (0.55-0.75)	0.002	0.90 (0.80-0.97)	0.143	0.99 (0.98-1.00)	0.528	0.80 (0.63-0.86)	0.019
>–1.47 z-score	0.80 (0.75-0.88)		0.92 (0.90-0.98)		0.99 (0.95-1.00)		0.88 (0.86-0.97)	
FEV_1								
<–2.00 z-score	0.67 (0.55-0.75)	0.002	0.90 (0.80-0.98)	0.276	0.99 (0.98-1.00)	0.791	0.76 (0.63-0.86)	0.001
>–2.00 z-score	0.80 (0.75-0.88)		0.92 (0.90-0.98)		0.99 (0.95-1.00)		0.91 (0.86-0.97)	

The median score with the interquartile range below in brackets for each level of a variable given a health utility; the significance score is the result of a Mann-Whitney U test for differences between the median values.

Table 4. Association of genetic defects with lung function and health utilities.

Gene with defect	FVC z-score	FEV_1 z-score	VAS*	TTO*	SG*	EQ5D*
RSPH9 (n=7)	-0.98 (-1.29, -0.53)#	-1.32 (-1.49, -0.59)#	0.77 (0.73-0.88)	0.90 (0.89-0.98)	1.00 (0.99-1.00)	0.90 (0.86-0.92)
CFAP300 (n=5)	-2.08 (-2.99, -1.33)	-2.61 (-3.99, -1.52)	0.75 (0.65-0.85)	0.86 (0.83-0.91)	0.98 (0.96-0.99)	0.81 (0.80-1.00)
DNAH11 (n=4)	-1.25 (-2.25, -0.53)	-1.94 (-3.12, -1.32)	0.75 (0.69-0.78)	0.91 (0.81-0.98)	0.99 (0.97-1.00)	0.83 (0.76-0.93)
DNAH5 (n=2)	-3.07 (-4.03, -2.10)	-3.88 (-5.41, -2.35)	0.81 (0.75-0.88)	0.94 (0.90-0.98)	1.00 (1.00-1.00)	0.86 (0.86-0.86)
TTC25 (n=2)	-1.53 (-2.39, -0.66)	-1.94 (-3.30, -0.58)	0.80 (0.75-0.85)	0.95 (0.92-0.98)	0.97 (0.95-0.99)	0.93 (0.86-1.00)
Other (n=4)	-1.64 (-3.33, -1.16)	-3.15 (-4.48, -1.68)	0.75 (0.69-0.85)	0.85 (0.65-0.95)	0.96 (0.92-0.99)	0.83 (0.69-0.86)
Unknown (n=7)	-3.27 (-3.56, -1.04)	-3.42 (-3.92, -1.99)	0.55 (0.48-0.75)#	0.93 (0.87-0.97)	0.98 (0.97-0.99)	0.70 (0.63-0.85)°

*Median (IQR); VAS, visual analog scale; TTO, time trade off; SG; standard gamble; EQ5D, EuroQoL 5 dimensions; #statistically significant difference compared to all other genetic defects at the 0.05 significance level; °statistically significant difference compared to all other genetic defects at the 0.10 significance level.

and lower respiratory symptoms (VAS ΔR^2: 0.103, p=0.034; EQ5D ΔR^2: 0.124, p=0.011). For models with TTO set as the dependent variable, physical functioning alone was the most significant predictor (TTO ΔR^2: 0.166, p=0.023), while for SG the most predictive variable was hearing symptoms (SG ΔR^2: 0.276, p=0.005). Table 6 summarises the examined models and the results of hierarchical regression.

Discussion

In this study, we report, for the first time, preference-based HU scores for adult PCD patients using both direct and indirect elicitation methods. Overall, HU values in PCD patients were high with higher scores observed in SG and TTO, followed by EQ5D and VAS. VAS and EQ5D were associated with FVC and FEV_1 z-scores, while TTO and SG were not associated with any of the examined demographic and clinical factors. Molecular diagnosis was also not associated with HU scores irrespective of the elicitation method use. VAS and EQ5D were strongly correlated with specific QOL-PCD scales, although physical functioning and lower respiratory symptoms alone were predictive of VAS and EQ5D. Our results demonstrate that elicitation of HU, using either direct or indirect methods, in adult PCD patients is possible and that relatively high HU values are reported irrespective of the elicitation protocol. However, the SG approach showed a ceiling effect problem and significant limitations regarding its response options. This finding is not surprising and has been demonstrated in previous studies that assessed the performance of different preference-based measures, indicating the patients' adversity to risk [30-32]. A milder ceiling effect was also observed for EQ5D, which is consistent with previous studies in the general public [33] or specific patient groups [32,34,35]. In terms of responsiveness to clinically relevant measures such as indices of lung function (FEV_1 and FVC), the VAS and EQ5D appeared to be more responsive compared to TTO and SG. The limited responsiveness of TTO and SG in PCD can be explained by the underlying theoretical constructs of these instruments, where patients are respectively required to choose between alternatives, that involve trading life-years or accepting risk of death under uncertainty [26,27]. As such, the application of TTO and SG is more applicable in clinical settings, where patients are facing a high risk of death (e.g., cancer patients) and the choice of trading life-years or accepting risk is more straightforward. In contrast, patients suffering from PCD or other non-lethal diseases are expected to provide relatively higher baseline values of TTO and SG and demonstrate low responsiveness as

Table 5. Spearman correlation matrix of QOL-PCD scales and health utilities in PCD.

QOL-PCD scales	VAS	TTO	SG	EQ5D
Physical functioning	0.58*	0.37*	0.28	0.64*
Vitality	0.37*	0.23	0.08	0.49*
Emotional functioning	0.43*	0.08	0.18	0.58*
Treatment burden	-0.09	0.05	-0.02	-0.05
Role	0.16	0.04	0.02	0.26
Social functioning	0.28	-0.09	-0.13	0.18
Health perspective	0.18	0.13	0.17	0.14
Upper resp.	0.38*	0.23	0.08	0.49*
Lower resp.	0.58*	0.16	0.10	0.72*
Hearing symptoms	0.03	0.06	0.38*	-0.009

VAS, visual analog scale; TTO, time trade off; SG, standard gamble; EQ5D, EuroQoL 5 dimensions; *significant at the 0.05 level.

demonstrated in the present as well as in previous studies [36].

When compared to cystic fibrosis (CF), a similar but usually more severe disease, the HU calculated in our adult PCD cohort are generally higher. More specifically, EQ5D and VAS values obtained from unstratified samples of adult CF patients from different countries across Europe were substantially lower compared to the PCD-specific 0.86 for EQ5D and 0.75 for VAS as calculated here. CF EQ5D ranged from 0.525 in Sweden to 0.87 in Spain, whereas CF VAS ranged from 0.460 in Bulgaria to 0.697 in Italy [37]. In addition, Bradley *et al*. stratified CF patients according to pulmonary exacerbations status and reported EQ5D mean values in the range of 0.85 (0.80-0.89), 0.79 (0.67-0.91) and 0.60 (0.44-0.76) for patients with no, mild or severe pulmonary exacerbations respectively [38]. Interestingly, the EQ5D mean estimate calculated for CF patients with the least morbidity (0.85) is similar to our median EQ5D estimate for PCD (0.86). This observation is in line with previous reports that demonstrated that CF patients with milder symptoms experience similar clinical severity to PCD patients [39].

Molecular diagnosis was not found to be associated with any of the HU measures examined. To date, very few studies examined genotype-phenotype associations in PCD [40-42] and a worse clinical picture has been reported for patients with CCDC39 [40,42] or CCDC40 mutations [40-42]. Among our cohort only one patient was diagnosed with biallelic mutations in CCDC40 and we could not corroborate these findings. Nevertheless, in our study, we

Table 6. Impact of individual QOL-PCD scales on the variance of health utility scores.

Model	QOL-PCD scales	R squared	R squared change	p
VAS				
Model 1	PF	0.316	0.316	0.001
Model 2	PF, LRS	0.419	0.103	0.034
Model 3	PF, LRS, EF	0.427	0.008	0.548
Model 4	PF, LRS, EF, URS	0.434	0.006	0.593
Model 5	PF, LRS, EF, URS, V	0.434	0.000	0.900
Model 6	PF, LRS, EF, URS, V, HS	0.445	0.011	0.497
TTO				
Model 1	PF	0.166	0.166	0.023
Model 2	PF, LRS	0.170	0.004	0.714
Model 3	PF, LRS, EF	0.197	0.027	0.348
Model 4	PF, LRS, EF, URS	0.198	0.000	0.918
Model 5	PF, LRS, EF, URS, V	0.240	0.042	0.250
Model 6	PF, LRS, EF, URS, V, HS	0.260	0.020	0.426
SG				
Model 1	PF	0.001	0.001	0.900
Model 2	PF, LRS	0.012	0.012	0.567
Model 3	PF, LRS, EF	0.014	0.002	0.859
Model	PF, LRS, EF, URS	0.029	0.015	0.529
Model 5	PF, LRS, EF, URS, V	0.048	0.019	0.481
Model 6	F, LRS, EF, URS, V, HS	0.324	0.276	0.005
EQ5D				
Model 1	PF	0.414	0.414	<0.001
Model 2	PF, LRS	0.538	0.124	0.011
Model 3	PF, LRS, EF	0.556	0.018	0.302
Model 4	PF, LRS, EF, URS	0.562	0.006	0.567
Model 5	PF, LRS, EF, URS, V	0.569	0.007	0.522
Model 6	PF, LRS, EF, URS, V, HS	0.573	0.004	0.631

VAS, visual analog scale; TTO, time trade off; SG, standard gamble; EQ5D, EuroQoL 5 dimensions; PF, physical functioning; LRS, lower respiratory symptoms; EF, emotional functioning; URS, upper respiratory symptoms; V, vitality; HP, hearing symptoms.

demonstrate that patients with biallelic mutations in *RSPH9* gene are characterised by a more conserved lung function compared to the rest of the cohort. This finding is also supported by evidence from previous studies that largely report milder clinical symptoms in patients with defects in genes encoding radial spoke proteins as opposed to PCD patients with other genetic defects [41,43-45]. However, this relationship was not reflected in the association between molecular diagnosis and any of the HU measures assessed in this study, including VAS and EQ5D that were characterised by good responsiveness to lung function indices such as FEV_1 and FVC. Although HU in general reflect the health perception of the individual, this finding may suggest that other factors, beyond the health perception of the individual, also influence the value of the HU [46]. In particular, for HU obtained through indirect elicitation methods such as the generic EQ5D questionnaire, the patients are forced to encapsulate their complex chronic condition in five non-disease-specific categories, while their preferences for the health states described are obtained from the general public, which may differ from the preferences of chronic patients [47]. On the other hand, for HU obtained through direct elicitation methods (VAS, TTO, SG), the values may vary beyond what is expected by health perception alone as religious beliefs, available support, relationships with friends and family as well as overall enjoyment of life may come into consideration [48].

Finally, our study used a wide variety of elicitation methodologies to assess applicability and responsiveness of health utility measures, while a well-characterised population allowed for the assessment of the relationship of genotypic and phenotypic characteristics with health utilities using appropriate statistical methods. Nevertheless, the external validity of our study is limited by the low sample size and results are not directly generalizable to other populations that may experience different access to healthcare as well as different social and cultural norms. In addition, due to the limited number of participants we could not evaluate the effect of comorbidities or treatment patterns on HU while subgroup analysis for different age groups was not possible. Lastly, the cross-sectional nature of this study did not allow us to evaluate whether HU metrics can detect changes in health status over time. Overall, our findings can be considered preliminary in nature and additional studies, involving a greater number of patients, are required to fully elucidate the relationships between HU and genotypic, demographic, and phenotypic characteristics in PCD. Such studies will further contribute towards the ongoing dialogue about the impact of PCD on quality of life and allow for better evaluation of healthcare interventions and informed decision making in the clinical setting.

Conclusions

In summary, our study demonstrates that HU elicitation in PCD is feasible using both direct and indirect methods. HU scores are relatively high, with higher scores observed in SG and TTO, followed by EQ5D and VAS. VAS and EQ5D are associated with lung function z-scores as well QOL-PCD physical functioning and lower respiratory symptoms scores, while TTO and SG are largely not responsive to clinical characteristics and QOL-PCD scales. In addition, irrespective of the elicitation method, HU values are not

associated with the implicated genetic defect among our adult PCD population. Nevertheless, further studies, in larger PCD populations, are needed to elicit the true relationship of HU with HRQOL measures, clinical characteristics and PCD genotypes.

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