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Validation and implementation of the Dutch PHPQoL for primary hyperparathyroidism

Jaimie L H Zhang¹, Abbey Schepers¹, Jaap F Hamming¹, Lano Osman², Susan M Webb³, Lieke Welling¹, Elizabeth M Winter², Marieke Snel² and Natasha M Appelman-Dijkstra²

¹Department of Surgery Leiden University Medical Center, Leiden, The Netherlands

²Department of Internal Medicine division Endocrinology Leiden University Medical Center, Leiden, The Netherlands

³Department of Medicine, University Autònoma Barcelona, Endocrinology, Hospital Sant Pau, Institut de Recerca Sant Pau (IR SANT PAU), EndoERN, CIBERER Unit 747, ISCIII, Barcelona, Spain

Correspondence should be addressed to N M Appelman-Dijkstra: n.m.appelman-dijkstra@lumc.nl

Abstract

Background: Patients with primary hyperparathyroidism (PHPT) often present with nonspecific neuropsychological symptoms, which remain challenging to quantify. While parathyroidectomy (PTx) recently has been recommended for asymptomatic patients, its benefit remains unclear as existing evidence relies on generic health-related quality of life (HRQoL) tools. In contrast, the disease-specific PHPQoL questionnaire offers more sensitive and clinically relevant symptom assessment. This study aims to translate and validate the PHPQoL for Dutch use and to evaluate the effect of PTx on HRQoL in both symptomatic and asymptomatic PHPT patients.

Methods: In this single-center prospective study, PHPT patients with at least one surgical indication underwent either PTx or conservative treatment based on medical requirement and patient preference. Clinicians classified patients as asymptomatic if no hypercalcemia-related complaints were present. HRQoL questionnaires were assessed using the PHPQoL, SF-36, and EQ-5D questionnaires at inclusion and 3 months after treatment. Statistical significance was set at $P < 0.001$.

Results: Of the 100 patients included (mean age: 61.5 ± 12.4 years, 77% female), 89 underwent PTx (symptomatic: $n = 47$, asymptomatic: $n = 42$), and 11 received conservative treatment. The PHPQoL demonstrated strong psychometric properties and correlated well with generic HRQoL questionnaires. Following PTx, mean PHPQoL scores improved from 52.2 to 65.9 ($P < 0.001$); in asymptomatic patients, scores rose from 58.3 to 71.7 ($P < 0.001$).

Conclusion: The Dutch version of the PHPQoL is a valid and reliable tool for assessing PHPT and demonstrates significant HRQoL improvements following PTx, including in asymptomatic patients, which may be underestimated by generic instruments.

Keywords: primary hyperparathyroidism; health-related quality of life; quality of life; hypercalcemia; parathyroidectomy; cinacalcet; hypercalcemia; parathyroid disease

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder caused by excessive secretion of parathyroid hormone (PTH) by one or more parathyroid glands, resulting in hypercalcemia (1). This condition can have

deleterious effects on the cardiovascular system, kidneys, bones, and muscles, and may also cause neuropsychological/subjective symptoms that impair health-related quality of life (HRQoL) (2, 3).

The definitive treatment of PHPT is surgical removal of the affected gland(s) via parathyroidectomy (PTx). Historically, guidelines did not recommend PTx for patients with solely neuropsychological complaints (4), as the impact of surgery on HRQoL remained uncertain and the underlying causal mechanisms were poorly understood (5, 6, 7, 8, 9, 10). Evidence in this subgroup is inconclusive: observational studies have reported improvement in neuropsychological aspects of HRQoL (11, 12, 13), whereas results from short-term randomized controlled trials are ambiguous (14, 15, 16). This issue has become increasingly relevant, as earlier detection identifies more patients with mild disease – characterized by minimal and/or neuropsychological symptoms yet persistently reduced HRQoL (15, 16).

At the time this study was initiated, guidelines still advised against surgery for patients presenting with solely neuropsychological complaints. In the most recent guidelines, PTx is advised even for asymptomatic patients, despite limited evidence for its effects on neurocognitive function and HRQoL (17). A key limitation of the literature supporting these recommendations is the reliance on generic HRQoL questionnaires, which may lack the sensitivity needed to detect subtle but clinically relevant changes in PHPT-related symptoms. The disease-specific PHPQoL questionnaire was developed to address this gap. Tailored to the symptom profile of PHPT, it has demonstrated strong reliability and correlates well with generic HRQoL measures (18). Incorporating the PHPQoL may therefore provide a more nuanced and clinically relevant assessment of disease burden and treatment benefit.

We therefore aimed to translate and validate the PHPQoL for Dutch use, representing an important advancement in enhancing research methodologies and improving outcome assessment in PHPT-related clinical care (19). In addition, we sought to evaluate the effect of PTx on HRQoL in both symptomatic and asymptomatic PHPT patients.

Method

Study design and data extraction

A prospective, single-center study was conducted in an academic setting comprising two components: i) linguistic validation of the PHPQoL questionnaire in a Dutch cohort and ii) assessment of treatment effect in patients with PHPT.

The PHPQoL was translated from Spanish to Dutch, as necessitated by its original development and validation in Spain (19, 20). In summary, this process involved forward-backward translation and cognitive debriefing with a representative group of PHPT patients. Iterative

discussions following each step rectified linguistic discrepancies, resulting in the final Dutch version of the PHPQoL. Subsequently, consecutive PHPT patients presenting to the outpatient clinic of the Department of Endocrinology and Endocrine Surgery, Leiden University Medical Centre, were included under usual clinical practice conditions during the period of 2018–2022. The inclusion period was extended due to the impact of COVID-19. Eligible patients were ≥ 18 years with biochemically confirmed PHPT, defined as a PTH level above the upper limit of normal (reference range: 0.7–8.0 pmol/L) with elevated or normal calcium levels. Other causes of hypercalcemia were ruled out by evaluating vitamin D status, renal function, 24-hour urinary calcium excretion, and imaging studies. The exclusion criterion was an inability to complete the questionnaires. Following inclusion, patients were offered surgery when meeting at least one surgical criterion in accordance with the 2014 Fourth International Workshop on the Management of Asymptomatic PHPT (4). Patients who declined surgery or were deemed unfit for surgery underwent conservative management. Clinicians classified patients as asymptomatic if no neuropsychological or physical PHPT-related symptoms were present.

At inclusion, sociodemographic data (age, sex, and nationality) and clinical variables (PHPT symptoms, time since diagnosis, surgical indications, medication use, laboratory values (calcium values were albumin-corrected), and medical history) were collected. Participants completed the Dutch PHPQoL along with the SF-36 and EQ-5D HRQoL questionnaires during their initial outpatient visit following PHPT diagnosis. For surgical patients, postoperative monitoring included assessment for complications and at least one outpatient visit, during which blood values were examined to confirm resolution of PHPT. Postoperative questionnaires were administered at 2 weeks and 3 months, with follow-up concluding at 3 months. For patients managed conservatively, questionnaires were re-administered approaching the end of the patient inclusion period, alongside blood value assessment during an outpatient visit.

For surgical patients who failed to return postoperative questionnaires, reminders were sent up to 1 year following surgery. Regarding missing data, patients who did not submit preoperative questionnaires were excluded from longitudinal HRQoL analyses. Missing postoperative data were addressed using the last observation carried forward method. Surgical patients with persistent postoperative hypercalcemia were excluded from all longitudinal analyses.

The power calculation to assess sensitivity to change was based on the study by Webb *et al.* (19): a minimum of 88 patients were required to detect treatment-related differences with a standard deviation of 0.3 (small or moderate effect size), a significance level of 0.05, and a

statistical power of 0.80. Accounting for a potential 10% loss to follow-up, the sample size was increased to 97.

The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Quality of life questionnaire for patients with primary hyperparathyroidism (PHPQoL)

The PHPQoL is a disease-specific questionnaire consisting of 16 items that assess the frequency of PHPT-related symptoms experienced over the preceding 4 weeks (Supplementary material (see section on [Supplementary materials](#) given at the end of the article)) (19). Each item is scored on a 5-point Likert scale. The total score ranges from 0 to 64 and is converted to a 0–100 scale, with lower scores indicating greater disability (19).

Short Form 36 (SF-36)

The SF-36 is a validated instrument for measuring generic health-related quality of life in individuals aged 14 years and older. It assesses eight domains: physical functioning (PF), social functioning (SF), role limitations due to physical health (PR), role limitations due to emotional problems (ER), mental health (MH), vitality (V), bodily pain (BP), and general health perceptions (GH). Domains consist of 2–10 items, each with Likert-scale response options ranging from 2 to 6. Domain scores were transformed to a 0–100 scale, with lower scores reflecting greater impairment (21). Physical and mental component summary scores (PCS and MCS) were derived using American population norms, as Dutch-specific reference data were unavailable (22). Age-matched Dutch reference values were sourced from Aaronson *et al.* (23).

EuroQoL-5D-3L (EQ-5D)

The EQ-5D is a widely used generic health status measure encompassing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is assessed by a single item with three response levels on a Likert scale (24). Responses were converted into utility scores using the Dutch population value set, anchored at 0 (death) and 1 (perfect health) (25). These utility scores were then transformed to a 0–100 scale to align with the scoring range of other questionnaires used in this study (EQ-5D S). The questionnaire also includes a visual analogue scale (EQ-5D VAS), on which patients rate their health from 0 to 100 (respectively, representing the worst and best health imaginable). The EQ-5D has demonstrated robust reliability and validity. Age-matched Dutch reference values were obtained from Janssen *et al.* (26).

Statistics

Descriptive analyses were performed for both the questionnaire translation and cognitive debriefing interviews. Internal consistency of the PHPQoL was assessed using Cronbach's alpha coefficient, with values ≥ 0.70 indicating good consistency (27). Spearman's rank correlation coefficient (ρ) was employed to assess associations between variables. Although the PHPQoL is traditionally reported as a single composite score, this study additionally provided individual item scores to capture symptom-specific information. Sensitivity to change was assessed by comparing PHPQoL scores at baseline and at the end of follow-up. Effect sizes (Cohen's *d*) were calculated and interpreted as small (0.20), moderate (0.50), or large (0.80) effects.

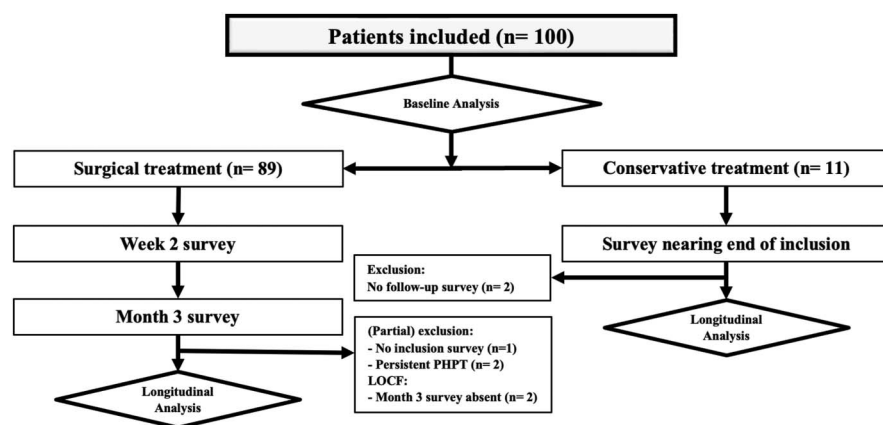
Concurrent validity was evaluated by examining correlations between baseline PHPQoL scores and those from other health-related quality of life (HRQoL) instruments. Longitudinal validity was assessed by correlating changes in PHPQoL scores with corresponding changes in other questionnaires over the 3-month follow-up period. Linear regression analyses explored associations between baseline PHPQoL scores (dependent variable) and relevant HRQoL-related predictors (independent variables), including age, sex, duration since PHPT diagnosis, serum calcium, serum parathyroid hormone (PTH), and presence of skeletal or renal manifestations (osteoporosis, nephrolithiasis, nephrocalcinosis, and fragility fractures).

Statistical tests were selected based on data distribution and variable type, including paired and independent samples *t*-tests, Mann–Whitney U test, Wilcoxon signed-rank test, and Chi-square test, as appropriate. Analyses were conducted using SPSS version 25 (IBM Corporation, The Netherlands). To control for multiple comparisons (over 50 tests), Bonferroni correction was applied, setting the threshold for statistical significance at $P < 0.001$.

Results

Patient inclusion and baseline characteristics

During the study period, 100 PHPT patients were included, of whom 89 underwent PTx and 11 received conservative treatment (Fig. 1). No alternative causes of hypercalcemia were identified. Reasons for choosing conservative treatment were patient preference ($n = 6$) and inoperability ($n = 5$). Among the surgical group, one patient had missing baseline questionnaires, two failed to return questionnaires at 3 months postoperatively, and two experienced persisting hypercalcemia. In the conservative group, two patients failed to return follow-up questionnaires without a documented medical reason.

**Figure 1**

Flow chart of included patients. (LOCF: last observation carried forward).

The mean age of the cohort was 61.5 ± 12.4 years, and 77% were female (Table 1). Patients often presented with multiple surgical indications, with a median of 2 (IQR: 1–3) per individual. The most frequent indications were hypercalcemia (45%), hypercalciuria (43%), and osteoporosis (43%). Calcium-lowering medications were commonly prescribed at the time of inclusion: 32% of patients received cinacalcet, and 56% were on bisphosphonates. Baseline mean serum calcium and PTH levels were, respectively, 2.73 ± 0.21 mmol/L and 17.1 ± 19.9 pmol/L. Comorbidities were reported in 72% of patients. When the cohort was stratified by symptom presence, the only significant difference observed was a higher number of surgical indications in symptomatic patients ($P < 0.001$).

PHPQoL validation and the effect of PTx

The PHPQoL demonstrated good internal consistency, with a Cronbach's α of 0.93. Across the entire cohort, the PHPQoL scores significantly increased from 52.2 ± 21.3 at baseline to 65.9 ± 22.5 at 3 months postoperatively ($P < 0.001$, Fig. 2), corresponding to a

moderate effect size (Cohen's $d = 0.79$) and indicating good sensitivity to change. When restructured to individual scores per question, most symptoms showed significant improvement on the Likert scale, except for ambulatory limitation, exertional dyspnea, and nocturnal awakening ($P = 0.001$ – 0.129 , Fig. 3).

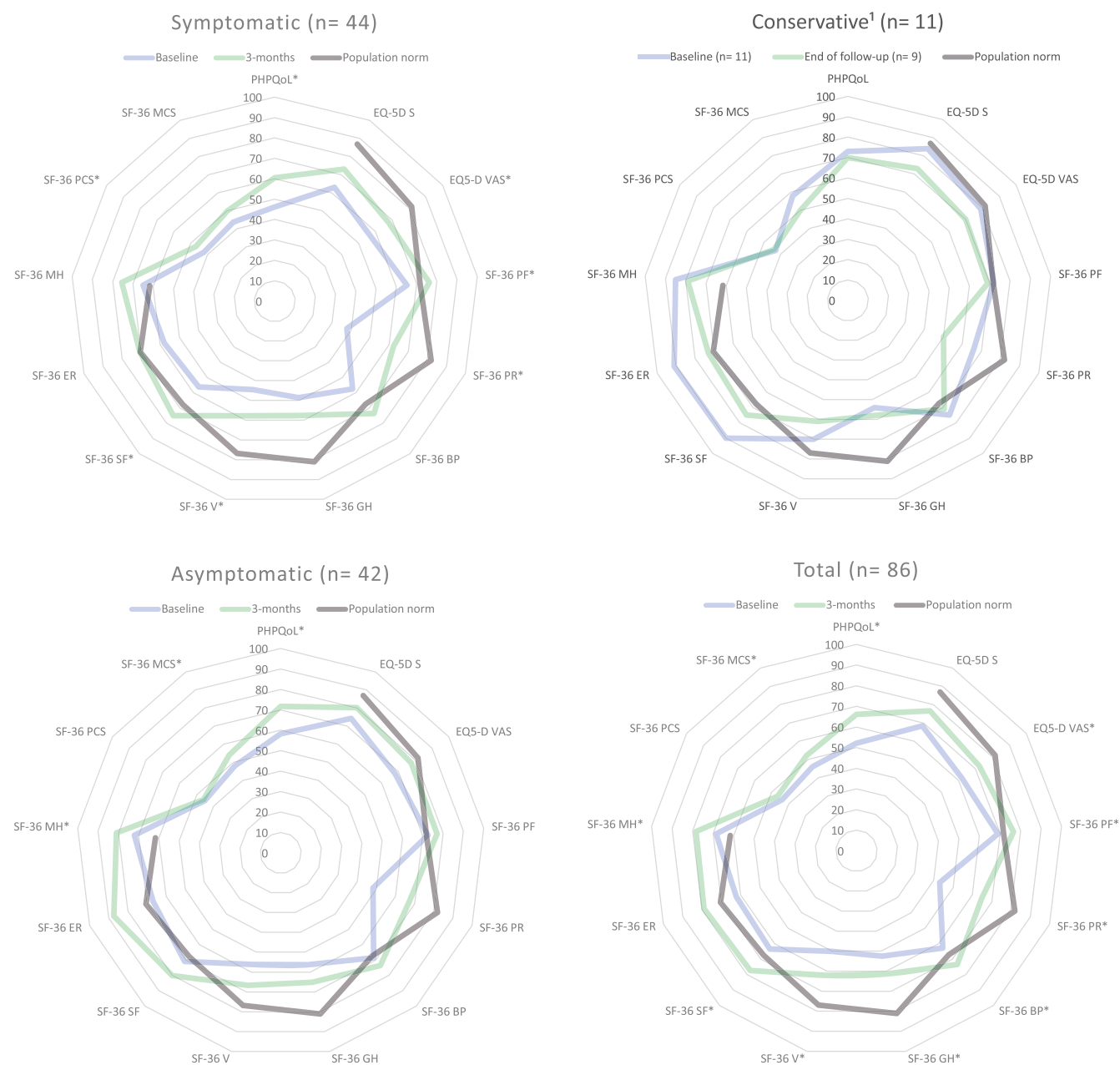
Subgroup analysis revealed no significant difference in baseline PHPQoL scores between symptomatic and asymptomatic patients (46.2 ± 22.6 vs 58.3 ± 18.1 , $P = 0.010$). At 3 months postoperatively, both groups experienced significant improvements: symptomatic patients' scores improved by 13.3 points to 60.5 (29% increase, $P < 0.001$, Fig. 3), while asymptomatic patients improved by 13.6 points to 71.7 (23% increase, $P < 0.001$). The between-group difference in postoperative scores remained non-significant (symptomatic: 60.5 ± 22.7 vs asymptomatic: 71.7 ± 21.0 , $P = 0.020$). Asymptomatic patients reported significant improvement in specific symptoms, including morning fatigue, activity impairment, feeling depressed, and concerns regarding PHPT and its possible complications, all with $P < 0.001$ (Fig. 3).

Table 1 Baseline characteristics of patients.

	Conservative (n = 11) Mean $\pm$ SD/%	PTx symptomatic (n = 47) Mean $\pm$ SD/%	PTx asymptomatic (n = 42) Mean $\pm$ SD/%	Total (n = 100) Mean $\pm$ SD/%	P-value*
Age	69.4 $\pm$ 13.8	57.0 $\pm$ 12.0	64.5 $\pm$ 10.7	61.5 $\pm$ 12.4	0.002
Sex					0.59
Male	46%	19%	24%	23%	
Female	64%	81%	76%	77%	
Years since diagnosis	3.6 (0.3–9.3)	0.6 (0.2–2.3)	0.5 (0.2–3.8)	0.6 (0.2–3.5)	0.49
Number of surgical indications	1 (1–2)	2 (2–3)	2 (1–2)	2 (1–3)	<0.001
Cinacalcet	27%	32%	33%	32%	0.89
Bisphosphonate	64%	57%	52%	56%	0.63
Comorbidities	82%	66%	76%	72%	0.29
Serum calcium (mmol/L)	2.65 $\pm$ 0.17	2.72 $\pm$ 0.21	2.76 $\pm$ 0.23	2.73 $\pm$ 0.21	0.29
Urinary calcium (mmol/24 h)	7.3 $\pm$ 2.2	9.9 $\pm$ 4.2	9.2 $\pm$ 4.6	9.3 $\pm$ 4.24	0.52
PTH (pmol/L)	14.2 $\pm$ 10.1	17.3 $\pm$ 21.2	17.6 $\pm$ 20.5	17.1 $\pm$ 19.9	0.95
Alkaline phosphatase (U/L)	99.4 $\pm$ 21.7	107.1 $\pm$ 38.6	87.3 $\pm$ 36.4	97.8 $\pm$ 37.0	0.016
Phosphate (mmol/L)	0.87 $\pm$ 0.15	0.87 $\pm$ 0.19	0.93 $\pm$ 0.19	0.90 $\pm$ 0.19	0.21

Continuous variables are presented as mean $\pm$ SD or median (IQR), depending on their distribution. Bold indicates statistical significance.

*Comparison between groups: PTx symptomatic-asymptomatic.

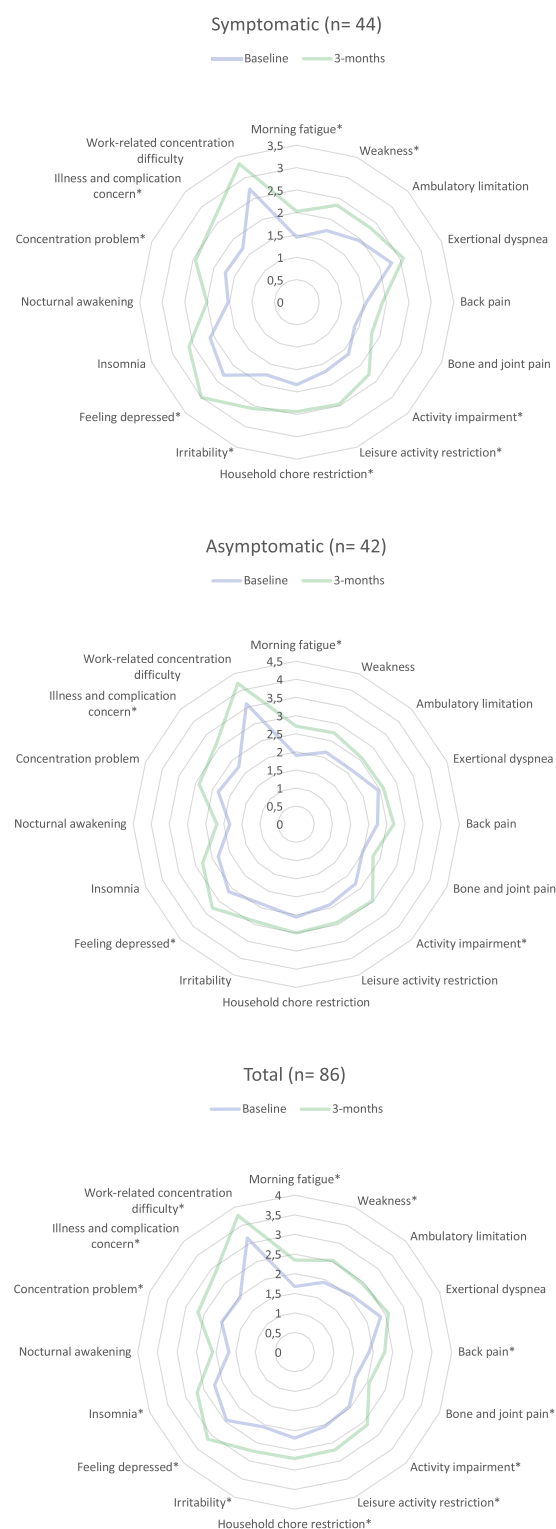
**Figure 2**

Radar chart of the mean scores of different HRQoL questionnaires at baseline (blue), at the end of follow-up (PTx: 3-month postoperative, conservative treatment mean follow-up duration: 3.5 ± 1.9 years, green), and the population norm (gray). ¹Statistical tests were not performed in the conservative treatment group. *Statistically significant difference between baseline and month 3 values with $P < 0.001$. (EQ-5D S: EQ-5D score, EQ-5D VAS: EQ-5D visual analogue scale score, SF-36 PF: physical function, SF-36 PR: physical role, SF-36 BP: bodily pain, SF-36 GH: general health, SF-36 V: vitality, SF-36 SF: social function, SF-36 ER: emotional role, SF-36 MH: mental health, SF-36 PCS: physical component summary, SF-36 MCS: mental component summary).

Generic HRQoL at baseline was lower in the entire cohort compared with age-matched population norms (Fig. 2). Following PTx, most generic HRQoL parameters improved significantly ($P < 0.001$). Those without significant improvement included the EQ-5D score (68.4–76.6), SF-36 ER (62.3–79.0), and SF-36 PCS (43.7–46.5), with P -values ranging from 0.001 to 0.002.

When stratified by symptom presence, most improvements in generic HRQoL among asymptomatic patients were no longer statistically significant ($P = 0.002$ – 0.137), with the exception of SF-36 MH (68.5–78.3) and SF-36 MCS (46.0–52.5, both $P < 0.001$).

Concurrent validation of the PHPQoL at baseline revealed moderate-to-high correlation with SF-36 scores

**Figure 3**

Radar chart of the PHPQoL questionnaire divided per question, with mean values at baseline (blue) and 3-month postoperatively (gray).

*Statistically significant difference between value at baseline and month 3 with $P < 0.001$.

($r = 0.65$ – 0.82 , $P < 0.001$, Table 2) and high correlations with EQ-5D scores ($r = 0.77$ – 0.82 , $P < 0.001$). A similar pattern was observed for the longitudinal score changes, albeit with slightly lower correlation coefficients: moderate-to-high correlation with SF-36 scores ($r = 0.63$ – 0.79 , $P < 0.001$) and high correlation with EQ-5D scores ($r = 0.74$ – 0.80 , $P < 0.001$).

Biochemical outcomes and PHPQoL predictors

Patients' laboratory values normalized significantly following PTx. Serum calcium decreased from 2.73 ± 0.22 to 2.34 ± 0.11 mmol/L, and PTH levels declined from 17.0 ± 20.2 to 5.1 ± 1.5 pg/mL (both $P < 0.001$), indicating curative resections, although two patients exhibited persistent postoperative hypercalcemia.

Multivariate linear regression indicated that 24.8% of the variance in baseline PHPQoL scores was explained by the independent variables, demonstrating a significant overall impact ($R^2 = 0.248$, $F = 4.608$, $P < 0.001$, Supplementary Table S1). Age was positively associated with PHPQoL scores ($P < 0.001$), suggesting that older individuals report higher perceived HRQoL. Gender was the next most influential predictor ($P = 0.018$), with female patients tending to report lower PHPQoL scores.

Conservative management and HRQoL

Eleven patients received conservative treatment, of whom four were asymptomatic. Due to the small sample size, statistical testing was not performed, and the findings remain descriptive. At baseline, these patients tended to be older, more often male, with a longer time since diagnosis, and with fewer laboratory abnormalities (Table 1). The mean interval between baseline and follow-up assessments was 3.5 ± 1.9 years, during which all HRQoL outcomes appeared stable (Fig. 2).

Clinical impact

Between baseline and 3 months postoperatively, 31% of patients (27 of 87) reported 'somewhat improved' general health on the SF-36 global transition item ('Compared to one year ago, how would you rate your health in general now?'), comprising 14 symptomatic and 13 asymptomatic patients. In addition, 32% (28 of 87) reported 'substantial improvement' in self-perceived health (symptomatic: $n = 15$; asymptomatic: $n = 13$). Using the minimal clinically important difference of ≥ 9 PHPQoL points reported by Webb *et al.* (18), 59% (51 of 87) achieved a clinically relevant improvement (symptomatic: $n = 27$; asymptomatic: $n = 24$).

Table 2 Concurrent and longitudinal correlation coefficients between PHPQoL scores and those obtained from the SF-36 and EQ-5D.

Questionnaire (mean)	PHPQoL (n = 99)		PHPQoL (n = 97)	
	Concurrent	P-value	Longitudinal	P-value
SF-36				
Physical function	0.65	<0.001	0.71	<0.001
Physical role	0.79	<0.001	0.77	<0.001
Bodily pain	0.76	<0.001	0.74	<0.001
General health	0.69	<0.001	0.70	<0.001
Vitality	0.82	<0.001	0.83	<0.001
Social function	0.82	<0.001	0.79	<0.001
Emotional role	0.66	<0.001	0.63	<0.001
Mental health	0.76	<0.001	0.71	<0.001
PCS	0.67	<0.001	0.66	<0.001
MCS	0.76	<0.001	0.68	<0.001
EQ-5D				
Score	0.82	<0.001	0.80	<0.001
VAS	0.77	<0.001	0.74	<0.001

Bold indicates statistical significance. (PCS, physical component summary; MCS, mental component summary).

Discussion

The clinical presentation of PHPT has changed drastically in recent decades, now often presenting with diverse, non-classical symptoms. This shift necessitates a critical re-examination of the efficacy of PTx in improving HRQoL. Although generic instruments have been widely used, they are considered less specific for capturing the symptom profile of PHPT (11, 28, 29, 30). The PHPQoL questionnaire offers a targeted approach to evaluating HRQoL in this population. In the present study, the Dutch version of the PHPQoL was validated in a cohort of patients with PHPT, using the SF-36 and EQ-5D as generic HRQoL comparators.

The PHPQoL demonstrated strong psychometric properties and correlated well with reference questionnaires. Post-PTx, PHPQoL scores improved significantly in both 'symptomatic' and 'asymptomatic' patients, whereas improvements in generic HRQoL measures were less pronounced, particularly among asymptomatic individuals. Of the patient characteristics examined, only age was significantly associated with baseline PHPQoL scores, with older patients reporting higher perceived HRQoL. Baseline calcium levels did not influence PHPQoL scores, consistent with previous reports (18, 31). The Dutch version of the PHPQoL proved to be a useful tool, as it exhibited good internal consistency, sensitivity to change, validity, and feasibility for patients to complete. Its scores remained stable in conservatively treated patients and showed moderate-to-high concurrent and longitudinal correlations with the SF-36 and EQ-5D, confirming the results of previous studies validating the same questionnaire in different countries (18, 32, 33).

Baseline PHPQoL scores, serum calcium, and PTH levels in our cohort were comparable to those reported in previous PHPQoL studies (18, 31, 34). At 3 months postoperatively, the mean PHPQoL score improved by 27%, consistent with

the aggregated range of 17–22% reported elsewhere. Stratified by symptom presence, this score improvement was 23% in the asymptomatic group and 31% in the symptomatic group. At first, we thought the PHPQoL would be unable to differentiate between symptomatic and asymptomatic patients at baseline; however, in retrospect, the magnitude of postoperative improvement in the asymptomatic group suggests the presence of unrecognized complaints not captured by generic HRQoL instruments, a finding consistent with earlier PHPQoL studies (18, 31). In contrast, improvements expressed in generic HRQoL measures were less pronounced, particularly among asymptomatic patients. By comparison, PHPQoL gains exceeded the minimal clinically important difference, with most patients also reporting perceived health improvement on the SF-36. The observation that patients clinically classified as asymptomatic still experience statistically and clinically significant improvements highlights an unrecognized symptom burden when relying solely on clinician assessment. These findings underscore the limited sensitivity of generic HRQoL instruments in capturing PHPT-related benefits and emphasize the value of disease-specific instruments such as the PHPQoL, both in research and clinical decision-making, particularly for identifying subtle or subjective symptoms that may influence surgical indications.

The current study demonstrated significant improvements in general HRQoL measures 3 months following PTx, with the exception of the SF-36 emotional role, mental component summary, and physical component summary scores. Consistent with our findings, a recent systematic review by Livschitz *et al.* (35) reported that PTx most notably improved the SF-36 mental component summary, vitality, and BP, with significant improvements observed in 64–94% of included studies. Improvements in physical component scores and general health were less consistent, reported in only 44–57% of

studies. Available evidence regarding the impact of PTx in asymptomatic patients remains largely observational and short-term. Notably, only one RCT involving 191 asymptomatic patients without surgical indications has assessed HRQoL outcomes over an extended period of 10 years (36), reporting only modest improvements based on the SF-36 and the psychopathological rating scale. Despite substantial loss to follow-up and crossover, it demonstrated that impaired HRQoL as measured by generic instruments or the presence of psychological symptoms alone may not constitute sufficient indications for surgery, and that disease-specific patient-reported outcome measures, such as the PHPQoL, may better identify those likely to benefit from PTx, an observation supported by our present findings.

In our cohort, most PHPT-related symptoms captured by the PHPQoL improved postoperatively, with the exception of ambulatory limitation, exertional dyspnea, and nocturnal awakening. Among asymptomatic patients, improvements were only observed in morning fatigue, activity impairment, depressed mood, and concerns related to PHPT and its possible complications. These findings indicate that the PHPQoL can help elucidate symptomatology in patients with anamnistically unclear presentations, thereby supporting surgical decision-making.

Our study provides important insights, although it has several limitations. Symptom assessment was based on clinician judgment, reflecting real-world clinical practice; however, this approach introduces potential subjectivity, underscoring the need for a reliable, standardized tool to quantify symptoms. Recruitment was hindered by the COVID-19 pandemic, which delayed surgical procedures specifically for patients with milder PHPT. As a result, the inclusion period extended beyond initial projections, and some participants returned questionnaires more than 12 months after baseline. This delay may have introduced recall bias or temporal variation in patient-reported outcomes. The non-randomized design also raises the possibility of a placebo effect. Nevertheless, the strong correlations between HRQoL improvements and biochemical normalization suggest that the observed benefits were primarily attributable to PTx. Several subgroup analyses revealed clinically relevant trends that did not reach statistical significance, likely due to limited sample size; a larger cohort could provide greater statistical power, particularly in clarifying benefits for asymptomatic patients, who may ultimately be more accurately classified as having atypical presentations. Finally, this was a short-term study based on prior findings suggesting that HRQoL remains stable from 3 months to 1 year postoperatively (18). While this statement is supported by other studies lasting 1 to 2 years, longer-term data are needed to confirm the durability of these benefits (31, 34).

In conclusion, this study represents the first evaluation of the PHPQoL in the Netherlands, comparing it with the two most used generic HRQoL questionnaires. Our findings demonstrate that PTx significantly enhances HRQoL in PHPT patients 3 months postoperatively. The PHPQoL

exhibits excellent psychometric properties and has several advantages over generic HRQoL questionnaires, particularly its greater sensitivity to detecting changes and its ability to identify symptoms most likely to improve after PTx, thereby aiding clinical decision-making. Our findings further support the benefit of PTx in asymptomatic patients, especially with respect to psychological well-being, and argue for the inclusion of psychological complaints as a surgical indication. We recommend the routine use of the PHPQoL in clinical practice to improve the assessment and management of PHPT. Overall, our results reinforce the PHPQoL as a robust, disease-specific instrument for evaluating quality of life in this population.

Supplementary materials

This is linked to the online version of the paper at
<https://doi.org/10.1530/EC-25-0400>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Author contribution statement

Jaimie LH Zhang helped in data collection, analysis, original draft preparation, and writing review and editing. Abbey Schepers and Natasha M Appelman-Dijkstra contributed to methodology, conceptualization, writing review and editing, and supervision. Jaap F Hamming, Susan M Webb, Lieke Welling, Elizabeth M Winter, and Marieke Snel helped in writing review and editing. Lano Osman helped in data collection and writing review and editing.

Ethics

The 'Medisch-Ethische Toetsingscommissie Leiden Den Haag Delft' approved this study protocol.

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