Development and validation of Nasal Polyposis Quality of Life Questionnaire (NPQ)

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Short Title: A new QoL tool for Nasal Polyposis

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Abstract

Background*: To date, no disease-specific tool is available to assess the impact of Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) on Health Related Quality of Life (HRQoL). Therefore, the purpose of this study was to develop and validate a questionnaire specifically designed to this aim: the Nasal Polyposis Quality of Life questionnaire –NPQ.*

Methods*: According to the current guidelines, the development and validation of the NPQ occurred in two separate steps involving different groups of patients.*

Results*: In the development process of NPQ an initial list of items of 40 items was given to 60 patients with CRSwNP; the 27 most significant items were selected and converted into questions. The validation procedure involved 107 patients (mean age 52.9±12.4). NPQ revealed a five-dimensional structure and high levels of internal consistency (Cronbach's alpha 0.95). Convergent validity (Spearman' coefficient r=0.75; p< 0.01), discriminant validity (sensitivity to VAS score), reliability in a sample of patients with a stable health status (Interclass Coefficient 0.882) were satisfactory. Responsiveness to clinical changes was accomplished. The minimal important difference was 7.*

Conclusion*: NPQ is the first questionnaire for the assessment of HRQoL in CRSwNP. Our results provide that the new tool is valid, reliable, and sensitive to individual changes.*

Keywords: Chronic rhinosinusitis, nasal polyps, Patient Reported Outcomes, Quality of Life, Validation

INTRODUCTION

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP\) is a chronic inflammatory disease of the paranasal sinuses affecting 2 - 4% of the general population [1]. It is the most severe subtype of CRS, characterized by symptoms often lasting for many years. Management of CRSwNP is difficult and recurrences are frequent, despite medical treatment and surgery approaches. As a consequence, CRSwNP has a considerable impact on' health related quality of life (HRQoL). This expression refers to the impact of an illness and its therapy upon a patient, as perceived by the patient himself [2,3]. The burden of troublesome symptoms (nasal blockage, loss of smell, rhinorrhea, and sneezing), the presence of comorbid diseases (chronic rhinosinusitis, asthma, aspirin sensitivity), the necessity of long term medical therapies, the need of surgical treatments, the changes to habits and lifestyle, all negatively impact physical, emotional and social aspects of daily life.

Despite the literature in this field is not rich, available data confirm the clinical findings [4]. Some studies explored the subjective burden of CRSwNP by mean of SF-7036 [5], a generic measure that permit to assess health status in patients and healthy subject. Compared to general population, patients with CRSwNP had worse scores in all SF-36 domains except for physical functioning [6]. The disease burden has been detected also comparing CRSwNP with other chronic diseases, such as obstructive pulmonary disease [7], asthma [8] and coronary artery disease [9]. No correlation was found between SF-36 scores and age, gender, nasal symptoms, CT scan, and polyp size [10]. HRQoL has been also assessed by mean of the Sinonasal Outcome Test (SNOT-22) [11] a speciality-specific questionnaire that covers a broad range of rhinologic and general health issues. This widely-used tool has is not specific for the phenotype with NP and

for its characteristics has been used to assess the presence and the severity of sino-nasal disorders in clinical conditions really different from CRSwNP: smell dysfunction [12], sino-nasal symptoms in cystic fibrosis [13], allergic rhinitis [14], sleep apnea [15], COPD [16], hereditary haemorrhagic telangiectasia [17], Wegener's granulomatosis [18].

The need of a specific questionnaire to assess HRQoL in patients seems to be justified by several reasons:

- a specific questionnaire that encompasses all relevant aspects of HRQoL in CRSwNP does not exist;
- the use of both generic and specific tools to assess HRQoL is recommended [2];
- the use of generic or speciality-specific instruments is insufficient in capturing the impact of CRSwNP on patient's life and the changes of HRQoL.

The aim of the study was to develop and validate a specific questionnaire to assess HRQoL in patients affected by CRSwNP.

MATERIALS AND METHODS

The development and validation of the new questionnaire occurred in two separate steps involving different groups of patients. The method used for the two phases is described in detail below.

Consecutive patients who visited the Otorhinolaryngology and Personalized Medicine, Asthma and Allergy units from Istituto Clinico Humanitas between September 2018 and May 2020, were invited to participate in the study.

The Ethics Committee of the Humanitas University (Milan) approved the study protocol (approval no. P.R. 1920). The protocol complies with the general principles

of Good Clinical Practice and the Declaration of Helsinki as amended in Edinburgh in 2000. Participation was voluntary and anonymous, and informed consent was obtained from all patients before study entry.

The inclusion criteria were as follows: confirmed diagnosis of CRSwNP; age ≥18 years; comprehension of spoken and written Italian language; availability and willingness to participate in the study.

Participants were excluded in case of the presence of other ear–nose–throat disorders.

Development process

In order to make certain that the questionnaire included items appropriate and relevant for CRSwNP patients, items generation and selection was conducted on the basis of current guidelines [19-21]**:**

Item generation. The first step had the aim to collect potentially relevant and troublesome problems related to CRSwNP on the basis of the following sources: (i) literature review of the available HRQL questionnaires used with CRSwNP patients; (ii) round- tables with ENT specialists and pulmonologists; (iii) unstructured interviews to 10 adult outpatients with CRSwNP. This resultant list included practical, emotional, social and physical aspects of daily life that could be influenced by CRSwNP.

Item selection. The second step was comprised of an item importance ranking, in order to identify the most relevant problems related to CRSwNP. The questions found during the item generation procedure, were randomly listed and administered to patients who were asked to indicate: a) which of the items they experienced as consequence of CRSwNP; the response options were yes/no; b) how relevant each of the identified items was, by a 5-points response option, indicating the degree of importance related to each item (1=not important, 4 =very important)

In this first phase, a sample of 60 consecutive outpatients with CRSwNP has been accrued during a 2-month period. On the basis of collected data we calculated:

1. the percentage of patients who identified each item as a consequence of CR-SwNP (frequency range: 0–100);
2. the mean importance attributed to each item (range: 0–4);
3. the overall impact of each item, calculated as the product of the frequency and the mean importance divided by 100 (range: 0–4).

Selected items have been converted to questions where patients had to indicate how much they had been troubled by each problem during the last 2 weeks on a 5-point

Likert scale (1= not at all, 5 =very much).

This format of the questionnaire has been administered to a different group of patients for the validation process. Patients were selected using a convenience sampling method. The aim was to include almost 100 patients. The name of the new questionnaire is Nasal Polyposis Quality of Life (NPQ) questionnaire.

Validation process

Patients were assessed twice with a 4-week interval between visits.

At both visits, a physician collected a complete and accurate medical history reporting the ongoing therapy and patients filled in the NPQ along with the following tools:

- Visual analogue scale (VAS): patients were asked to indicate on a horizontal line measuring 10 cm the degree of CRSwNP severity, giving a score from 0 to 10 (worse). The score obtained can be divided into mild (VAS 0-3), moderate (VAS 3-7) and severe (VAS > 7) [1].
- The SNOT-22 (11) encompassess 22 items scored from 0 (meaning no problem reported) to 5 (as bad as it can be) giving a score to maximum 110 points; where, the higher the score the worse is the patient's QoL related to the disease. It has been adapted and validated in several languages and it is now available also in Italian [22].

At Visit 2, patients filled the same questionnaires of the Visit 1 and a Global Rating Scale to assess any change in health status.

The psychometric properties of the NPQ were tested as following:

- Construct validity was evaluated by mean of factorial analysis; the principal component method with Varimax rotation was adopted.
- Convergent validity was calculated by Spearman correlations to examine the relationships between the new questionnaire and an established measure (SNOT-22). Convergent validity is confirmed with correlations ranging from 0.4 to 0.8. Two instruments are considered too similar if the correlation is 0.8 or more (the tested instrument has no added value) [23].
- Discriminant validity was evaluated comparing patients according their VAS score by using ANOVA (Fischer's test)
- Internal consistency was estimated using Chronbach's correlation coefficient on the extracted factors. Measures with reliability of 0.50–0.70 or greater have been recommended for the purpose of comparing group [24].
- Reliability was evaluated by means of the Intraclass Correlation Coefficient (ICC) in the subsample of patients with a stable health status (GRS = 0). An ICC of >0.75 indicates excellent reproducibility while an ICC between 0.4 and 0.75 indicates a good reproducibility [24].
- Responsiveness was assessed, analyzing the correlation between changes in the score of the new questionnaire and changes in GRS (GRS ≠ 0) and VAS by means of a non-parametric test (Spearman correlation coefficient).
- Clinical significance was explored by assessing the minimal important difference (MID). The receiver operating characteristics (ROC) curve

method was applied [25]. The entire cohort for one dichotomization point (i.e., ‘no change’ vs ‘any improvement or deterioration’) was adopted.

The possible effect of age (Spearman’s correlation coefficient), gender, smoking habits and comorbid asthma (Fisher’s ANOVA) on patients’ answers was also tested. The frequency distribution of the answers was calculated to evaluate whether patients used the entire answer scale and whether all possible scores were obtained.

RESULTS

Development process

Sixty patients completed the development-phase questionnaire of 40 items. Most of these patients (63.3%) were female, and the mean (SD) age was 41.4 (8.3) years, ranging from 18 to 74 years.

On the basis of patients’ answers, items included in the questionnaire were those that scored highest in impact. Where an arbitrary cut-off value of 1.5 was used for impact, 13 items were excluded. Table 1 summarizes the results of this first phase, indicating the items selected due to the total importance.

Validation process

107 subjects were enrolled in the study. The mean age was 52.9 with a SD of 12.4; the majority were male (61.7%) and non-smoker (92.5%).

Comorbid asthma was found in 63 (58.9%) of patients.

Regarding atopy (as at least one allergen sensitization via skin prick test), 54

216(50.5%) were found positive. Acetyl salicylic acid (ASA) intolerance, meaning 217patients reporting some kind of respiratory symptoms upon aspirin or any 218nonsteroidal anti-inflammatory drugs (NSAIDS intake, was found in 14 (13.1%) 219patients; 5 subjects out of 107 (4.7%) were affected by Samter's triad.

- Construct validity: the factorial analysis with eigenvalue> 1 extracted five factors which explaine up to 66.97% of the total variance. Items belonging to each factor are listed in Table 2.
- Convergent validity: Spearman' correlations between NPQ scores and SNOT-22 were significant (r=0.75; p< 0.01)
- Discriminant validity*:* the group of patients with VAS > 7 had NPQ scores significantly higher than patients with VAS ≤7 (81.88 ±21.02 vs 61.4 ±15.65, p-value < 0.001).
- Internal consistency*:* Cronbach's alpha coefficient value of 0.95 was obtained for the whole instrument, exceeding the minimum internal consistency standard of 0.70 recommended for group comparison.
- Reliability*:* Interclass Coefficient (ICC) was 0.882, exceeding the cut-off of 0.75 indicating an excellent test reliability.
- Responsiveness*:* the assessment of a subsample of 44 patients reporting an improvement or deterioration in health status (GRS $\neq$ 0) demonstrate that a significant Spearman correlation between the variation of NPQ Total Score between the two visits and the change in VAS score (0.628 p< 0.001) and in GRS (-0.528 p<0.001) (Figure 1).

- Clinical significance*:* results of the ROC analyses are presented in Table 3. A 7-point change in RAPP maximizes sensitivity, specificity, and the number of individuals correctly classified., identifying the MID.

By the use of T-test, no significant difference was found in mean CRS-NP-QoL total score value comparing gender, comorbid asthma, atopy and ASA sensitivity. Smokers had a higher NPQ total score mean value in respect to non-smokers (90.6 ± 20.1 vs 74.3 ± 20.5, p= 0.03). No significant correlation was found between age and NPQ total score by the use of a linear regression analysis.

DISCUSSION

HRQoL has become a crucial outcome in chronic conditions, allowing to capture the patient's perspective about disease and treatment.

The availability of generic and rhinologic-specific questionnaires allowed to highlight that CRSwNp significanltly affects patients HRQoL. However there is no specific validated tool to assess HRQoL impairment of patients suffering from CRSwNP, that account approximately for 25% to 30% of CRS cases[26]. Recently it has been shown that nasal polyposis might have a variable impact on HRQoL [27] and that patients with CRSwNP present a different HRQoL profile compared to those with CRSsNP [28].

To address this gap we developed and validated the first disease specific tool to detect HRQoL impairment in patients with CRSwNP, by following the

established methodological guidelines and a recognized framework of questionnaire design [19-21]. The procedure we adopted provides evidences that the new instruments appropriately reflects HRQoL of patients suffering from CRSwNP. In fact, the development process guarantees that the item selection has been determined by the patients on the basis of their experience.

The new questionnaire consists of 27 items, that can be summed up to a total score and to five factorial scores. As expected, a moderate, significant correlation was obtained between NPQ and SNOT-22.

Discriminant validity was demonstrated through the tool's ability to discriminate between groups defined according to the VAS.

NPQ was shown to be an internally reliable tool as indicated by very high Cronbach α coefficients (0.95). It was also a reliable questionnaire as supported by satisfactory ICC in stable patients (0.882). High responsiveness to changes were confirmed by a significant correlation between the change of NPQ. Total score between the two visits and the change in VAS score and in GRS. The ROC analysis indicates that 7 point is the smallest change that patients perceive as an improvement or deterioration

The new questionnaire has several advantages: it is simple to complete and to score; it owns the necessary psychometric properties; the cutoff MID makes it easy to determine the clinical significance of the results and changes over time. Moreover, answers were not influenced by socio-demographic characteristics, thus enabling the NPQ to be used regardless of the patient's sex, age and education.

Because of these characteristics, NPQ is appealing as an instrument to assess the patient experience of CRSwNP. It is also potentially useful to monitor the impact of both disease and treatment from the patient's perspective owing to its

satisfactory responsiveness to changes.

Although we reached the primary aim of our study by providing evidence to support the validity, reliability, and responsiveness of NPQ, our findings should be considered in the light of the following potential limitations.

First, the generalizability of the results should be limited because the sample was nonrandomized and the patients were enrolled in one specialistic center. Second, no objective measures of disease control and severity, besides patient's reported outcomes, were adopted to determine the reliability and the sensitivity to change. Third, the acceptability of the new tool for both patients and physicians has not been evaluated. However these limitations may be faced through further studies.

In conclusion, NPQ is the first questionnaire for the assessment of HRQoL in CRSwNP. It is valid, reliable, and sensitive to individual changes. It is able to detect the specific burden of CRSwNP on HRQoL, This tool should yield data to improve our ability to effectively monitor the burden of disease and treatment on patients with CRSwNP.

CONFLICT OF INTEREST

Ilaria Baiardini received personal fees from Boehringer Ingelheim, Sanofi, GSK, Novartis, Mundifama, Menarini outside the submitted work.

Giovanni Paoletti reports personal fees from Novartis and Lusofarma, outside the submitted work.

Luca Malvezzi Received grants and personal fees from: Sanofi; Novartis; Astrazeneca outside the submitted work.

Francesca Puggioni received Personal fees from Astrazeneca, Sanofi, GSK, Menarini, Chiesi, Mundipharma, Valeas, Alk Abello, Allergy Therapeutics , Behringer , Grifols outside the submitted work.

Giacomo Malipiero reports personal fees from Allergy Therapeutics, outside the submitted work.

Giorgio Walter Canonica reports grants and personal fees from Menarini, Alk Abello', Anallergo Boehringer Ingelheim, Chiesi, Circassia, Genentech, Guidotti Malesci, GSK, Hal Allergy, Meda, Merck, Merck Sharp & Dome Novartis Recordati-InnuvaPharma, Roche, Sanof Stallergenes, UCB Pharma, Uriach Pharma, Teva Astrazeneca, Thermo Fisher, Valeas, Vibor Pharma, outside the submitted work.

Enrico Heffler received grants and personal fees from: AstraZeneca; Sanofi; Novartis; GSK; Circassia; Nestlè, Purina, outside the submitted work.

Francesca Racca received grants and personal fees from: GSK outside the submitted work.

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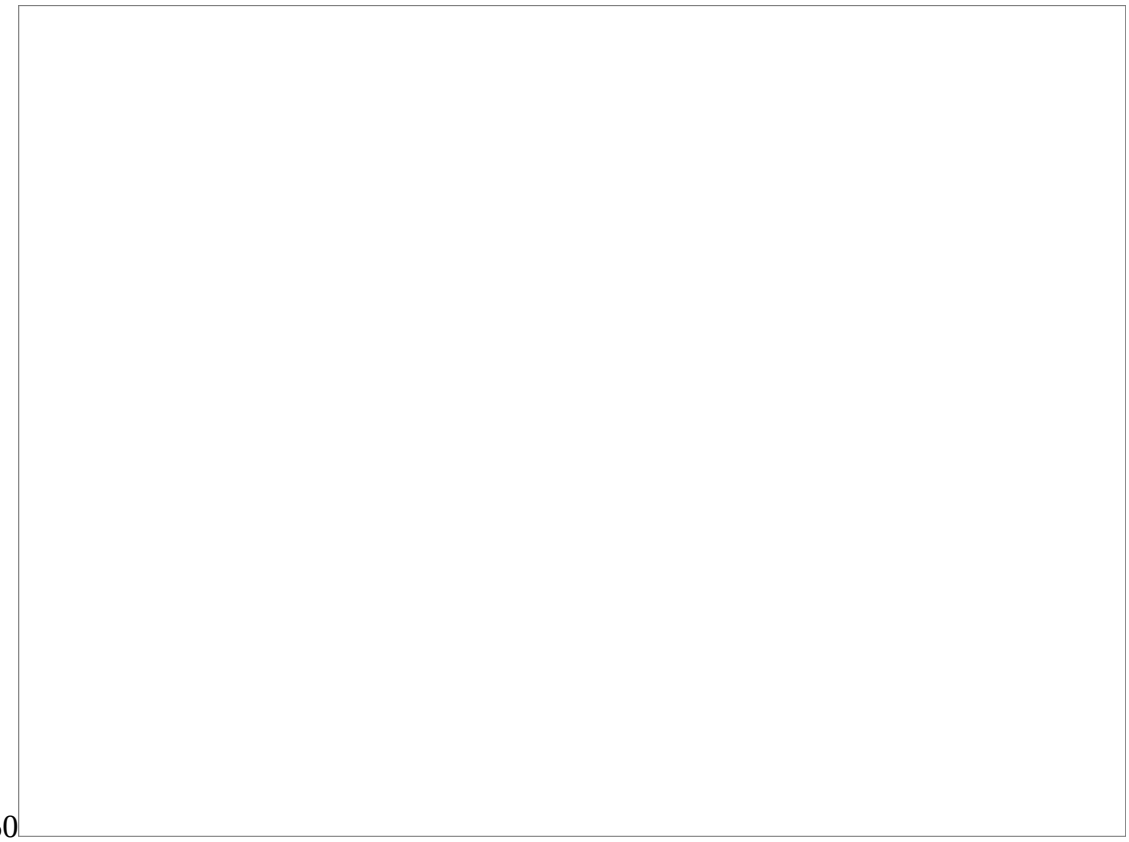
doi:10.1177/1945892420927244

FIGURE LEGEND

Figure 1. NPQ total score mean values according to age, smoking habits, asthma, atopy and ASA sensitivity



64

452TABLES

454**Table 1. Development process: results of item reduction**

455

N item	Item	Frequency (0-100)	Mean Importance (0-4)	Overall impact (0-4)
1	**Sleep problems**	**73.33**	**2.81**	**2.06**
2	Having to spend money	65	2.26	1.47
3	**Dry mouth**	**76.67**	**2.67**	**2.05**
4	**Restricted in sport activities**	**63.33**	**2.66**	**1.69**
5	**Bad breath**	**65**	**2.72**	**1.76**
6	Restricted in physical activities of daily life	55	2.67	1.46
7	Wake up during night to drink	60	2.39	1.43
8	**Having a bad taste in the mouth**	**60**	**2.67**	**1.60**
9	**Difficulty enjoyng food and wine**	**81.67**	**3.41**	**2.78**
10	**Feeling irritable**	**70**	**2.95**	**2.06**
11	**Difficulty concentrating**	**58.33**	**2.94**	**1.71**
12	**Feeling tired**	**66.67**	**3.1**	**2.07**
13	**Loss of smell**	**86.67**	**3.81**	**3.38**
14	**Feeling uncomfortable with**	**60**	**2.89**	**1.73**

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	other people			
15	**Feeling embarassed due to the symptoms**	**63.33**	**2.61**	**1.65**
16	**Kneaded mouth**	**63.33**	**2.71**	**1.71**
17	**Being worried**	**73.33**	**2.79**	**2.04**
18	Anxiety	50	2.26	1.13
19	**Feeling embarassed in social life**	**63.33**	**2.42**	**1.53**
20	Dark circles	53.33	2.34	1.24
21	Swollen face	55	1.01	0.56
22	Having to do CT scans	53.33	1.91	1.02
23	Hearing problems	50	2.5	1.25
24	**Being bothered by medication side effects**	**70**	**2.8**	**1.96**
25	**Being bothered for the possibility of surgery**	**81.67**	**2.89**	**2.36**
26	Being annoyed by frequent medical control	50	2.2	1.10
27	**Feeling stressed**	**65**	**2.49**	**1.62**
28	**Feeling to have poor disease control**	**71.67**	**3.37**	**2.41**
29	**Nasal voice**	**78.33**	**2.7**	**2.11**
30	**Snoring**	**76.67**	**2.67**	**1.71**
31	Having to do invasive clinical	58.33	2.23	1.30

	exhaminations			
32	Having difficulties in intimate life	48.33	2.13	1.03
33	**Essere preoccupato che i farmaci a lungo andare siano meno efficaci**	69.74	3.01	2.10
34	Kissing difficulty	50	2.23	1.11
35	**Having difficulties in controlling symptoms**	**85**	**2.45**	**2.08**
36	**Fear that the problem will recur**	**85**	**3.21**	**2.73**
37	**Afraid not to notice to stink (when you sweat)**	**75**	**3.22**	**2.41**
38	Facial pain	45	2.33	1.05
39	**Headache**	**71.67**	**2.67**	**1.91**
40	**Make less than you vould like**	**57.89**	**3.06**	**1.77**

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457Bold faces indicate highly important items (overall impact ≥ 1.5)

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458

459**Table 2. Factors identified using principal components analysis on full data set**

460**(bold typeface shows the component upon which each item loaded most highly):**

461**1 – Daily life impact; 2 – Mouth problems; 3 – Embarrassment; 3 – Treatment**

462**impact; 4 – Loss of smell**

463

Item	Factors				
	1	2	3	4	5
Sleep distrubance	**0.520**	0.341	0.240	0.311	0.270
Dry throat	**0.570**	0.298	0.311	0.090	0.274
Being limited in sport activities	**0.602**	0.378	-0.111	0.159	0.275
Halitosis	0.077	**0.731**	0.099	0.028	0.067
Difficulty enjoyng food and wine	0.165	0.124	0.129	-0.008	**0.801**
Being irritable	**0.583**	0.511	0.227	0.266	0.061
Being worried by medication side effects	0.341	-0.056	0.394	**0.656**	-0.051
Feeling embarassed in social life	0.492	0.069	**0.656**	0.172	0.145
Nasal voice	0.138	0.198	**0.720**	0.021	0.136
Being worried by the disease	**0.558**	0.111	0.358	0.446	0.046
Feeling to have	**0.721**	-0.025	0.234	0.257	0.278

poor disease control					
Afraid not to notice to stink (when you sweat)	0.325	0.218	0.217	0.111	**0.593**
Headache	0.046	0.443	0.**497**	0.030	0.199
Fear that the problem will recur	**0.658**	-0.080	0.167	0.356	0.252
Being worried for the possibility of surgery	0.092	0.129	-0.053	**0.792**	0.022
Being stressed	0.077	**0.562**	-0.126	0.304	0.204
Snoring	**0.691**	0.372	0.170	0.407	0.027
Difficulty concentrating	**0.693**	0.315	0.263	-0.002	0.153
Loss of smell	0.115	0.092	0.105	0.082	**0.836**
Feeling embarassed due to the symptoms	0.490	0.078	**0.493**	0.380	0.261
Having a bad taste in the mouth	0.251	**0.723**	0.433	-0.069	0.036
Kneaded mouth	0.339	**0.644**	0.404	0.091	0.215
Feeling tired	**0.691**	0.506	0.012	0.227	-0.002
Being worried by long term	0.326	0.172	0.098	**0.662**	0.171

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drug efficacy					
Feeling uncomfortable with other people	**0.554**	0.059	0.529	0.281	0.181
Having difficulty in controlling symptoms	**0.761**	0.004	0.181	0.212	0.201
Not performing well	**0.847**	0.218	0.141	0.005	0.031

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Table 3. The MID of CRSwNP-QoL obtained with the ROC analysis with different cutoff

Cutoff ≥	Sensitivity (%)	1-Specificity (%)
11	0.77	0.69
9	0.80	0.69
7*	0.83	0.63
5	0.83	0.44
3	0.87	0.06

*cutoff point chosen