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CHAPTER 5

Comparison of questionnaires to assess health related quality of life in patients with COPD and respiratory insufficiency

Adapted from:

The Severe Respiratory Insufficiency questionnaire scored best in assessment of health related quality of life.

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ABSTRACT

Objective: There are limited data on health related quality of life (HRQL) in COPD patients with chronic hypercapnic respiratory failure during an admission requiring ventilatory support. The aim was to assess and compare the reliability and validity of the Clinical COPD Questionnaire (CCQ), Chronic Respiratory Questionnaire (CRQ), Mageri Respiratory Failure (MRF-28) and the Severe Respiratory Insufficiency (SRI) questionnaires in patients with very severe COPD.

Study design and setting: 180 hospitalized patients filled out the CCQ, CRQ, MRF-28, SRI, Groningen Activity Restriction Scale (GARS), Hospital Anxiety and Depression Scale (HADS) and the Medical Research Council dyspnea scale (MRC). Reliability was examined by assessing distribution of total scores, floor and ceiling effects and internal consistency (using Cronbach's α coefficient). Construct validity between questionnaires and also the other measurements were tested with spearman ρ .

Results: All 4 questionnaires were feasible in this setting and had reasonable characteristics for distribution of total scores, floor and ceiling effects, internal consistency, and construct validity. On balance, the SRI scored best. Additionally, the SRI had a remarkable high explained variance by HADS, GARS, and MRC (73%).

Conclusion: The SRI performed slightly better than the CCQ, CRQ and MRF-28 which renders it the preferred questionnaire for scoring HRQL in patients with very severe COPD.

What's new?

- Key finding: The Clinical COPD Questionnaire (CCQ), Chronic Respiratory Questionnaire (CRQ), Mageri Respiratory Failure (MRF-28) and the Severe Respiratory Insufficiency (SRI) questionnaires showed to be reliable and valid questionnaires in COPD patients with chronic hypercapnic respiratory failure requiring ventilatory support.
- What this adds to what is known: On balance, the SRI scored best, making it the preferred questionnaire for measurement of health-related quality of life in patients with very severe COPD.
- What is the implication, what should change now: We suggest that future studies on the effects of chronic noninvasive ventilation in COPD use the SRI in addition to a more general disease specific questionnaire.

INTRODUCTION

Health related Quality of Life (HRQL) assessment in patients with chronic obstructive pulmonary disease (COPD) has become more common over the last two decades, and its importance in clinical trials has been recognized by many health care institutions.¹ Quite a few disease specific questionnaires in the field of COPD have been developed, some of which have been shown to be valid, reliable and responsive in several stages of severity of this disease, for example the Chronic Respiratory Questionnaire (CRQ)² and the Clinical COPD Questionnaire (CCQ).³ Others were designed for a more specific subset of COPD patients. Both the Mageri Respiratory Failure-28 Questionnaire (MRF-28)⁴ and the Severe Respiratory Insufficiency (SRI) questionnaire⁵ were originally developed for a mixed group of patients with respiratory failure (not necessarily COPD) receiving chronic noninvasive positive pressure ventilation (NPPV). In addition they have also shown to be valid and reliable specifically in COPD patients with stable hypercapnic respiratory failure (CHRF).⁶ One trial on chronic NPPV in COPD with CHRF⁷ showed that the SRI was more related to anxiety and depression whilst the MRF-28 added the cognitive domain compared to the CRQ and therefore suggested using both the SRI and the MRF-28 as they assess different aspects of HRQL in these patients.

The lack of agreement on which HRQL questionnaire to use, has contributed to the fact that evidence for the use of chronic NPPV in patients with stable COPD is still contradictory.⁸⁻¹⁰ Amongst others, the pooling of results on HRQL is hampered in this way.

Not only is chronic NPPV in stable COPD of interest, but also the role of chronic NPPV in COPD after an episode of acute respiratory failure requiring ventilatory support in hospital.¹¹ In Europe a few studies on chronic NPPV after acute exacerbation are currently in process and therefore it is of importance to find the appropriate questionnaires for this precise area. As there are limited data on HRQL in this specific group the aim of the current study is to assess and compare the reliability and validity of the CCQ, CRQ, MRF-28 and SRI in COPD patients with CHRF during an admission requiring ventilatory support.

METHODS

Patients

Between 2008 and August 2011, 180 patients from 45 Dutch hospitals were included. These data are part of a larger randomized controlled trial studying the effects of chronic NPPV. Patients met the following inclusion criteria: Chronic Obstructive Pulmonary Disease Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III or IV, invasive or non invasive ventilation during acute respiratory failure and minimally 48 hours without ventilatory support (maximally until discharge), persistent hypercapnia ($\text{PaCO}_2 > 6.0 \text{ kPa}$) during daytime at rest without ventilatory support. Exclusion criteria were: age < 18 or ≥ 80 years; Obstructive Sleep Apnea (Apnea Hypopnea Index: $\text{AHI} > 15$ /hr), neuromuscular disease, or significant heart failure. The study was approved by the local ethics committee and all patients gave written consent.

Health related quality of life questionnaires

Patients completed the following questionnaires concerning health related quality of life; the Clinical COPD Questionnaire (CCQ),³ the Chronic Respiratory Questionnaire self reported (CRQ)¹², the Mageri Respiratory Failure Questionnaire -28 (MRF-28)⁴ and the Severe Respiratory Insufficiency (SRI) questionnaire.⁵ The CCQ is a self-administered, 10-item questionnaire which can be divided into three domains: symptom, functional state and mental state. Scores range from 0 to 6 with high scores indicating extremely poor health status. The CRQ (self reported) contains 20 items and measures physical function and emotional function, divided into four domains: dyspnoea, fatigue, emotion and mastery. Scores range from 1 (worse) to 7 (best). The MRF-28 contains 28 items which are divided into 3 domains; daily activity, cognitive function and invalidity. The scores range from 0 (best) to 100 (worse). The SRI contains seven domains covering 49 items: respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being and social functioning. Scoring ranges between 0-100, with high scores representing better HRQL.

Other measurements

The following parameters were measured as possible determinants of health related quality of life. Arterial blood gasses > 48 hours after ending acute ventilatory support were obtained from blood from the radial artery with the patient breathing room air. Lung function measurements included routine spirometry by means of a pneumotachograph. The Groninger Activity and Restriction Scale (GARS) assesses activity and disability of daily living and consists of 18 items.¹³ The Hospital Anxiety and Depression Scale (HADS) was used to determine levels of depression and anxiety.¹⁴ It consists of 14 questions from which seven are on detection of anxiety and seven on depression (two subscales). Dyspnoea was measured using the Medical Research Council scale (MRC).¹⁵

Statistical analysis

Reliability

Distribution of total scores and internal consistency as a measure of reliability were calculated for each questionnaire. Internal consistency was calculated with Cronbach α for all domain scores separately of the four questionnaires. This is a measure for how closely related the items are as a domain. A Cronbach $\alpha > 0.70$ was considered good.¹⁶

Ceiling effects and floor effects were analyzed for the CCQ, CRQ, MRF-28 and the SRI by calculating the percentage of patients with maximal or minimal domain- and total scores for each questionnaire. Floor and ceiling effects between 1-15% were defined as acceptable effects, and $> 15\%$ as high.¹⁷

Validity

As a gold standard does not exist, construct validity was examined by assessing how the different constructs (domain scores) correlated with other measures assessing the same construct.¹⁸ First, domain and total scores of both the CCQ and CRQ were correlated with the domain and total scores of the more specific questionnaires MRF-28 and SRI by calculating spearman ρ . An $r > 0.70$ was considered good.¹⁶ Secondly, physiological domains were correlated with physical measurements performed during admission, and psychological domains were correlated with psychological parameters measured during admission. A p-value of < 0.01 was considered statistically significant.

Multiple regression analysis

Univariate analysis was performed to identify relevant parameters for multiple regression analyses (a p-value of < 0.01 was used.) The eight parameters identified in the univariate analysis were entered as explanatory (independent) variables in a backward multiple regression analysis with total scores of the questionnaires treated as the response variable (dependent). The explanatory variables included were as follows: sex, frequency of admissions for COPD in preceding year, duration of current admission, frequency of exacerbations in preceding year, forced expiratory volume in 1 second (FEV_1), GARS total score, HADS anxiety score, and MRC score. Admission frequency was divided by the median into two categories defined as few (≤ 1) vs. frequent (>2) COPD admission in preceding year. In the same manner duration of current admission in days was divided into short (≤ 15) vs. long (>16) and exacerbation frequency in preceding year was divided into few (≤ 2) vs. frequent (>3). Exacerbation was defined as acute in onset and treated at home with antibiotics and/or prednisolone.

The percentage of explained variance of each independent variable in this resulting model was estimated by calculating the change in R^2 of the total score in a stepwise forward regression model. Results were given with the standardized regression coefficient (B), 95% confidence interval, and proportion of explained variance (R^2). Statistical calculations were performed using PASW Statistics 18 (SPSS inc., Chicago, IL, USA).

RESULTS

Patients

Of the 180 patients included in the study, 170 completed the questionnaires (Table 1). Six patients withdrew and four patients died due to respiratory failure. Demographic data and other possible determinants are presented in Table 1. Forty patients were not able or refused to come of oxygen for arterial blood gas analysis. PaCO₂ and FEV₁ from this group were not different.

Table 1. Patient characteristics

Age (yrs)	64 (8.0)
Male n (%)	42
Pack years	43.9 (27.3)
BMI (kg/m ²)	24.7 (5.7)
LTOT n (%)	78
Intubated during NIPPV n (%)	13
Duration ventilation (days)	6.3 (4.1)
Duration admission (days)	17.1 (7.6)
Admissions (yr ⁻¹)	2.3 (1.5)
Exacerbations (yr ⁻¹)	2.8 (3.1)
FEV ₁ (L) [§]	0.67 (0.25)
FEV ₁ (% pred)	25.8 (8.1)
FVC (L)	2.09 (0.71)
FEV ₁ /FVC (%)	32.9 (9.0)
pH [¶]	7.38 (0.04)
PaCO ₂ (kPa [¶])	7.8 (1.2)
PaO ₂ (kPa [¶])	7.8 (2.0)
HCO ₃ (mmol/L [¶])	33.7 (4.7)
BE (mmol/L [¶])	8.3 (8.1)
HADS anxiety	7.7 (5)
HADS depression	7.8 (5)
GARS	36.9 (8)
MRC	3.9 (1)

Abbreviations: M, male; BMI, body mass index; LTOT, long-term oxygen therapy; NIPPV, non-invasive positive pressure ventilation; FEV₁, forced expiratory volume in one second; % pred, % predicted; FVC, forced vital capacity; PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen tension; HCO₃, bicarbonate; BE, base excess; HADS, Hospital Anxiety and Depression Scale (separate scores for anxiety and depression); GARS, Groningen Activity Restriction Scale; MRC, Medical Research Council dyspnoea scale.

Data presented as mean ± SD unless otherwise stated.

[§] Post-bronchodilator

[¶] While breathing room air.

Reliability

Distribution of scores

Distribution of all total scores is illustrated graphically (Fig. 1). The CCQ and SRI show a normal distribution whereas the CRQ and MRF-28 are skewed towards the low end of the scale (low quality of life).

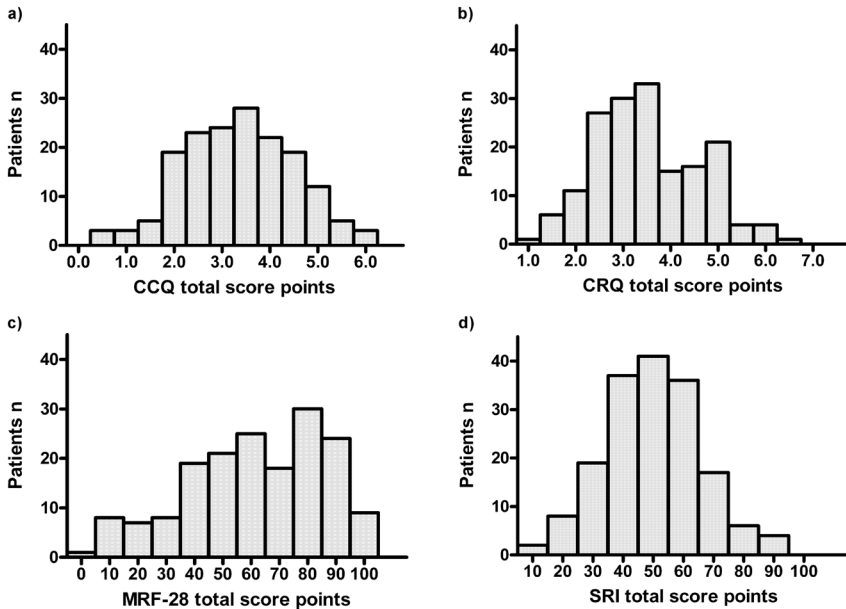


Figure 1. Frequency distribution histogram of total scores of the CCQ, CRQ, MRF-28 and SRI.

(A and C) For the CCQ and MRF-28 Questionnaires, high scores indicate low quality of life. (B and D) For the CRQ and SRI, low scores indicate low quality of life. CCQ, Clinical COPD Questionnaire; CRQ, Chronic Respiratory Questionnaire; MRF-28, Mageri Respiratory Failure-28 questionnaire; SRI, Severe Respiratory Insufficiency questionnaire.

Internal consistency

Nearly all domains of the 4 questionnaires showed a high consistency (Table 2), with most scores over 0.80, especially the emotion domain of the CRQ (0.90). Cronbach's α was lower for the symptom domain of the CCQ (0.65) and the social relationships domain of the SRI (0.68).

Table 2. Internal consistency and scoring of the CCQ, CRQ, MRF-28 and SRI

	Cronbach's α-coefficient	Items n	Score range	Minimum score n (%)[#]	Maximum score n (%)[#]	Mean\pmSD score
CCQ						
Symptom	0.65	4	0-6	0	5 (3.0%)	3.1 \pm 1.1
Functional	0.87	4	0-6	2 (1.2%)	20 (17.7%)	4.0 \pm 1.4
Mental	0.83	2	0-6	19 (11.4%)	15 (9%)	2.5 \pm 1.8
Total		10	0-6	1 (0.6%)	5 (3%)	3.4 \pm 1.2
CRQ						
Dyspnoea	0.86	5	1-7	15 (9%)	5 (3%)	3.14 \pm 1.4
Fatigue	0.87	4	1-7	24 (14.2%)	1 (0.6%)	2.67 \pm 1.3
Emotion	0.90	7	1-7	4 (2.4%)	2 (1.2%)	3.99 \pm 1.3
Mastery	0.80	4	1-7	3 (1.8%)	6 (3.6%)	3.92 \pm 1.4
Total		20	1-7	4 (2.4%)	1 (0.6%)	3.52 \pm 1.1
MRF-28						
Daily activities	0.84	11	0-100	9 (5%)	20 (12%)	62.40 \pm 29.00
Cognition	0.81	4	0-100	52 (31%)	39 (23%)	45.88 \pm 39.29
Invalidity	0.78	5	0-100	16 (9%)	69 (41%)	72.59 \pm 32.19
Total		28	0-100	0	3 (1.8%)	61.16 \pm 23.61
SRI						
Respiratory complaints	0.82	8	0-100	1 (0.6%)	1 (0.6%)	46.11 \pm 19.01
Physical functioning	0.80	6	0-100	11 (6.5%)	0	31.88 \pm 20.39
Attendant symptoms + sleep	0.77	7	0-100	1 (0.6%)	2 (1.2%)	57.55 \pm 19.38
Social relationships	0.68	6	0-100	0	1 (0.6%)	61.41 \pm 17.88
Anxiety	0.80	5	0-100	3 (1.8%)	3 (1.8%)	47.39 \pm 24.03
Well-being	0.85	9	0-100	1 (0.6%)	0	55.29 \pm 20.58
Social functioning	0.81	8	0-100	1 (0.6%)	0	45.06 \pm 19.73
Summary score		49	0-100	0	0	49.24 \pm 15.71

Abbreviations: CCQ, Clinical COPD Questionnaire; CRQ, Chronic Respiratory Questionnaire; MRF-28, Mageri Respiratory Failure-28 questionnaire; SRI, Severe Respiratory Insufficiency questionnaire; For the CCQ and MRF-28, maximum scores indicate low quality of life. For the CRQ and SRI, low scores indicate low quality of life.

[#] Number of patients.

Floor and ceiling effects

The CCQ, CRQ and MRF-28 showed floor and ceiling effects on nearly all domains separately and on total score (Table 2). These ranged from acceptable to high. Very high floor and ceiling effects of over 15% were found in the cognitive domain of the MRF-28, with 52 (31%) patients scoring the minimal possible score (high quality of life concerning cognition) and 39 (23%) patients scoring the maximal score (low quality of life concerning cognition). Also, 69 (41%) patients scored the maximal score on the invalidity domain of the MRF-28 indicating a high level of impairment. This was also the case for the maximum score on the functional domain of the CCQ in 20 (17.7%) patients. The CRQ shows a clear floor effect on the fatigue domain with 24 (14.2%) patients scoring the minimal (worst) score. The SRI shows a few acceptable ceiling and floor effects for some domains (highest score is 6,5% minimum score on physical functioning), but no effects for the total score.

Validity

Construct validity between questionnaires

Spearman rank correlations between the domain- and total scores of the CCQ, CRQ, MRF-28 and SRI were modest but significant (Table 3) for all but two domains: the daily activity domain of the MRF-28 did not correlate with the emotion domain of the CRQ, and the cognition domain of the MRF-28 did not correlate with the symptom domain of the CCQ. High correlations were found between the well-being domain of the SRI with both the mental domain of the CCQ (0.73) and the emotion domain of the CRQ (0.77). Also, the anxiety domain of the SRI showed a good correlation with the mastery domain of the CRQ (0.70).

Construct validity between HRQL and other measurements

Domain and total scores of all four questionnaires showed significant correlations with the HADS (Table 4). Specifically strong correlations were found with the following psychological domains: the mental domain of the CCQ (0.74), the emotion domain and total score of the CRQ (0.77 and 0.76), and the anxiety, well-being and summary score of the SRI (0.74, 0.78 and 0.80, respectively). The GARS was also significantly correlated with all domain- and total scores, demonstrating the highest correlations with the daily activity domain of the MRF-28 (0.76) and the physical functioning domain of the SRI (0.74). Nearly all domains were significantly correlated with the MRC but with weak to modest correlations (0.26-0.51). The number of exacerbations in previous year showed weak correlations (0.21-0.28) with at least one domain of each HRQL questionnaire. Blood gas parameters, pack years, number of admissions in previous year, and duration of ventilation in days during acute exacerbation did not show any significant correlations with domain- or total score of the questionnaires.

Table 3. Spearman rank correlation between the more general disease questionnaires CCQ, CRQ and the more specific MRF-28 & SRI questionnaires

	CCQ				CRQ				
	Sym	Func	Ment	Tot	Dys	Fat	Em	Mas	Tot
MRF-28									
Daily activities	0.36	0.59	0.30	0.52	-0.51	-0.41	-	-0.22	-0.37
Cognition	-	0.34	0.32	0.32	-0.33	-0.31	-0.33	-0.34	-0.39
Invalidity	0.24	0.43	0.30	0.40	-0.49	-0.45	-0.32	-0.31	-0.45
Total score	0.38	0.64	0.44	0.59	-0.60	-0.56	-0.41	-0.41	-0.58
SRI									
Respiratory complaints	-0.69	-0.65	-0.50	-0.73	0.56	0.60	0.45	0.50	0.62
Physical functioning	-0.44	-0.68	-0.41	-0.63	0.57	0.49	0.37	0.42	0.54
Attendant symptoms + sleep	-0.35	-0.41	-0.53	-0.50	0.42	0.46	0.48	0.43	0.53
Social relationships	-0.22	-0.43	-0.50	-0.39	0.28	0.33	0.56	0.53	0.56
Anxiety	-0.36	-0.48	-0.67	-0.59	0.49	0.52	0.67	0.70	0.74
Well-being	-0.32	-0.40	-0.73	-0.53	0.45	0.39	0.77	0.64	0.72
Social functioning	-0.35	-0.53	-0.54	-0.55	0.52	0.52	0.51	0.49	0.62
Summary score	-0.51	-0.67	-0.67	-0.74	0.63	0.63	0.71	0.71	0.82

Abbreviations: CCQ, Clinical COPD Questionnaire; CRQ, Chronic Respiratory Questionnaire; MRF-28, Mageri Respiratory Failure-28 questionnaire; SRI, Severe Respiratory Insufficiency questionnaire. Sym, symptom; Func, functional; Ment, mental state; Tot, total; Dys, dyspnoea; Fat, fatigue; Em, emotion; Mas, mastery.

Only significant correlations are shown ($p < 0.01$).

Backward and forward stepwise multiple regression analyses revealed that 73% of the variance in the SRI total score could be explained by the HADS anxiety score, the GARS score, and the MRC (Table 5). The aforementioned three variables also accounted for 52% of the variance in the CCQ total score. Of the variance in the MRF-28 total score, 62% was explained by the GARS score and the HADS anxiety score. Of the variance in total score of the CRQ, 62% was explained by HADS anxiety score, MRC, sex and exacerbation frequency in the previous year.

Table 4. Spearman rank correlation coefficients between physical and psychological parameters and the CCQ, CRQ, MRF-28 and SRI

	CCQ						CRQ						MRF						SRI					
	Sym	Func	Ment	Tot	Dys	Fat	Em	Mas	Tot	Dai	Cog	Inv	Tot	RC	PF	AS	SR	AX	WB	SF	SS			
Pack years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
BMI (kg/m ²)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.20	-			
Duration of admission (days)	-	0.21	-	-	-	-	-	-	-	-	-	-	-	-	0.21	-	-	-	-	-	-			
Length of ventilation (days)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Admissions (yr ⁻¹)	-	-	-	-	-	-	-	0.27	-	-	-	-	-	-	-	-	-	-	-	-	-			
Exacerbations.yr ⁻¹	-	0.21	0.28	0.25	0.26	-	0.21	0.25	0.27	0.22	-	-	0.23	-	-	-	-	-	-	-	0.22			
FEV ₁ L ^s	-	0.32	-	0.25	-	-	-	-	-	0.26	-	0.24	0.29	-	0.37	-	-	0.21	-	-	0.24			
FEV ₁ % pred	-	0.24	-	-	-	-	-	-	-	0.20	-	-	0.23	-	0.26	-	-	-	-	-	-			
FVC L	-	0.23	-	-	-	-	-	-	-	-	-	-	-	-	0.25	-	-	-	-	-	-			
FEV ₁ /FVC %	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
pH	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
PaCO ₂ kPa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
PaO ₂ kPa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
HCO ₃ mmol.L ⁻¹	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
BE mmol.L ⁻¹	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
HADS anxiety	0.40	0.52	0.74	0.62	0.48	0.51	0.77	0.68	0.76	0.40	0.40	0.44	0.58	0.56	0.46	0.56	0.59	0.74	0.78	0.60	0.80			
HADS depression	0.33	0.52	0.60	0.56	0.47	0.49	0.64	0.51	0.66	0.41	0.40	0.57	0.61	0.43	0.50	0.42	0.55	0.59	0.71	0.65	0.72			
GAFS	0.37	0.64	0.26	0.53	0.52	0.41	0.23	0.29	0.42	0.76	0.22	0.48	0.68	0.54	0.74	0.26	0.21	0.38	0.26	0.54	0.56			
MRC	0.33	0.48	0.33	0.46	0.46	0.44	0.26	0.36	0.43	0.44	-	0.37	0.44	0.41	0.49	0.27	-	0.33	0.28	0.51	0.46			

Only significant correlations ($p < 0.01$) are shown. Abbreviations: CCQ, Clinical COPD Questionnaire; CRQ, Chronic Respiratory Questionnaire; MRF-28, Mauderi Respiratory Failure-28 questionnaire; SRI, Severe Respiratory Insufficiency questionnaire. Sym, symptom; Func, functional; Ment, mental state; Tot, total; Dys, dyspnoea; Fat, fatigue; Em, emotion; Mas, mastery; Dai, daily activities; Cog, cognition; Inv, invalidity; RC, respiratory complaints; PF, physical functioning; AS, attendant symptoms and sleep; SR, social relationships; AZ, anxiety; WB, psychological well-being; SF, social functioning; SS, summary score; BMI, body mass index; FEV₁, forced expiratory volume in one second; % pred, % predicted; VC, vital capacity; PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen tension; HCO₃, bicarbonate; BE, base excess; HADS, Hospital Anxiety and Depression Scale (separate scores for anxiety and depression domain); GAFS, Groningen Activity and Restriction Scale; MRC, Medical Research Council dyspnoea scale. [§] Post-bronchodilator. Only significant correlations ($p < 0.01$) are shown.

Table 5. Multiple regression analysis

	CCQ total score points		CRQ total score points		MRF-28 total score %		SRI total score %	
	B	R ²	B	R ²	B	R ²	B	R ²
HADS anxiety	0.11 (0.08-0.14)	0.37	-0.14 (-0.17- -0.12)	0.54	1.68 (1.18-2.17)	0.10	-2.15 (-2.43- -1.86)	0.62
GARS	0.04 (0.02-0.06)	0.12			1.78 (1.48-2.09)	0.52	-0.46 (-0.67- -0.25)	0.09
MRC	0.22 (0.07-0.38)	0.03	-0.28 (-0.39- -0.17)	0.06			-2.34 (-3.94- -0.74)	0.02
Freq exacerbations [§]			-0.30 (-0.52- -0.08)	0.01				
Sex female [¶]			-0.29 (-0.51- -0.07)	0.01				
Cumulative R ²		0.52		0.62		0.62		0.73

Only variables included in the final model are shown.

Abbreviations: CCQ, Clinical COPD Questionnaire; CRQ, Chronic Respiratory Questionnaire; MRF-28, Mageri Respiratory Failure-28 questionnaire; SRI, Severe Respiratory Insufficiency questionnaire; HADS anxiety, Hospital Anxiety and Depression Scale (separate scores for anxiety domain); GARS, Groningen Activity Restriction Scale; MRC, Medical Research Council dyspnoea scale. B, unstandardised regression coefficient (95% confidence interval). R², proportion of explained variance for independent variables included in the backward model.

Only variables included in the final model are shown.

[§] Freq exacerbations, frequent exacerbations (<=2 exacerbations yr⁻¹), 1=frequent exacerbations (>2 exacerbations yr⁻¹).

[¶] 0 = male, 1 = female.

DISCUSSION

This study shows that the CCQ, CRQ, MRF-28 and SRI are all reliable and valid questionnaires in hospitalized patients with CHRF who are still hypercapnic 48 hours after ending (non invasive or invasive) ventilatory support for an acute COPD exacerbation. The SRI is superior when taking the different aspects studied into account. This is the first study comparing all four questionnaires in this specific homogeneous group of patients with end stage COPD.

First, the distribution of scores is of importance. All questionnaires showed good reliability, but as these patients are in end stage of their disease, it is essential that also in this group, scores are normally distributed and not all clustered towards one end of the scale. In the latter case, there would be no room for further deterioration, and usually improvement is picked up less easily with such clustering. In the present study the CCQ, CRQ and MRF-28 showed clear floor and ceiling effects (ranging from acceptable to high effects) on nearly all domain scores. The CCQ functional domain, and the MRF-28 cognition and invalidity domains showed high ceiling effects with more than 15% of patients scoring the worst possible score. This implies that for this group of patients, extreme items are missing in these domains of the questionnaires. The SRI did show slight floor and or ceiling effects on most domain and total scores but all but one of these were below 2% of patients. Remarkably, for the MRF-28 the cognition domain showed 31% of patients scoring the minimal possible score (high quality of life concerning cognition) and at the same time 23% scoring the maximal score (low quality of life concerning cognition). An important explanation for these high numbers is the limited answering range of response of the MRF-28, i.e. a two- option response (yes/no). The CCQ, CRQ and SRI all have more answering options being 7-, 7- and 5-point scales respectively. Adding to this is the fact that the cognitive domain score of the MR-28 consists of four items, which is quite small compared to numbers of items in other domains and to other questionnaires.

Second, we examined construct validity. The MRF-28 daily activities domain and the SRI physical functioning domain showed strong relationships with disabilities in daily living as measured by the GARS whereas the CCQ and CRQ showed modest correlations. For the psychological construct: the CCQ mental domain, CRQ emotion domain and SRI anxiety as well as the well-being domain showed high correlations (0.74-0.78) with the HADS anxiety score. The MRF-28 does not have a psychological domain. The absence of such a domain is a weak point in our view, as for instance anxiety is inextricably linked to dyspnoea as earlier studies have described.¹⁹ Also, the presence of anxiety and/or depression remains an important risk factor for re-hospitalization within a 12-month period in COPD patients with poor HRQL.²⁰

As was expected, the HRQL scores did not have strong correlations with physiological parameters. Lung function measurements showed a few weak correlations with certain domain and total scores, while blood gas measurements even showed no significant correlations with HRQL. This confirms findings of earlier studies^{21,22} and clearly demonstrates how patients with similar lung function impairment or other

physiological limitations can differ in their HRQL. Notably, little correlation to none was found between HRQL scores and length of ventilation, duration of admission and total amount of admissions in the previous year. This signifies the importance of using HRQL questionnaires not only alongside physiological measurements, but perhaps even as primary outcome in patients with end-stage COPD.

Multiple regression analysis revealed the different components on which each questionnaire is focused. The HADS was the only variable to contribute to explained variance in total scores of all four questionnaires. Because the HADS anxiety showed higher coefficients with the CCQ, CRQ and SRI, this probably plays a more prominent role in total HRQL score. For the MRF-28, the highest contribution is clearly from daily activities, as reflected by the correlation with the GARS. The HADS anxiety score, the GARS (measuring impact on ADL), and the MRC (a relatively crude measure of shortness of breath, an important symptom in COPD) explained 73% of the variance in the SRI total score, suggesting the SRI may be a good measure of HRQL with respect to those particular factors.

Curtis and Patrick¹⁸ described in an article on health status in COPD patients, that head-to-head comparisons of existing instruments are needed to improve the use and interpretability of disease specific questionnaires. To our knowledge, this is the first study comparing multiple HRQL questionnaires in COPD patients with CHRF after an acute exacerbation. However, they also mentioned the need for assessment of responsiveness and identifying minimally important differences, which is a limitation of the present study as this was not performed. Additionally, the reproducibility of the questionnaires was not investigated. By repeating the measurements in stable persons after a certain period, (test-retest), the degree to which similar answers are given can be investigated.¹⁷ As the present study was performed during an admission for an acute exacerbation, stable measurements and good reproducibility over a longer period were not expected and hence not assessed. It is however important in intervention studies of NPPV, to assess test-retest reliability or validity from the standpoint of differences between scores for the same individuals at different time points. This study lends support to the use of the SRI but further work is required to determine its validity in an intervention study where HRQL would be measured at multiple time points to assess the efficacy of the intervention.

Duiverman et al.⁷ investigated reproducibility in patients with stable COPD with CHRF and found good reproducibility for the CRQ, MRF-28 and SRI. A recent study also showed high test-retest reliability for the CCQ,²³ but this was in a mixed group of COPD patients with only a small number of patients with severe COPD (GOLD IV).

As could be expected, the total scores of the CRQ, MRF-28 and SRI were lower in our hospitalized group compared to the scores of 72 patients from Duiverman et al., who investigated HRQL in stable COPD with CHRF.⁷ The hospitalized group indeed showed lower quality of life on CRQ, MRF-28 and SRI total scores, as well as on all domain scores separately. Although the study by Duiverman et al. used the CRQ interview-led version and we used the CRQ self reported version, scoring and structure of both versions are similar.¹²

We found similar results when comparing our results with a recent study,²¹ in which the CCQ and the CRQ self reported version were studied in 296 patients with mild to moderate COPD (GOLD I and II). The present group again showed lower HRQL on all domain and total scores of the CCQ and CRQ compared to these patients with moderate COPD. This study by Reda et al. also looked at responsiveness after 26 and 52 weeks of smoking cessation. Both questionnaires were found to detect clinically meaningful differences in scores, but only the CCQ continued to do so after 52 weeks making this questionnaire possibly more suitable for the longer clinical intervention trials. An additional advantage of the CCQ is its feasibility, since it is one of the few HRQL questionnaires that can be filled out quickly as it contains only 10 items.

As mentioned earlier, the main reason why the present study was performed, was the lack of uniformity in studies investigating the effects of NPPV on patients with CHRF, whether in stable condition or after an acute exacerbation. Many different questionnaires have been used in the past, making it much more difficult to combine results and assess effectiveness of NPPV. The MRF-28 and SRI are both questionnaires specifically designed for patients with respiratory insufficiency. It is not surprising that as they cover a broader aspect of potential limitations patients with CHRF can experience, they are more suitable for this group. The strength of the MRF-28 is the fact that it contains a cognition domain (although with floor and ceiling effects) and the biggest merit of the SRI is the addition of the psychological well-being domain. But even when performing new studies in patients with CHRF, we would suggest also using one of the more general disease specific questionnaires on HRLQ, like the CCQ or the CRQ as they are widely used and it could still be relevant to compare results with patients who are not respiratory insufficient. An advantage of the CCQ is it's practical character (quick to fill out for patients), while the CRQ has the advantage that it has been used frequently over several years in different groups with COPD.

In conclusion, in this study we show that the CCQ, CRQ, MRF-28 and SRI are all reliable and valid questionnaires in patients with CHRF who are still hypercapnic 48 hours after ending (non invasive or invasive) ventilation for an acute COPD exacerbation. Even though the CCQ and CRQ were not specifically made for patients with CHRF, they had quite acceptable measurement properties, as did the specifically designed MRF-28 and SRI. On balance, the SRI performed slightly better than the CCQ, CRQ and MRF-28 in this specific group when comparing distribution of scores, floor and ceiling effects, construct validity and explained proportion of variance. For this reason and since the SRI also contains a psychological domain, we recommend this questionnaire in this group of end-stage COPD patients with CHRF.

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