

**Health-related quality of life in COPD patients with chronic respiratory failure.**

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**Short title:** Quality of life in severe COPD

**Word count text body:** 3000

## **ABSTRACT**

**Background:** The Mageri Respiratory Failure (MRF-28) and Severe Respiratory Insufficiency (SRI) questionnaire were recently developed to assess health-related quality of life (HRQoL) in patients with chronic respiratory failure, although not exclusively in COPD patients.

**Questions:** Whether the MRF-28 and SRI are reliable and valid HRQoL questionnaires in COPD patients with chronic hypercapnic respiratory failure.

**Patients and Methods:** Seventy two COPD patients with chronic hypercapnic respiratory failure underwent pulmonary function testing; exercise testing; and filled in the MRF-28, SRI, the Chronic Respiratory Questionnaire (CRQ), the Hospital Anxiety and Depression Scale, the Groningen Activity and Restriction Scale, and two dyspnoea indexes.

**Results:** Physical domain scores of the questionnaires correlated with exercise tolerance, dyspnoea, and daily activities, while psychological domains correlated strongly with anxiety and depression. Anxiety scores accounted for 51% and 56% of the total explained variance in total CRQ and SRI scores respectively. The emphasis of the MRF-28 was restrictions in activities of daily living (52% of total variance).

**Answer:** The MRF-28 and SRI are reliable and valid questionnaires in COPD patients with chronic hypercapnic respiratory failure. While the emphasis in the MRF-28 is on activities of daily living, the SRI, like the CRQ, is more related to anxiety and depression.

*Word count abstract:* 200

**Key words:** pulmonary disease, chronic obstructive; quality of life; respiratory insufficiency

## **Abbreviations**

HRQoL: health-related quality of life

COPD: chronic obstructive pulmonary disease

CHRF: chronic hypercapnic respiratory failure

MRF-28: maugeri respiratory failure questionnaire

SRI: severe respiratory insufficiency questionnaire

CRQ: chronic respiratory questionnaire

FEV<sub>1</sub>: forced expiratory volume in the first second

PaCO<sub>2</sub>: arterial carbon dioxide pressure

PaO<sub>2</sub>: arterial oxygen pressure

MRC: medical research counsel

BDI: baseline dyspnoea index

GARS: groningen activity and restriction scale

HADS: hospital anxiety and depression scale

ICC: intraclass correlation coefficient

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide [1]. As COPD is a progressive disease, the number of COPD patients with severe disease and chronic respiratory failure will increase the coming decades. It has been shown that patients with chronic respiratory failure have poor survival. A 5-year mortality of 70-100% was reported [2]. Survival rates are difficult to improve once patients have become respiratory insufficient. Despite treatment with long-term oxygen or home mechanical ventilation median survival was still only three years [3].

Although survival rates are difficult to improve, therapeutic interventions in severe COPD might nevertheless improve health-related quality of life (HRQoL) [4, 5]. The Chronic Respiratory Questionnaire (CRQ) is a widely used disease specific questionnaire which has been shown to be reliable, valid, and responsive in COPD patients [6]. It has also been used in more severe patients [7-9]. However, it was not designed for patients with chronic respiratory failure and might not include items specifically important for these patients. Therefore, a need was felt for questionnaires specific for patients with respiratory failure [10]. The Maugeri Respiratory Failure questionnaire (MRF-28) and the Severe Respiratory Insufficiency Questionnaire (SRI) were developed especially for these patients [11, 12]. Both questionnaires contain items on problems that patients with chronic respiratory failure experience. However, both questionnaires were developed in a group of patients with respiratory failure of different origin, already treated with home mechanical ventilation for a longer period. Reliability and validity of the MRF-28 and SRI have not been investigated in a homogeneous group of patients with COPD who actually suffer from chronic respiratory failure.

The purpose of the present study was to determine whether the MRF-28 and SRI are reliable and valid HRQoL questionnaires in COPD patients with chronic hypercapnic respiratory failure (CHRF). We therefore evaluated: 1) reliability of the 3 questionnaires, amongst others by assessing reproducibility, 2) concurrent validity by comparing SRI and MRF-28 scores to CRQ scores; 3) construct validity of the 3 questionnaires by correlating the scores with relevant physiological parameters, dyspnoea ratings, and psychological status, in COPD patients with CHRF.

## **METHODS**

### **Patients**

All participants were in stable condition, out of rehabilitation at least 18 months, and were treated with medication and long-term oxygen if necessary. None of them was or had been on long-term ventilation. Inclusion criteria were COPD GOLD stage III or IV [13] with chronic hypercapnic respiratory failure ( $FEV_1 < 50\%$  predicted,  $PaCO_2 > 6.0$  kPa, at rest while breathing room air) [14]. Exclusion criteria were cardiac or musculoskeletal diseases limiting exercise performance, or obstructive sleep apnoea syndrome (apnoea/hypopnoea index  $\geq 10$  episodes/ hour). Details are given in the online supplement.

The study was approved by the local Medical Ethical Committee. All participants gave written informed consent to participate. The study is registered at ClinicalTrials.Gov.

### **Measurements**

Patients underwent pulmonary function testing [15-17], a maximal incremental cycle ergometry, and a 6-minute walking test [18, 19]. HRQoL was measured by the Mageri Respiratory Failure questionnaire (MRF-28) [11], the Severe Respiratory Insufficiency questionnaire (SRI) [12], and the Chronic Respiratory Questionnaire (CRQ) [6]. The MRF-28 contains 3 subscales related to daily activities, cognition, and invalidity, and a total score with additional items related to fatigue, depression and problems with treatment. MRF-28 scores range from 0-100; higher scores indicate worse HRQoL [11]. The SRI contains 7 subscales related to respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being, social functioning, and a summary scale. SRI scores range from 0-100; higher scores indicate better HRQoL [12].

Dyspnoea was assessed with the Medical Research Council (MRC) [20] and the Baseline Dyspnoea Index (BDI) [21, 22]. Activities of daily living were assessed by the Groningen activity and restriction scale (GARS) [23], and mood state by the hospital anxiety and depression scale (HADS) [24]. Additional information about the tests and questionnaires is presented in the online supplement.

## **Study design**

Tests were performed on 3 different days. On day 1 first the CRQ was administered. Patients filled in the MRF-28, SRI, MRC, BDI, HADS and GARS by themselves in random order. The 6-minute walking test and cycle ergometry were performed on 2 different days, to allow the patients to rest sufficiently. Pulmonary function testing was performed at least 3 hours before or after an exercise test. After 12 weeks, the tests were repeated in similar order.

## **Analysis and statistics**

Reliability was assessed by internal consistency, distribution of the scores, and test-retest reproducibility. Internal consistency was determined by Cronbach's alpha coefficient. Test-retest reproducibility was approximated by intraclass correlation coefficients (ICC) in 23 patients who completed the questionnaires for a second time after 12 weeks and who had no exacerbations in those 12 weeks [25]. Reproducibility could not be tested in 36 patients who did have an exacerbation, in 7 patients changed in therapy, in 3 patients because they withdrew, and in 3 patients who died in this 12-week period.

To evaluate construct validity of the questionnaires, we investigated whether the HRQoL scores correlated with other measures that assessed the same construct [26]. Physical domains should correlate with related physical parameters, while psychological domains should correlate with psychological parameters. The construct was further scrutinized by backward multiple regression analysis identifying patterns in parameters that could best explain the variance in the questionnaires total scores. Variables entered in the backward model were chosen on basis of existing literature together with a  $p < 0.10$  in the univariate regression analyses. Because a strong correlation was found between the HADS anxiety and HADS depression score ( $\rho 0.69$ ), and between the GARS score and the six minute walking test ( $\rho 0.77$ ), we entered only one variable of these respective parameters. For the final model, as independent variables were chosen gender, exacerbation frequency during the previous year; FEV<sub>1</sub>, GARS scores, lactate at rest, HADS anxiety score, and BDI score. Exacerbation frequency was divided by the median into two categories (few exacerbations:  $\leq 3$ / year versus frequent exacerbations:  $>3$ / year). Dependent variables were MRF-28, SRI and CRQ total scores.

SPSS 14.0 was used for all analyses. A p-value  $< 0.01$  was considered significant.

## RESULTS

### Patients

Baseline measurements were performed in 86 patients. Fourteen patients were excluded from the analyses as they were not hypercapnic (9 patients), had an apnoea/ hypopnoea index  $\geq 10$  (3 patients), or an FEV<sub>1</sub>>50% predicted (1 patient). One patient was unable to fill in questionnaires. Therefore, a total of 72 patients were included for the present study (table 1). All patients were hypercapnic as per protocol. Thirty-one of them were also hypoxemic (PaO<sub>2</sub> rest <8.0 kPa at room air at rest). Thirty-three patients were on long-term oxygen therapy. We found no significant differences in pulmonary function, exercise tolerance, and any of the questionnaire scores between the patients who were or were not hypoxemic, except for a significantly lower pH and higher PaCO<sub>2</sub> in the hypoxemic patients. All patients were treated with inhaled  $\beta_2$ -agonists or anticholinergic medication; 60 patients used inhaled corticosteroids; 33 patients were treated with oral corticosteroids. We found no significant differences in any of the questionnaire scores between the patients who were or were not on steroids (inhaled and/ or oral).

### Reliability

Scores were obtained over a large range for the MRF-28, SRI, and CRQ (table 2, Figure 1). The MRF-28 cognition domain showed obvious floor and ceiling effects, with 11 patients (15%) scoring the maximum (=worst possible score), and 19 patients (26%) scoring the minimal (=best possible score). Floor and ceiling effects were also observed for the daily



activities and invalidity domain. For the CRQ and SRI no obvious floor and ceiling effects were observed.

Internal consistency of the MRF-28 was high for the daily activity domain, but lower for the cognition and invalidity domain (table 2). Internal consistency of the CRQ was high for all domains; while for the SRI domains it was good except for the attendant symptoms and sleep domain for which internal consistency was lower (0.66). Test-retest reproducibility was good for the MRF-28 (ICC 0.92), SRI (ICC 0.81), and CRQ (ICC 0.87).

## **Validity**

### ***Concurrent validity***

The MRF-28 and SRI total score correlated significantly with all CRQ domains (table 3). The best correlations for both questionnaires were found with the CRQ fatigue domain. The anxiety and well-being domain of the SRI correlated highest with the CRQ emotion domain. The MRF-28 cognition domain did not correlate with any of the CRQ domains. The SRI attendant symptoms and sleep did not correlate with the CRQ dyspnoea domain.

### ***Construct validity***

The physical domains of the questionnaires, which are the MRF-28 daily activities domain, the SRI physical functioning domain, and the CRQ dyspnoea domain, correlated strongly with GARS ( $\rho=0.75$ ,  $\rho=0.86$ ,  $\rho=0.42$  respectively), and with dyspnoea scores and the 6-minute walking distance. The highest correlations with these physical parameters were found

for the SRI domain. Emotional domains, which are the SRI anxiety and SRI psychological wellbeing domain, and the CRQ emotion and mastery domain, correlated strongly with both HADS anxiety and depression. Again the highest correlations were found for the SRI psychological well-being domain.

Only the MRF-28 daily activities and invalidity domains and three SRI domains correlated weakly to moderately with pulmonary function parameters, while none of the CRQ domains did. The MRF-28 invalidity domain contains questions on effort and social activities. It correlated moderately both with physical and psychological parameters. However, no MRF-28 domain correlated as strongly with mood state as did the psychological domains of the other questionnaires. The cognition domain did not correlate with any parameters at all, also not with arterial blood gases. Overall, the SRI contains domains that correlated most strongly both with physical and psychological parameters. Interestingly, several domains of the SRI correlated with bicarbonate levels (table 4).

### ***Determinants of HRQoL***

Of the variance in the MRF-28 total score, 66% was explained by gender, GARS score, HADS anxiety score, and BDI. The largest part of the variance in MRF-28 total score was explained by the GARS score (52%). Of the total variance in SRI summary score 72% was explained by HADS anxiety, GARS, and exacerbation frequency. The largest part of the total explained variance (56%) was attributable to the HADS anxiety score. Of the total variance in CRQ total score, 63% was explained by gender, lactate at rest, HADS anxiety, and BDI scores, with the largest part (51%) explained by HADS anxiety score (table 5).

To strengthen our conclusions based on the present model with seven variables, we tested the model with only GARS and HADS anxiety included. For the CRQ and SRI, this model was

again dominated by the HADS anxiety, while for the MRF-28 it was dominated by the GARS.

## **DISCUSSION**

The present study shows for the first time that the recently developed MRF-28 and SRI are reliable and valid HRQoL questionnaires in a homogeneous group of COPD patients with CHRf. Overall, the MRF-28 total score was more related to activities of daily living, and less to psychological functioning. The SRI total score, like the CRQ total score, was most strongly related to anxiety and depression. In addition, the SRI total score was also substantially related to daily activity level.

Two results from the present study advocate the use of the MRF-28 and/or SRI in addition to or instead of the CRQ in patients with chronic respiratory failure. First, the MRF-28 and SRI contain items on specific problems that patients with CHRf might encounter that are not included in the CRQ. Secondly, we showed that construct validity was slightly better for the MRF-28 and especially the SRI compared to the CRQ in these patients. The version of the CRQ as used in the present study necessitates an interviewer, while the MRF-28 and SRI are self-administrated. The MRF might be more attractive in the practical sense as it contains 28 items and took the patients about 10 minutes to complete, while the SRI contains 49 items and takes 20 minutes to complete. However, as answer possibilities were clearly indicated both questionnaires were easy to complete for the patients.

The importance of addressing the care for patients with end-stage COPD is increasingly recognised [27]. Once a chronic respiratory failure develops, a patient often becomes limited

by specific symptoms and complaints that negatively influence HRQoL [28]. Patients might experience severe breathlessness at minimal effort or already at rest. High carbon dioxide levels might cause headaches or concentration problems. These problems reduce the ability to perform activities of daily living. Social relationships and activities become problematic and patients might become depressed or anxious.

A good HRQoL questionnaire should include all the items that are considered to be important for HRQoL in these patients [10]. Because the CRQ was not designed in patients with respiratory failure, a need was felt for a HRQoL questionnaire that included items complaints and symptoms specific for patients with chronic respiratory failure [10]. However, the MRF-28 and SRI were designed in a mixed group of patients with chronic respiratory failure, not exclusively in patients with COPD [11, 12]. The present study investigated these questionnaires in a homogeneous group of COPD patients with chronic hypercapnic respiratory failure. We suggest that in the future, the MRF-28 and SRI could probably be added to or even substitute the CRQ in the assessment of HRQoL in COPD patients with C(H)RF.

The MRF-28 and SRI add the following items that are considered to be important in these patients. The MRF-28 adds the cognition domain, which contains 4 items on the effects of impaired memory, attention and concentration on daily living. It has been shown that neurophysiological functioning is impaired in COPD patients, especially in patients who were hypoxemic [29]. In our hypercapnic COPD patients, 74% answered at least 1 and 56% at least 2 out of 4 questions of the cognition domain as being true. So, cognitive problems are frequently encountered by patients with CHRF. Still, we did not find a relationship with resting blood gases. However, the cognition domain is very short and probably too limited to

find this relationship. In addition, an obvious floor and ceiling effect was observed for this domain (table 2). These limitations advocate the addition of more items in the cognition domain.

The SRI (physical functioning) domains correlated with bicarbonate levels, the most robust parameter for the severity of CHRF. As only the SRI seemed to be able to pick up the influence of bicarbonate levels on physical functioning and social activities, we advocate the use of the SRI in intervention studies aimed at improving the degree of respiratory failure. This is in line with a previous study that showed a high correlation between a reduction in bicarbonate level following establishment of home mechanical ventilation and an increase in the SRI summary scale [30].

Construct validity of the MRF-28 and SRI was better compared to construct validity of the CRQ in this patient group. MRF-28 and especially the SRI scores correlated more strongly with other measures that assessed the same construct. As compared to the CRQ dyspnoea and fatigue domains, the MRF-28 daily activity domain and SRI physical functioning domain correlated more strongly with daily activities, dyspnoea, and exercise tolerance. In addition, the SRI psychological domains correlated more strongly with mood state as compared to the respective CRQ domains. The MRF-28 contains no psychological domain. The invalidity domain contains items both on feeling of invalidity, effort, and social activities. Therefore, it was also unsurprising that correlations with psychological parameters were only moderate. The MRF-28, SRI, and CRQ emphasize different aspects of HRQoL. For the CRQ, anxiety accounted for a large part of the total explained variance in total score. This is in line with the study of Haijro et al who found that HADS anxiety next to BDI scores accounted for a large percentage of variance in CRQ [31]. For the SRI, as for the CRQ, anxiety also accounted for a

large part of the total variance in the summary scale. In addition, for the SRI, restrictions in activities of daily living accounted for a substantial part (13%). However, in the MRF-28, the emphasis was on restrictions in the degree of activities of daily living. HADS anxiety, on the contrary, explained only 5% of the total variance in MRF-28 score. As mood state was shown to have substantial effects on HRQoL in patients with chronic hypercapnic respiratory failure [32], the underexposure of psychological aspects is a disadvantage of the MRF-28. Therefore, we recommend using the MRF-28 in addition to the SRI and not as a substitute. Now that we evaluated reliability and validity of the two new questionnaires in a homogeneous group of COPD patients with CHRF not on mechanical ventilation, responsiveness of the different questionnaires should be evaluated in intervention studies on for example pulmonary rehabilitation and home mechanical ventilation.

The MRF-28 and SRI are not widely used yet, which makes it difficult to compare our scores with previous studies. We found somewhat higher MRF-28 scores (indicating worse HRQoL) compared to Carone [11]. This can be explained by the fact that our patients had more severe airflow obstruction. Janssens et al investigated the MRF-28 in a group of patients treated with HMV, but included only 15% COPD patients [33]. Clini et al used the MRF-28 as an outcome measure in their study on HMV in COPD, however, they mentioned only change in scores and no absolute scores [34]. Recently, Carone et al showed that pulmonary rehabilitation increases MRF-28 scores in COPD patients with chronic respiratory failure. Scores were comparable except for a better (lower) cognition domain score in our study, which might be explained by a lower age in our patients [5]. Our SRI scores were comparable to the scores found by Windisch [12].

In conclusion, to include the most extensive measurement of HRQoL in COPD patients with CHRF, we recommend using the SRI. The emphasis in the MRF-28 is mostly on restrictions in activities of daily living, but it underscores the importance of psychological aspects in these patients. However, the MRF-28 adds the cognition domain with which prevalent and relevant problems in these patients are addressed. Therefore the addition of this domain might be a reason to add the MRF-28 in intervention studies.

**Acknowledgements.** The authors would like to thank Desiree Jansen (Department of Epidemiology, University Medical Center Groningen, University of Groningen) for statistical advice.

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## Tables

**Table 1:** Patient characteristics

	Mean $\pm$ SD
Gender, male/ female	39/ 33
Age, years	62 $\pm$ 8.6
Number on long-term oxygen	33
Number on oral/ inhaled steroids	33/ 60
Exacerbations, number/ yr	4.0 $\pm$ 3.2
BMI, kg/m <sup>2</sup>	27.1 $\pm$ 6.2
FEV <sub>1</sub> , L	0.80 $\pm$ 0.31
FEV <sub>1</sub> , % predicted	30 $\pm$ 11
VC, L	2.60 $\pm$ 0.77
FEV <sub>1</sub> /VC, %	31 $\pm$ 9
TLC, % predicted	125 $\pm$ 18
RV%TLC	64.8 $\pm$ 8.4
P <sub>1</sub> max, kPa	5.3 $\pm$ 2.1
pH	7.39 $\pm$ 0.03
PaO <sub>2</sub> , kPa (room air)	8.1 $\pm$ 1.2
PaCO <sub>2</sub> , kPa (room air)	6.8 $\pm$ 0.6
HCO <sub>3</sub> <sup>-</sup> , mmol/ L	28.8 $\pm$ 2.4
BE, mmol/ L	4.1 $\pm$ 2.0
6-MWD, m	284 $\pm$ 119
GARS score	42 $\pm$ 11
HADS depression	7.5 $\pm$ 5
HADS anxiety	7.2 $\pm$ 4
BDI total score	3.6 $\pm$ 1.8
MRC	3.5 $\pm$ 0.9

**Table 1:** *Footnote:* Data are presented as mean  $\pm$  SD. Exacerbations: the number of patient-reported exacerbations over the previous year; BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume in 1 second; VC: vital capacity; TLC: total lung capacity; RV%TLC: residual volume as percentage of total lung capacity; P<sub>1</sub>max: maximal inspiratory pressure; PaO<sub>2</sub>: arterial oxygen pressure; PaCO<sub>2</sub>: arterial carbon dioxide pressure; HCO<sub>3</sub><sup>-</sup>: bicarbonate; BE: base excess; 6-MWD: 6-minute walking test distance; GARS: Groningen Activity and Restriction Scale (score range from best (18) to worst (72)); HADS: Hospital Anxiety and Depression Scale (separate scores for anxiety and depression, score range best (0) to worst (21)); BDI: baseline dyspnoea index (score range best (12) to worst (0)); MRC: Medical Research Council dyspnoea scale (score range best (1) to worst (5)).

**Table 2:** MRF-28, SRI and CRQ scores and internal consistency

	Items (n)	Patients with minimum score (n)	Patients with maximum score (n)	Mean $\pm$ SD	$\alpha$
<b><i>Maugeri Respiratory Questionnaire</i></b>					
Daily activities (0-100)	11	3	6	60.6 $\pm$ 28.9	0.83
Cognition (0-100)	4	19	11	44.1 $\pm$ 35.2	0.69
Invalidity (0-100)	5	4	15	63.1 $\pm$ 29.6	0.60
Total (0-100)	27	0	0	55.5 $\pm$ 22.0	
<b><i>Severe Respiratory Insufficiency Questionnaire</i></b>					
Respiratory complaints (0-100)	8	0	0	46.7 $\pm$ 15.5	0.73
Physical functioning (0-100)	6	0	0	38.5 $\pm$ 18.5	0.73
Attendant symptoms and sleep (0-100)	7	0	0	59.7 $\pm$ 16.9	0.66
Social relationships (0- 100)	6	0	0	63.2 $\pm$ 18.0	0.78
Anxiety (0-100)	5	1	0	48.2 $\pm$ 19.8	0.70
Well-being (0-100)	9	0	0	57.0 $\pm$ 18.3	0.84
Social functioning (0-100)	8	1	0	46.2 $\pm$ 17.5	0.73
Summary score (0-100)	49	0	0	51.3 $\pm$ 13.6	
<b><i>Chronic Respiratory Questionnaire</i></b>					
Dyspnoea (5-35)	5	1	0	16.2 $\pm$ 5.5	0.73
Fatigue (4-28)	4	1	0	13.8 $\pm$ 4.9	0.82
Emotion (7-49)	7	1	0	30.3 $\pm$ 7.7	0.78
Mastery (4-28)	4	1	0	17.6 $\pm$ 5.4	0.80
Total (20-140)	20	0	0	78.1 $\pm$ 19.3	

**Table 2: footnote:** Shown are respectively the domains (minimal and maximal scores which can be obtained), number of items, number of patients with minimum and maximum score, mean scores  $\pm$  SD, and  $\alpha$ : Cronbach's alfa for internal consistency.

**Table 3:** Spearman's rank correlations between MRF-28, SRI, and CRQ

	<b>Chronic Respiratory Questionnaire</b>				
	Dyspnoea	Fatigue	Emotion	Mastery	Total
<b>Maugeri Respiratory Failure Questionnaire</b>					
Daily activities	-0.44	-0.51	-0.33	-0.25	-0.45
Cognition	-	-	-	-	-
Invalidity	-0.44	-0.49	-0.45	-0.41	-0.54
Total	-0.52	-0.61	-0.49	-0.36	-0.60
<b>Severe Respiratory Insufficiency Questionnaire</b>					
Respiratory complaints	0.57	0.59	0.40	0.34	0.54
Physical functioning	0.46	0.61	0.47	0.42	0.59
Attendant symptoms and sleep	-	0.39	0.38	0.27	0.39
Social relationships	0.44	0.57	0.59	0.45	0.63
Anxiety	0.35	0.57	0.65	0.60	0.67
Well-being	0.38	0.60	0.79	0.70	0.79
Social functioning	0.42	0.57	0.51	0.41	0.60
Summary score	0.53	0.74	0.73	0.62	0.81

**Table 3:** *Footnote:* only significant correlations are shown

**Table 4:** Spearman's rank correlations between physiological parameters and MRF-28, SRI, and CRQ scores

	MRF-28				SRI							CRQ					
	<i>daily</i>	<i>cog</i>	<i>inv</i>	<i>total</i>	<i>RC</i>	<i>PF</i>	<i>AS</i>	<i>SR</i>	<i>AX</i>	<i>WB</i>	<i>SF</i>	<i>SS</i>	<i>dys</i>	<i>fat</i>	<i>em</i>	<i>mas</i>	<i>total</i>
Exacerbations	0.36	-	0.30	<b>0.40</b>	0.37	0.43	-	0.43	0.35	-	0.45	<b>0.46</b>	0.35	0.33	0.31	0.27	<b>0.37</b>
FEV <sub>1</sub> % pr	0.27	-	0.40	<b>0.33</b>	-	0.33	-	-	0.26	0.27	0.26	<b>0.27</b>	-	-	-	-	-
VC, L	0.39	-	0.27	<b>0.30</b>	-	0.27	0.33	-	-	0.28	0.35	<b>0.32</b>	0.28	-	-	-	<b>0.26</b>
RV%TLC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
P <sub>I</sub> max, kPa	0.34	-	-	-	-	0.26	-	-	-	-	0.25	-	-	-	-	-	-
VO <sub>2</sub> max, ml/min/kg	0.31	-	0.40	<b>0.26</b>	-	0.38	-	-	-	-	0.25	-	-	-	-	-	-
6-mwd, m	0.53	-	0.50	<b>0.50</b>	0.38	0.60	-	0.48	0.29	0.25	0.58	<b>0.49</b>	0.33	0.39	0.30	0.23	<b>0.36</b>
PaO <sub>2</sub> , kPa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PaCO <sub>2</sub> , kPa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
pH	-	0.27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HCO <sub>3</sub> <sup>-</sup>	-	-	-	-	-	-	-	0.32	-	-	-	-	-	-	-	-	-
Lactate, mmol/L	-	0.24	-	<b>0.26</b>	-	0.30	-	0.33	-	0.29	0.36	<b>0.30</b>	-	0.26	0.36	0.29	<b>0.33</b>
GARS	0.75	-	0.59	<b>0.70</b>	0.49	0.86	-	0.53	0.40	0.36	0.66	<b>0.65</b>	0.42	0.52	0.39	0.33	<b>0.47</b>
HADS depression	0.52	-	0.48	<b>0.57</b>	0.41	0.54	0.26	0.61	0.54	0.68	0.58	<b>0.68</b>	0.29	0.61	0.60	0.56	<b>0.65</b>
HADS anxiety	0.43	-	0.56	<b>0.56</b>	0.50	0.51	0.39	0.56	0.69	0.79	0.54	<b>0.75</b>	0.30	0.54	0.75	0.72	<b>0.74</b>
BDI	0.67	-	0.58	<b>0.68</b>	0.57	0.67	-	0.43	0.41	0.40	0.51	<b>0.59</b>	0.53	0.63	0.40	0.32	<b>0.54</b>
MRC	0.49	-	0.50	<b>0.47</b>	0.43	0.59	-	0.30	0.26	-	0.43	<b>0.41</b>	0.41	0.33	-	-	<b>0.27</b>



**Table 4: Footnote:** Only significant correlations ( $p < 0.01$ ) are shown. Correlations with total scores are shown in bold italics.

MRF-28 domains: daily activities (daily), cognition (cog), invalidity (inv); SRI domains: respiratory complaints (RC), physical functioning (PF), attendant symptoms and sleep (AS), social relationships (SR), anxiety (AX), psychological well-being (WB), social functioning (SF) and a summary scale (SS); CRQ domains: dyspnoea (dys), fatigue (fat), emotion (em), and mastery (mas).

$\text{VO}_2\text{max}$ : maximal oxygen uptake during cycle ergometry; Lactate: lactate levels from arterial blood sample. For the remaining abbreviations see footnote Table 1.

**Table 5:** Backward multiple regression analyses

	MRF-28 total score (%)		SRI total score (%)		CRQ total score (points)	
	<i>B</i>	<i>R</i> <sup>2</sup>	<i>B</i>	<i>R</i> <sup>2</sup>	<i>B</i>	<i>R</i> <sup>2</sup>
GARS, points*	0.7 (0.3 to 1.1)	0.52	-0.4 (-0.6 to -0.3)	0.13	-	-
HADS anxiety, points <sup>†</sup>	1.2 (0.3 to 2.1)	0.05	-1.7 (-2.2 to -1.2)	0.56	-2.3 (-3.0 to -1.5)	0.51
BDI, points <sup>‡</sup>	- 4.1 (-6.4 to -1.7)	0.08	-	-	2.5 (0.7 to 4.2)	0.06
Gender, female	6.0 (0.8 to 12.7)	0.01	-	-	-8.6 (-14.6 to 2.5)	0.03
Exacerbations, frequent (>3/yr)	-	-	-4.9 (-8.7 to -1.1)	0.03		
Lactate, mmol/L	-	-	-	-	-6.7 (-12.0 to -1.4)	0.03
Cumulative <i>R</i> <sup>2</sup>		0.66		0.72		0.63

**Table 5:**

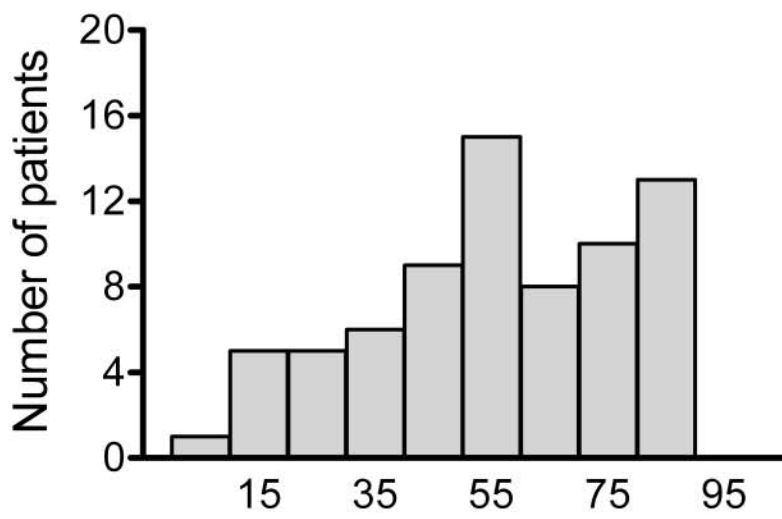
*Footnote:* Included as independent variables in the models were gender, exacerbation frequency, FEV<sub>1</sub>% predicted, lactate, GARS score, HADS anxiety score and BDI. Only variables that were included into the final models are shown.

*B:* unstandardised regression coefficient (95% CI), which indicates predicted increase in questionnaire total scores for 1 unit increase in the given variable. *R*<sup>2</sup>: proportion of explained variance for independent variables included in the backward model. \* GARS: score from best to worst: 18 to 72 points; HADS anxiety score from 0 to 21 points; BDI score from 12 to 0 points; Gender: 0=male; 1= female; exacerbation frequency: few exacerbations (coded as zero; ≤ 3 exacerbations/year) vs. frequent exacerbations (coded as 1; >3/year). For the remaining abbreviations see footnote table 1 and footnote table 4.

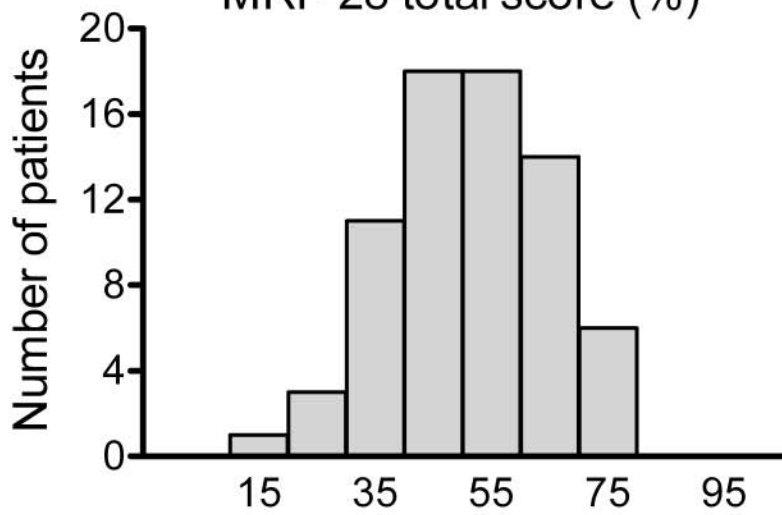
## **Figure legend**

**Figure 1:** Variation in total scores of the questionnaires.

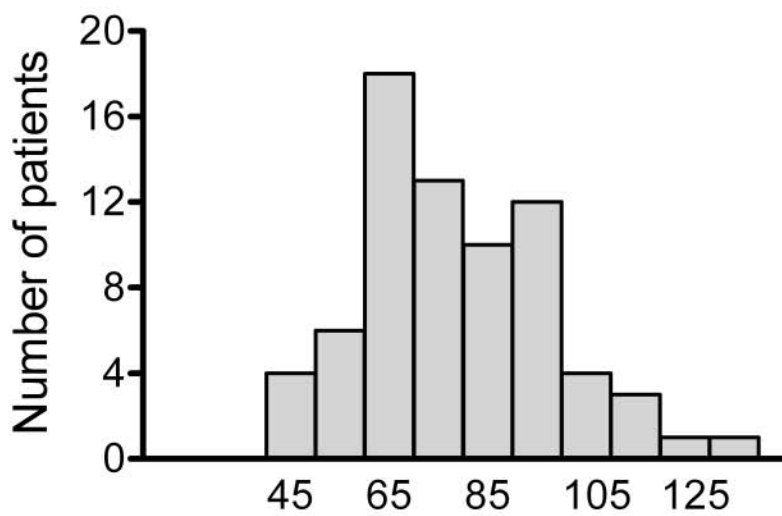
**Figure 1:** *Footnote:* MRF-28: Mageri Respiratory Failure total score, SRI: Severe Respiratory Insufficiency summary score and the CRQ: chronic respiratory questionnaire total score.



MRF-28 total score (%)



SRI summary score (%)



CRQ total score (points)

