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Original Research

Treatable traits in advanced emphysema patients eligible for bronchoscopic lung volume reduction with endobronchial valves

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ABSTRACT

Introduction: Patients with advanced emphysema eligible for bronchoscopic lung volume reduction (BLVR) using endobronchial valves (EBV) are characterized by severe static lung hyperinflation, which can be considered a treatable trait. Other treatable traits (TTs), which are assumed to be present in this highly selected patient group, have not been studied in detail nor how they may affect health-related quality of life (HRQL).
Aims: We aimed to evaluate a spectrum of TTs in COPD patients eligible for EBV treatment and their association with HRQL.
Methods: The SoLVE study (NCT03474471) was a prospective multicenter randomized controlled trial to examine the impact of pulmonary rehabilitation in COPD patients receiving EBV. The presence/absence of 16 TTs was based on pre-defined thresholds. HRQL was assessed with the St. George's Respiratory Questionnaire (SGRQ). Subjects were stratified into two groups, using the median split method, into higher or lower SGRQ total score. Logistic regression assessed the odds ratio (OR) of having a higher SGRQ total score per TT.
Results: Ninety-seven subjects were included, the mean number of TTs per patient was 8.1 ± 2.5. Low physical activity (95%), poor exercise capacity (94%) and severe fatigue (75%) were the most prevalent TTs. The sum of TTs present in a subject was associated with the SGRQ total score ($r = 0.53$; $p < 0.001$). Severe fatigue, depression, and anxiety were predictors of having a higher SGRQ total score.
Conclusions: A high prevalence and co-occurrence of multiple TTs were identified in emphysema patients eligible for EBV. Patients with a higher number of TTs were more likely to have worse HRQL.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation but contains a spectrum of clinical phenotypes based on different clinical disease expressions and responses to therapy [1,2]. An example of such a COPD phenotype is advanced emphysema with severe airflow limitation and static hyperinflation. Some of these patients can be eligible for bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBV) [2–4]. Nevertheless, in this specific phenotype pulmonary function tests alone are most probably insufficient to capture the clinical heterogeneity of other pulmonary and extra-pulmonary disease manifestations.

The treatable traits (TTs) concept was formulated to address this complexity and heterogeneity, and particularly identify the specific components present in a patient, consequently providing a rationale for precision medicine [5]. A recent study demonstrated that many TTs exist in COPD patients upon first-ever referral to a pulmonologist, and that TTs like severe fatigue and activity-related dyspnea were strongly associated with a severely impaired health-related quality of life (HRQL) [6].

A recognized TT is static hyperinflation related to advanced emphysema in which BLVR has been proven to be a highly effective

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intervention and an example of precision medicine [7]. We hypothesized that in patients eligible for EBV other TTs exist and negatively contribute to the patient's health status. A comprehensive and broad assessment of TTs in patients suitable for EBV has not been studied in detail.

Therefore, we aimed to evaluate TTs in patients with advanced emphysema eligible for EBV using an extensive baseline assessment, including pulmonary function tests, exercise tests, muscle strength test, body composition, and patient-reported outcome measures. Additionally, we studied which TTs were associated with a severely impaired HRQL.

2. Methods

The SoLVE study (NCT03474471) was a prospective multicenter randomized controlled trial to examine the impact and optimal timing of pulmonary rehabilitation (PR) on exercise physiology and patient-reported outcomes in COPD patients receiving EBV treatment. The study was approved by the ethics committees of both participating hospitals (METc 2018/241) and written informed consent was obtained from each participant. In this current study, the baseline assessments were used from all included subjects.

2.1. Study sample

Subjects with advanced emphysema were included in the study when eligible for BLVR with EBV and PR. Main inclusion criteria were the following: a physician diagnosis of COPD, FEV_1 ≤45% of predicted, FEV_1/FVC <70%, total lung capacity (TLC) > 100% of predicted, and residual volume (RV) > 175% of predicted. Patients had to be symptomatic with a COPD Assessment Test (CAT) total score ≥10 points. A high-resolution CT-scan with quantitative analysis required >50% destruction score (percentage of voxels less than −910 Hounsfield units) with a >95% complete major fissure for the target lobe. Exclusion criteria were: severe respiratory failure (PaCO2 >8.0 kPa and/or PaO2 <6.0 kPa) or very low exercise capacity (6-min walk test <160 m). Furthermore, subjects with significant chronic bronchitis, bronchiectasis, 3 or more hospitalizations due to pulmonary infection within the last 12 months, significant immunodeficiency, previous lobectomy or lung volume reduction surgery were excluded.

2.2. Measurements

The examined TTs in this study were selected because evidence-based interventions exist for them. The cut-off values were pre-defined and derived from literature or rationally chosen by the authors [8–16]. An overview of the selected TTs, the measurement instrument applied and the corresponding cut-off value are listed in Table 1. HRQL was assessed using the total score of St. George's Respiratory Questionnaire (SGRQ) [17].

2.3. Analyses

Descriptive statistics were used to present the data as means (± standard deviation (SD)), medians (ranges) or frequencies, as appropriate. The presence of the sixteen TTs in a subject was binary determined based upon the pre-defined cut-off values (Table 1). The prevalence of each TT was measured by calculating the percentage of patients who met the predetermined criteria. The association between the individual TT sum scores (ranging between 0 and 16) and the SGRQ total score were assessed using Pearson's correlation coefficients.

A median split analysis on the SGRQ total score was performed to identify which TTs were associated with a higher (=worse HRQL) score on the SGRQ. Logistic regression assessed the odds ratio (OR) of having a higher SGRQ total score per TT. Comparison between the two groups (lower *versus* higher SGRQ total score), resulting from the median split, were done using an independent T-test for continuous data if normally distributed, and Wilcoxon signed rank test if not normally distributed. For categorical data chi-square tests were used.

Statistical analyses were conducted using SPSS version 24 (IBM Corp., Armonk, NY, USA). A priori, the level of significance was set at $p < 0.05$.

Table 1
Summary of examined treatable traits, measurement instruments and applied cut-off values.

	Treatable trait	Measurement instrument	Cutt-off value
1	**Severe dyspnea**	Modified Medical Research council dyspnea scale [8]	mMRC ≥3
2	**Very severe airflow limitation**	Spirometry	FEV_1 < 30% of predicted
3	**Frequent exacerbations**	Clinical history	≥1 hospitalizations or ≥2 exacerbations
4	**Poor exercise capacity**	6-MWT [10]	<70% of predicted
5	**Low physical activity**	Accelerometer (DynaPort MoveMonitor, McRoberts BV, The Hague, the Netherlands)	<5000 steps per day [11,13]
6	**Hypoxemia**	Arterial blood gas at rest	PaO_2 < 8.3 kPa or usage of long-term oxygen therapy
7	**Hypercapnia**	Arterial blood gas at rest	$PaCO_2$ > 5.9 kPa
8	**Underweight**	Weight scale + height	BMI <21 kg/m^2
9	**Obesity**	Weight scale + height	BMI >30 kg/m^2
10	**Low muscle mass**	Dual energy X-ray absorptiometry + height	FFMI <17 kg/m^2 for males and <15 kg/m^2 for females [9]
11	**Decreased bone mineral density**	Dual energy X-ray absorptiometry	T-score < −2.5
12	**Impaired handgrip force**	Hydraulic hand dynamometer (Jamar)	<10th percentile [15]
13	**Impaired quadriceps force**	Electronic handheld dynamometer (MicroFET)	<70% of predicted [16]
14	**Severe fatigue**	Checklist individual strength-fatigue (CIF–F) [12]	CIS–F ≥ 36 points
15	**Anxiety**	Hospital Anxiety and Depression Scale- Anxiety (HADS-A) [14]	HADS-A ≥ 8 points
16	**Depression**	Hospital Anxiety and Depression Scale-Depression (HADS-D) [14]	HADS-D ≥ 8 points

FEV_1 = forced expiratory volume in 1 s; BMI = body mass index; FFMI = fat free mass index; PaO_2 = arterial oxygen tension; $PaCO_2$ = arterial carbon dioxide tension; 6-MWT = 6-min walking test.

3. Results

3.1. Patient characteristics

In total, 97 subjects were included in the SoLVE study, characteristics of these individuals are summarized in Table 2. In general, patients were characterized by very severe airflow limitation, very severe lung hyperinflation, and poor HRQL with a median total score of 60 points on the SGRQ total score.

3.2. Prevalence of TTs

The number of TTs per patient ranged from 2 to 15, resulting in a mean of 8.1 ± 2.5 TTs per patient (Fig. 1a). Low physical activity (95%), poor exercise capacity (94%), severe fatigue (75%) and low muscle mass (69%) were the most prevalent TTs (Fig. 1b). Eighty-nine patients (92%) had a unique combination of TTs. Only four identical TTs combination were identified in two patients. A significant association was found between 24% of the studied TTs. The majority had a weak association

Table 2
Patients characteristics.

	N	All patients (100%)	SGRQ <60 points (47%)	SGRQ ≥60 points (53%)
General characteristics				
Sex, male, %	97	37.1	31.1	41.2
Age, years	97	62.4 ± 6.8	62.2 ± 7.5	62.4 ± 6.1
BMI, kg/m^2	97	24.3 ± 3.8	23.7 ± 3.6	24.8 ± 4.0
<21, %		26.8	33.3	21.6
>30, %		8.2	4.4	11.8
FFMI, kg/m^2	89	15.0 ± 1.9	14.6 ± 1.6	15.3 ± 2.0
<17 for males or <15 for females, %		68.5	78.0	61.7*
BMD, g/cm^2	89	0.96 ± 0.11	0.95 ± 0.11	0.97 ± 0.11
<-2.5 T-score, %		33.7	36.6	31.9
Smoking pack years	97	39 (28–50)	39 (27–50)	38 (28–48)
Hospitalizations in previous year, n	97	0 (0–1)	0 (0–1)	0 (0–1)
≥1 hospitalization, %		34.0	26.7	41.2
Exacerbations in previous year, n	97	2 (1–3)	1 (0–2)	2 (1–3)*
≥2 exacerbations, %		50.5	40.0	58.8
Frequent exacerbations, %	96	58.8	48.9	66.7
Long-term oxygen therapy, %	96	19.6	13.3	25.5
Pulmonary function and arterial blood gas				
FEV_1, %pred	97	28.3 ± 7.8	27.9 ± 7.8	28.7 ± 7.9
FEV_1≤30%pred, %		62.9	66.7	58.8
GOLD classification of airflow limitation, %	97			
III		37.1	33.3	41.2
IV		62.9	66.7	58.8
FVC, %pred	97	80.8 ± 17.8	82.1 ± 19.2	79.5 ± 16.7
RV, %pred	97	230.7 ± 39.3	229.7 ± 38.9	232.3 ± 40.0
DL_{CO}, %pred	92	36.4 ± 8.8	35.7 ± 8.0	36.8 ± 9.4
$PaCO_2$, kPa	95	5.3 (4.9–5.9)	5.4 (5.1–5.8)	5.2 (4.8–5.9)
PaO_2, kPa	95	9.3 ± 1.2	9.4 ± 1.2	9.3 ± 1.2
Respiratory failure, %	95	29.8	31.1	40.8
Hypercapnia, %		18.9	15.6	20.4
Hypoxemia or long-term oxygen therapy, %		30.5	26.7	32.7
Physical performance				
6MWT, %pred	97	49.0 ± 13.6	51.9 ± 13.2	46.1 ± 13.6
<70, %		93.8	91.1	96.1
Steps/day	82	2140 (1160–3190)	2532 (1562–3296)	1933 (996–2954)
<5000 steps, %		95.1	97.3	93.3
Quadriceps muscle strength, %pred	95	83.2 ± 20.9	86.7 ± 19.4	80.2 ± 21.8
<70%pred, %		28.4	20.5	35.3
Hand grip force	95			
<10th percentile, %		2.1	0.0	3.9
Patient reported outcome measures				
mMRC, points	97	3 (2–3)	3 (2–3)	3 (2–3)
mMRC 2, %		32.0	32.0	32.0
mMRC 3, %		56.7	54.7	58.2
mMRC 4, %		11.3	13.3	9.8
SGRQ, points	96			
Symptoms		52 ± 17	40 ± 13	62 ± 14*
Activity		84 ± 12	77 ± 13	90 ± 7*
Impact		48 ± 15	36 ± 9	59 ± 11*
Total		60 ± 12	49 ± 7	69 ± 7*
HADS, points	96			
Anxiety		6 (4–10)	5 (3–8)	9 (6–11)
Depression		6 (4–10)	4 (3–8)	9 (6–11)
HADS-A≥8, %		42.7	24.4	58.8*
HADS-D≥8, %		42.7	24.4	58.8*
CIS–F, points	93	43 (36–49)	36 (29–43)	47 (42–52)*
CIS–F≥36, %		75.3	58.1	90.0*

Data are displayed as mean ± SD or percentage. BMI = body mass index; FFMI = fat free mass index; BMD = bone mineral density; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity, RV = residual volume; DLCO = diffusing capacity of the lung for carbon monoxide; GOLD = Global Initiative for Chronic Obstructive Lung Disease; $PaCO_2$ = arterial carbon dioxide tension; PaO_2 = arterial oxygen tension; 6-MWT = *6-min walking test; mMRC = modified Medical Research Council Dyspnea; SGRQ = St. George's Respiratory Questionnaire; HADS = Hospital Anxiety and Depression Scale; CIS–F = Checklist individual strength-fatigue;* *p < 0.05 vs. SGRQ<60.

with only one strong value between the TTs anxiety and depression (r = 0.71; p < 0.001).

3.3. TTs and health-related quality of life

A moderate positive correlation (r = 0.53; p < 0.001) between the total SGRQ score and the individual sum score of the TTs per patient was present (Fig. 2).

The median split method resulted in a lower (=better) total score SGRQ group (<60 points) and higher (=worse) total score SGRQ (≥60 points) with 6.8 ± 2.9 TTs and 8.3 ± 2.3 TTs, respectively (p < 0.05). Low muscle mass, exacerbation frequency, anxiety, depression, and severe fatigue were significantly more prevalent in the patients with a SGRQ total score of ≥60 points (Table 2, Fig. 3).

Severe fatigue (OR 6.5 95% confidence interval (CI) 2.12–19.56), anxiety (OR 4.4 95% CI 1.83–10.64) and depression (OR 4.4 95% CI 1.83–10.64) increased the likelihood of having a higher SGRQ total score.

4. Discussion

This study demonstrates that the specific phenotype of COPD patients eligible for BLVR with EBV has a high complexity as shown by the high number of TTs present. Indeed, on average patients exhibited 8 out of the 16 TTs, in which low physical activity, poor exercise capacity, severe fatigue and low muscle mass being the most prevalent. Having more TTs was associated with a decreased HRQL demonstrating the clinical importance of these traits. The presence of severe fatigue, anxiety and depression increased the likelihood of having a more impaired HRQL defined by a total score of ≥60 points on the SGRQ.

The TTs concept was proposed to improve the individualized management of patients with COPD, providing a framework to address the heterogeneity and complexity of the disease [5]. In the current study, we applied this method in advanced emphysema patients eligible for EBV treatment and pulmonary rehabilitation. Our study demonstrated that 92% of the subjects had a unique combination of TTs revealing that besides complexity also a considerate heterogeneity exists within this narrowly defined phenotype.

The characteristics of the subjects in the current study relates to what has been coined as the multi-organ loss of tissue (MOLT) COPD phenotype in which loss of lung tissue due to emphysema has been connected to excessive loss of tissue at extrapulmonary locations leading to muscle wasting and decreased bone mineral density [18]. This combination of traits has also been recognized as a "cachectic cluster" in a multimorbidity cluster analysis in COPD [19]. Our study reported a very high prevalence of low muscle mass (69%) and adds to the literature that this TT is commonly present in COPD patients [20,21]. Low muscle mass is important to identify since it is strongly associated with impaired health status and reduced exercise capacity [22,23].

Interestingly, our study does not confirm the classical depiction of an

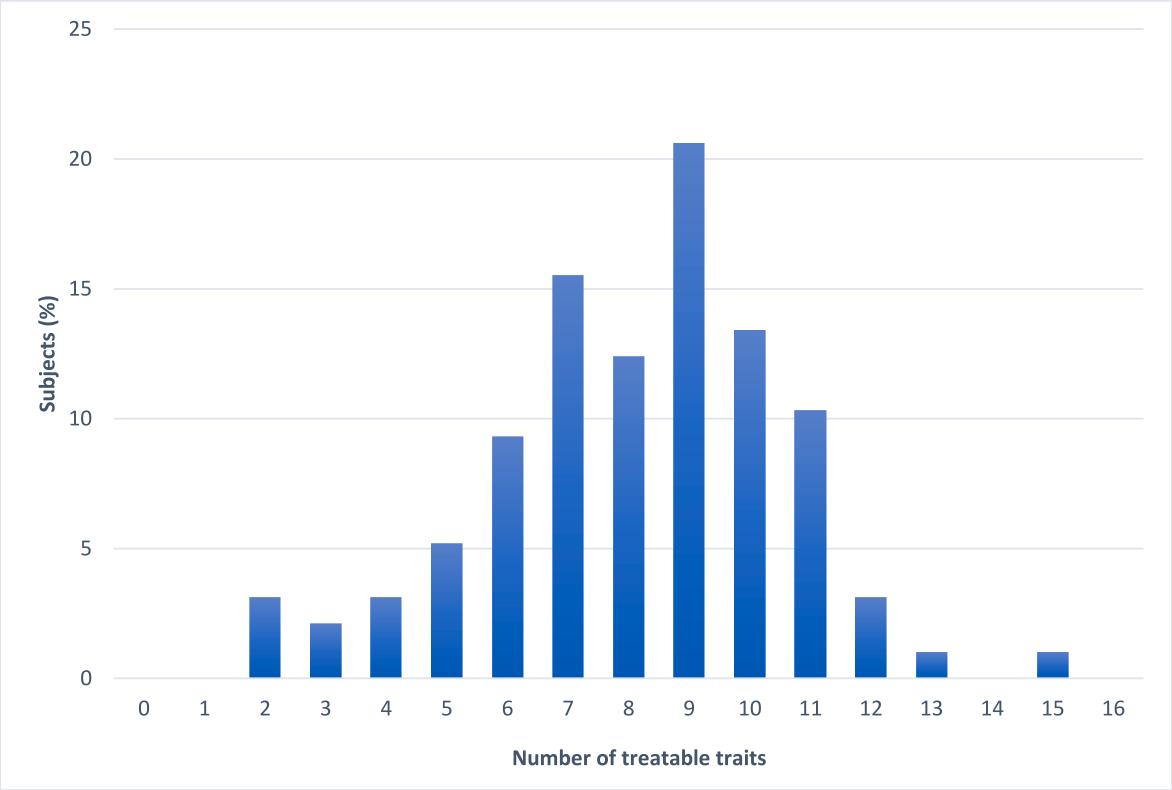

Fig. 1a. Histogram of total number of treatable traits per patient.

emphysema patient with a barrel chest and low body weight since we reported a mean BMI (24.3 kg/m^2) and only 27% of the subjects classified as underweight. The current study verifies that BMI alone is insufficient to detect low muscle mass and suggests that this maybe especially relevant in the advanced emphysema phenotype. Both BLVR and PR are established interventions that, at least partially, reverse muscle loss and increase muscle mass [24,25].

Besides low muscle mass this study demonstrates a high prevalence of muscle weakness as illustrated by impaired quadriceps force in 28% of the patients. Hand grip strength however, seems maintained which confirmed prior work by Bernard et al. that the preferential distribution for muscle weakness in COPD is the lower limb and that hand grip strength is relatively preserved (25). The important relation between peripheral muscle weakness and COPD leading to relevant clinical implications like reduced exercise capacity and HRQL has been widely acknowledged (26–28).

Anxiety and depression were prevalent in almost half (43%) of the subjects in this study and significantly discriminated subjects with lower and higher health related quality of life. The importance of identifying these TTs and their impact, including mortality has been well established. Although the etiology and dynamics of symptoms of anxiety in COPD is complex, this high prevalence might not be a surprise. Patients with severe emphysema and static and dynamic hyperinflation suffer from a high degree of exercise-related dyspnea, which is closely related to feelings of anxiety. In turn, anxiety can further induce dysfunctional breathing and dyspnea. Divo et al. demonstrated in the BODE cohort that anxiety, especially in females, had the highest hazard ratio for increased risk of death [26]. Furthermore, depression seems to be an independent risk factor for exacerbations of COPD [27]. Moreover, depression has shown to be strongly associated with a decline in quality of life in an English longitudinal cohort of COPD patients [28]. Different interventions, like pharmacotherapy, PR, and psychological interventions such as cognitive behavioral therapy, can contribute to reduce this psychological burden [29–31]. If BLVR has significant effect on reducing anxiety and depression has yet to be established.

Fatigue, defined as the subjective feeling of tiredness or exhaustion, is increasingly being studied and recognized as an important TT. Severe fatigue is one of the most common symptoms in COPD and is associated with decreased HRQL [32,33]. Our report verifies that this TT is highly prevalent in advanced emphysema patients and advocates that when screening for BLVR this symptom has to be addressed. Moreover, the prevalence of fatigue was highly predictive for a worse HRQL in our patients making it a potential interesting treatment target. Fatigue can be improved by pulmonary rehabilitation, self-management education and nutritional support [34,35]. Possibly, BLVR with EBV can also reduce fatigue via reducing work of breathing however this has not been studied.

COPD causes impairment in quality of life and improving this is essential from a patient perspective [4]. This study reported severely decreased HRQL and is comparable with studies researching the same specific patient group [36–38]. Also, the number of TTs present in a patient was moderately correlated with a lower HRQL. This is in line with van 't Hul et al. which demonstrated a similar association in a group of COPD patients with a first-time referral to a pulmonologist [6]. There are few randomized trials on the efficacy of the treatable traits approach for managing patients with COPD. McDonald et al. demonstrated in a pilot study that a TTs approach in COPD offered significant improvements in health status compared with standard care [39].

It is reasonable to assume that addressing the TTs in a multidimensional approach in advanced emphysema patients could also lead to improvement in HRQL. In addition, further research should focus on how these traits change over time when remeasured after BLVR, pulmonary rehabilitation or the combination of both.

Although the strength of our study comes from the comprehensive assessment of this specific phenotype there are some limitations that have to be addressed. Firstly, to be eligible for this study strict in- and exclusion criteria were applied potentially effecting the prevalence of specific TTs. Indeed, to be selected for BLVR, subjects had to be

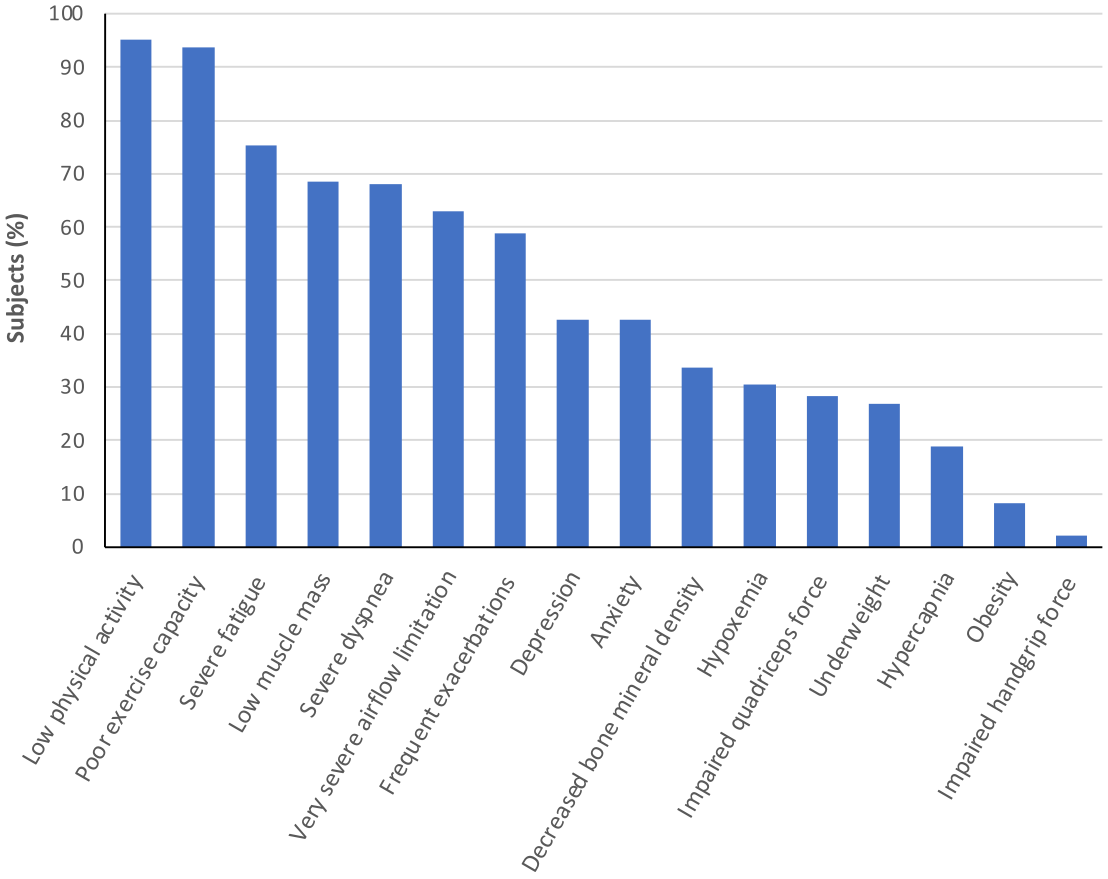

Fig. 1b. Frequencies of treatable traits in all subjects
Treatable traits are ordered from left to right based on their prevalence.

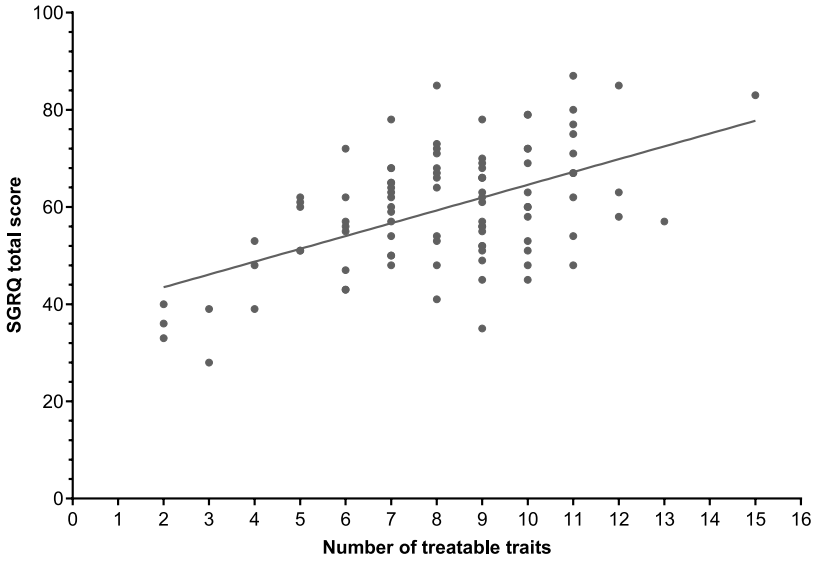

Fig. 2. Scatterplot of SGRQ total score and number of treatable traits per patient.

symptomatic and impaired, probably skewing some TTs towards a higher prevalence. Also, while the cut-off values for the TTs were carefully chosen and have been used in prior studies, different cut-off values for a specific TT are used in literature (for example, absolute values versus percentage of predicted in 6MWD) and could have influenced the outcomes. Additionally, although we performed a

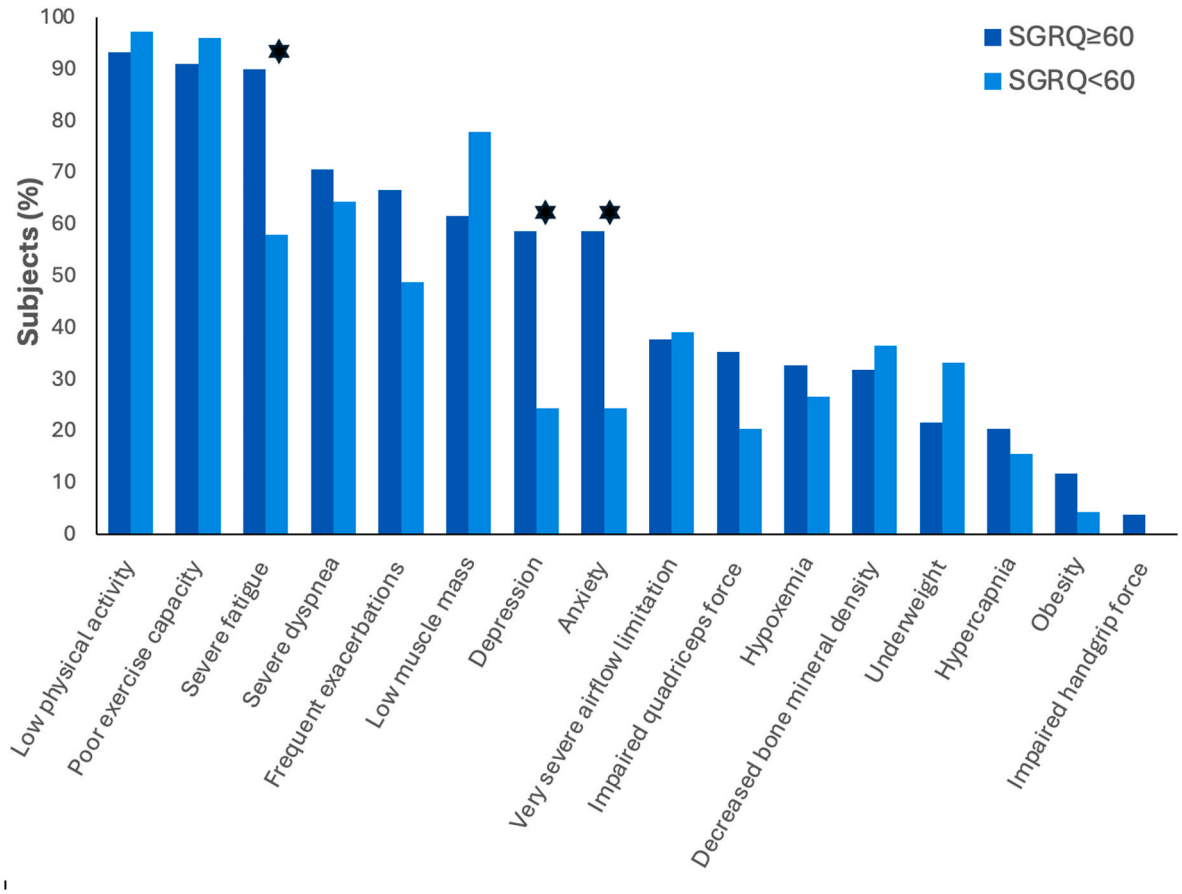

Fig. 3. Prevalence of the TT's when stratified for the two SGRQ total score groups. *Treatable traits with statistically significant odds ratio for SGRQ ≥60 points.

comprehensive assessment, some of the recognized TTs like adherence to pharmacotherapy, persistent systemic inflammation, and family/social support were lacking.

Finally, this study lacks a comparator severe COPD group not eligible for BLVR-EBV. Therefore, we cannot demonstrate that our reported TTs prevalence and distribution is unique for this specific group of patients.

In conclusion, COPD patients with advanced emphysema eligible for BLVR with EBV display a spectrum of treatable traits which were highly prevalent. Having more TTs and more specifically anxiety, depression or fatigue, is associated with a worse HRQL. Findings of this study advocate a multidimensional assessment and management of this specific COPD phenotype.

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CRediT authorship contribution statement

Rein Posthuma: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Marieke C. van der Molen:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Jorine E. Hartman:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Martijn A. Spruit:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Dirk-Jan Slebos:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Lowie E.G.W. Vanfleteren:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Anouk W. Vaes:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation.

Declaration of competing interest

There is no conflict of interest.

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