Physical status, symptoms and health-related quality of life during a severe exacerbation of COPD: recovery and discriminative capacity for future events

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Declaration of Interest: None

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Clinical trial registration number: NCT03250000

Abstract

Objective: Severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD) can have a negative impact on functional capacity, symptoms and health-related quality of life (HRQOL). This study aimed to i) investigate the recovery of muscle strength, functional capacity, symptoms, and HRQOL in patients after a severe AECOPD; ii) compare with matched patients with stable COPD (SCOPD); and iii) assess whether these assessments at hospital discharge could discriminate patients' risk for future events.

Methods: This observational study assessed patients with AECOPD during hospital discharge (T1) and one month after discharge (T2). Patients with SCOPD were assessed once. Quadriceps force, handgrip strength, short physical performance battery (SPPB), six-minute walk distance (6MWD), COPD assessment test (CAT), London chest activity of daily living (LCADL), modified medical research council, checklist individual strength-fatigue, patient health questionnaire, and physical activity (Actigraph) were measured. Exacerbation-related readmission and mortality within six months and 1-year were collected.

Results: Forty-four patients with AECOPD were matched with 44 patients with SCOPD. At T2, a significant improvement was found for the SPPB total score, 6MWD, CAT score, and LCADL score. Compared to patients with SCOPD, a worse LCADL score was found at T2 in patients with AECOPD. Patients with AECOPD that were readmitted or died had a worse SPPB classification and five-repetition sit-to-stand test at T1.

Conclusion: Patients after severe AECOPD improved in functional capacity and HRQOL one month after hospital discharge, but ADL performance was still worse compared to SCOPD. Patients who were readmitted or died had significantly worse scores on functional tests at hospital discharge.

Keywords: COPD, exacerbation, hospitalization, readmission, mortality

Abbreviations: ADL: activities of daily living; AECOPD: acute exacerbations of chronic obstructive pulmonary disease; BMI: body mass index; CAT: COPD assessment test ; CIS: checklist individual strength; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FFM: fat-free mass; FFMI: fat-free mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HGS: handgrip strength; HP: high performance; HRQOL: health-related quality of life; LCADL: London chest activity of daily living; LOS: length of hospital stay; LP: low performance; mMRC: modified medical research council; MP: medium performance; MVPA: moderate-to-vigorous physical activity; PA: physical activity; PHQ: patient health questionnaire; QF: quadriceps force; SCOPD: stable COPD; SD: standard deviation; SPPB: short physical performance battery; STROBE: STrengthening the Reporting of OBservational studies in Epidemiology; 4MGS: four-meter gait speed; 5STS: five-repetition sit-to-stand; 6MWD: six-minute walk distance; 6MWT: six-minute walk test.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) may experience acute events characterized by increased respiratory symptoms, called acute exacerbations (AECOPD)[1]. AECOPD are classified as severe when patients require hospitalization or visit the emergency room[1]. Severe AECOPD are associated with reduced health status, including a negative impact on peripheral muscle force, functional capacity, physical activity (PA) levels, symptoms and health-related quality of life (HRQOL)[2-6].

After a severe AECOPD, a recovery in functional capacity, PA and symptoms of dyspnea and fatigue is seen[2, 5, 7], but conflicting evidence exists for peripheral muscle force[2-4, 7]. Moreover, persistent symptoms have been reported up to six months after hospitalization[8] and a prolonged impact on HRQOL can occur[9]. Impairments in functional capacity, muscle strength and symptoms are associated with more limitations in activities of daily living[10]. The impact of severe exacerbations on health status has typically been studied using assessments during and after the exacerbation, making it challenging to evaluate the extent of the recovery. Therefore, a control group of matched patients with stable COPD (SCOPD) may help estimating whether patients reach stable values during recovery.

Studies in patients with SCOPD have shown an association between quadriceps force, six-minute walk test (6MWT), short physical performance battery (SPPB), 30-second chair stand test, one-minute sit-to-stand test, and the COPD assessment test (CAT) on one hand and mortality on the other hand[11-15]. While patients experiencing AECOPD are at high risk of developing new exacerbations in the future[16], few studies have investigated the association between measures of health status during a severe AECOPD and the risk of readmission[17-19].

This study aimed to examine the recovery of peripheral muscle strength, functional capacity, symptoms, and HRQOL in patients after a severe AECOPD and compare it with matched patients with SCOPD. Secondly, we explored whether peripheral muscle strength, functional capacity, symptoms, and HRQOL at hospital discharge could discriminate patients' risk for exacerbation-related readmission or mortality at six months and 1-year.

Materials and Methods

Study design

This prospective observational study was approved by the Medical Ethical Committee (Eudract-B-nr: B371201732540, July 2017). It was conducted in accordance with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline[20]. The data were partially presented during the European Respiratory Society congress.

Between July 2017 and March 2020, a convenience sample of hospitalized patients with a doctor-confirmed AECOPD, according to the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[21], was invited to participate in the study. Patients with SCOPD, defined as a minimum of six weeks without a severe AECOPD, were included at their yearly outpatient pulmonology consultation. Exclusion criteria were: admission to the intensive care unit; the presence of other lung diseases; unstable cardiovascular disease; orthopaedic conditions that impaired functional status; cognitive and neurological disorders that impaired the ability to comply with study procedures. Written informed consents were obtained from all participants before any data collection.

Patients with an AECOPD were assessed on the day of discharge (T1) and one month after discharge (T2). Patients with SCOPD were assessed once (S). Exacerbation-related hospitalization in the previous year, exacerbation-related readmission and mortality within

six months and 1-year were collected from the hospital records for patients with an AECOPD.

Patient characteristics

Age, sex and packyears were collected. Waist-hip ratio, and fat-free mass (FFM) by bio-electrical impedance analysis (Bodystat 1500) were measured[22]. Body mass index (BMI) and FFM index (FFMI) was calculated[23]. Length of hospital stay (LOS) and classification of comorbid conditions (using the Charlson Comorbidity Index)[24] were retrieved from the hospital records. Post bronchodilator spirometry was performed according to the ATS/ERS guidelines[25]. This test is embedded yearly in clinical routine, and the most recent stable measurement (i.e., at least three months apart from an AECOPD) was retrieved from hospital records.

Measurements

Isometric quadriceps force (QF) was assessed using a hand-held dynamometer (Microfet, Biometrics, NL). Patients were tested while sitting in the upright position. The assessor applied resistance and asked the patient to maximally contract the muscle against the resistance[26]. At least three maximal efforts were performed and the test was repeated until reproducible measurements (less than 10% variability) were obtained. The highest value was used for analyses and compared with normative values[27]. Handgrip strength (HGS) was measured isometrically using a hand-held dynamometer (Jamar, Preston, MI, USA) while sitting in the upright position with the elbow flexed 90 degrees and the wrist in a neutral position[28]. Three maximal efforts were performed and repeated until reproducible measurements (less than 10% variability) were obtained. The best was used for analysis and compared with normative values[29].

The SPPB was assessed, which consists of a five-repetition sit-to-stand test (5STS), a four-meter gait speed test (4MGS) and a balance test[30]. During the 5STS, patients were asked to rise from and sit down on a standardized chair (height of 48cm) with their hands folded across the chest. The test was performed according to the protocol described by Jones et al.[31]. Patients unable to perform the 5STS were given a score of 60 sec. For the 4MGS, patients were asked to walk a four-meter track at their usual walking speed, two times. Instructions and test settings were in line with the previously described protocol[32]. During the balance test, patients were instructed to maintain three stances (feet placed side by side, semi-tandem, tandem) for 10 sec. Each of the three components was scored from 0 (extreme mobility impairment) to 4 points (no mobility impairment), resulting in a SPPB summary score ranging from 0 to 12 points. Patients were classified as low performance (LP; 0-6 points), moderate performance (MP; 7-9 points), or high performance (HP; 10-12 points)[33].

Functional exercise capacity was measured using the 6MWT performed according to the ERS/ATS[34]. The test was performed once. The absolute distance walked in the test (6MWD) was used for analysis, and compared with normative values[35]. Patients with a 6MWD below 70% of the predicted value were classified as having an impaired functional exercise capacity[36].

To assess HRQOL, the CAT was used and a score of ≥18 indicated high symptom burden[37]. The London chest activity of daily living scale (LCADL) evaluated ADL performance[38]. The modified medical research council (mMRC) dyspnea scale identified patients with significant breathlessness (score ≥2)[39]. Fatigue was measured using the checklist individual strength (CIS)-fatigue subscale, with scores ≥36 indicating severe

fatigue[40]. Symptoms of depression were screened using the patient health questionnaire (PHQ-9) and a score of ≥10 was indicative of relevant depression[41].

Objective PA was measured during the first week after hospital discharge (T1), one month after discharge (T2) and in patients with SCOPD (S) using an accelerometer (Actigraph wGT3X-BT), worn on the right hip for seven consecutive days during waking hours. Data were extracted in 60 sec epochs. Non-wear time was defined as periods of consecutive zero counts for 90 minutes[42]. Days with a minimum of eight hours of wearing time were considered as a valid day and a minimum of four valid days, including minimally one weekend day, was required to be included in the analysis[43]. The outcomes included were step counts, light intensity PA (classified as 100-1951 counts per minute), and moderate-to-vigorous PA (MVPA) (classified as >1952 counts per minute)[44]. The threshold of a low PA was defined as <5000 steps per day[36].

Patients were divided in categories using the quadrant concept, based on functional exercise capacity (6MWD%pred) and PA (daily steps): "can't do, don't do" (6MWD <70%pred; <5000 steps/day), "can do, don't do" (6MWD ≥70%pred; <5000 steps/day), "can't do, do do" (6MWD <70%pred; ≥5000 steps/day), and "can do, do do" (6MWD ≥70%pred; ≥5000 steps/day)[36].

Statistical Analysis

Patients with AECOPD were matched with SCOPD using case-control matching in SPSS 28.0.1.1 for sex, age (match tolerance 10), and FEV_1%pred (match tolerance 15). Analyses were performed using JMP PRO 16.2.0. Data are expressed as mean (SD) or mean difference (SE), median (Q1; Q3) or median difference (Q1; Q3), or percentages. Normality and homoscedasticity were assessed with the Shapiro-and the Brown-Forsythe tests, respectively. Patients lost to follow up and completers at T2 and S were compared

using ANOVA with a post-hoc analysis (Each Pair, Student's t test) or Wilcoxon Each Pair test. A paired t-test or Wilcoxon Signed Rank test was used to compare assessments between T1 and T2. To compare assessments between T1 with S and between T2 with S, and to investigate outcomes in patients that were readmitted or died within six and 1-year, an independent t-test, Wilcoxon test or Welch test was used for continuous data. Categorical data were tested with Fisher's Exact test or Chi-Square test. Analysis of covariance (ANCOVA) or nominal logistic regression were used to adjust for age, sex, FEV_1%pred and previous hospitalizations. Variables presented as percentage of the predicted value were adjusted for FEV_1%pred and previous hospitalizations. A Bonferroni correction was applied for multiple comparisons, with alpha set at 0.05.

Results

A total of 69 patients hospitalized for an AECOPD (69 (9) years; 46% male; FEV_1 41 (16)%pred; median LOS 5 days), and 83 patients with SCOPD (66 (8) years; 51% male, FEV_1 50 (16)%pred) participated in the study. Twenty-five (36%) patients with an AECOPD were lost to follow up, whereas 44 patients with AECOPD completed the follow-up assessments at T2. Patient characteristics of all included patients are presented in Table S1 in the Supplementary. The 25 patients lost to follow-up had lower QF and HGS than the 44 patients that completed the assessments (Table S2 in the Supplementary).

Forty-four patients with AECOPD were matched with 44 patients with SCOPD. Characteristics of the matched patients are presented in Table 1. At T1, patients with AECOPD had mildly decreased to preserved peripheral muscle strength (QF 80%pred; HGS 104%pred), low functional exercise capacity (6MWD 52%pred), were highly symptomatic (75% of patients CAT score ≥18 points; 89% of patients mMRC ≥2; 77% of patients CIS-fatigue ≥36) and were physically inactive (2127 steps/day).

Table 1. Comparison of patient characteristics of matched patients

	Patients with AECOPD	**Patients with SCOPD**	**p-value**
	n = 44	**n = 44**	
Age (yrs)	68 (9)	67 (8)	0.44
Sex (% male)	52	52	1.00
Packyears	38 (24; 48)	36 (21; 52)	0.63
BMI (kg/m^2)	25.7 (5.6)	24.8 (4.3)	0.52
Waist-hip ratio	1.00 (0.08)	0.97 (0.08)	0.07
Lean mass (kg)	43.0 (35.9; 54.2)	43.9 (37.5; 56.2)	0.65
FFMI (kg/m^2)	15.4 (13.9; 18.9)	16.5 (13.8; 18.3)	1.00
CCI (total score)	4 (3; 5)	4 (3; 5)	0.80
Comorbidities: mild/moderate/severe (% of patients)	11/64/25	16/52/32	0.55
GOLD stage: I/II/III/IV (% of patients)	0/23/50/27	0/34/50/16	0.31
FEV_1 (%pred)	39.5 (28.6; 49.3)	45.0 (34.1; 58.0)	0.09
FVC (%pred)	65.6 (51.9 ;74.7)	67.1 (57.4; 79.5)	0.26
LOS (days)	5 (3; 9)	NA	

Data are expressed as mean (SD), median (Q1; Q3), or percentages. Abbreviations: BMI: body mass index; FFMI: fat-free mass index; CCI: Charlson comorbidity index; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; LOS: length of hospital stay; NA: not applicable.

Thirty patients had both functional exercise capacity and PA data. At T1, the majority (84%) of patients were classified as “can’t do, don’t do”; while 13% were classified as “can do, don’t do”; and 3% as “can do, do do”.

Compared to the patients with SCOPD, the 44 patients with AECOPD had significantly worse 4MGS, 6MWD, CAT score, LCADL score, mMRC grade, and CIS-fatigue score at T1 (Table 2).

At T2, a significant improvement was found for the SPPB total score, 4MGS, 6MWD, CAT score, and LCADL score, compared to T1. No other significant changes were found Detailed information is presented in Table 2.

At T2 the distribution over the functional exercise capacity and PA quadrants was: 54% in “can’t do, don’t do”; 33% in “can do, don’t do”; 10% in “can do, do do”; and 3% in “can’t do, do do”. Eleven patients changed between quadrants with the majority changing from “can’t do, don’t do” to “can do, don’t do” quadrant. Nine patients exceeded the minimal clinically important difference of 1100 steps/day[45] (Figure 1).

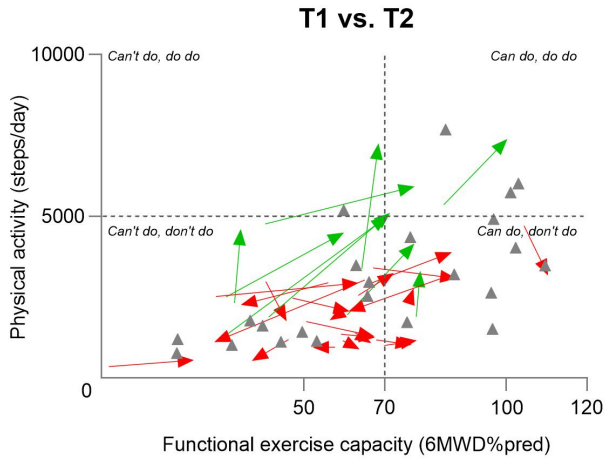

Figure 1. Changes in functional exercise capacity (6MWD%pred) and physical activity (steps/day). *Green arrows indicate patients with improvement in PA ≥1100 steps/day; red arrows indicate patients witch changes in PA <1100 steps/day. Arrow tails show value at T1; arrow heads show value at T2. Grey triangles show values of patients with stable COPD. Abbreviations: 6MWD: six-*

minute walk distance; PA: physical activity; T1: assessment at hospital discharge; T2: assessment one month follow up.

Compared to the patients with SCOPD, the 44 patients with AECOPD only had significantly worse LCADL score at T2 (Table 2). Individual values of patients are presented in Figure S1 in the Supplementary.

Table 2. Comparison of outcomes in matched patients

	Patients with AECOPD			**Patients with SCOPD**	**Adj. p-value**	
	T1 n = 44	T2 n = 44	**Difference**	S n = 44	S vs. T1	S vs. T2
Muscle force						
QF (N)	258 (202; 326)	237 (196; 327)	6 (-41; 43) p=0.84	255 (207; 393)	0.92	0.78
QF (%pred)	80.2 (68.3; 98.9)	80.4 (67.1; 98.3)	0 (-16.0; 13.2) p=0.67	87.7 (70.4; 105)	1.00	0.78
HGS (kg)	28 (22; 38)	30 (24; 38)	1 (-2; 2) p=0.37	30 (24; 46)	0.44	0.82
HGS (%pred)	103.8 (20.7)	101.9 (18.9)	-2.0 (13.7) p=0.34	108.1 (24.1)	0.76	0.38
Functional capacity						
SPPB total score (points)	10 (8; 11)	11 (8; 12)	1 (0; 2) **p<0.001***	10 (9; 12)	0.08	1.00
SPPB: LP/MP/HP (% of patients)	16/30/54	12/23/65	p=0.54	5/30/65	0.36	0.84
5STS (sec)	12.6 (9.8; 20.2)	10.3 (8.6; 19.6)	-0.4 (-3.2; 0.4) p=0.06	11.4 (10.2; 14.3)	0.50	0.94
4MGS (m/sec)	0.71 (0.59; 0.91)	0.85 (0.70; 0.98)	0.11 (-0.01; 0.19)	0.85 (0.71; 1.01)	**0.036***	1.00

			p=0.001*			
6MWD (m)	263 (101)	320 (105)	57 (99) **p=0.001***	357 (146)	**0.002***	0.38
6MWD (%pred)	52.1 (22.6)	65.1 (22.2)	11.0 (18.5) **p<0.001***	75.6 (30.5)	**<0.001***	0.18
6MWD <70%pred (% of patients)	84	54	**p=0.005***	43	**<0.001***	0.46
PROMs						
CAT total score (points)	21 (17; 27)	19 (13; 22)	-4 (-8; 1) **p=0.006***	17 (12; 22)	**0.002***	0.78
CAT total score ≥18 points (% of patients)	75	57	p=0.07	49	**0.022***	0.60
LCADL total score (points)	38 (26; 49)	31 (22; 42)	-4 (-12; 0) **p=0.005***	22 (15; 32)	**<0.001***	**0.004***
mMRC dyspnea (grade)	3 (2; 3)	2 (2; 3)	0 (-1; 1) p=0.13	2 (1; 3)	**0.012***	0.22
mMRC ≥2 (% of patients)	89	84	p=0.53	65	**0.018***	0.08
CIS-fatigue score (points)	46 (37; 50)	44 (33; 52)	-2 (-9; 4) p=0.29	35 (23; 47)	**0.008***	0.06
CIS-fatigue ≥36 (% of patients)	77	66	p=0.24	47	**0.006***	1.00

PHQ-9 score (points)	7 (4; 11)	6 (2; 10)	0 (-4; 2) p=0.30	6 (3; 12)	0.94	1.00
PHQ-9 score ≥10 (% of patients)	30	27	p=0.81	30	1.00	1.00
Physical activity	n = 36	n = 36		n = 23		
Steps (per day)	2127 (1174; 2940)	2063 (1090; 3745)	-34 (-386; 1116) p=0.23	2625 (1420; 4348)	0.20	0.60
Light intensity PA (min/day)	177 (74)	175 (83)	-2 (55) p=0.82	182 (69)	1.00	1.00
MVPA (min/day)	1.36 (0.57; 4.79)	1.43 (0.43; 4.68)	0.12 (-1.18; 2.18) p=0.43	2.29 (0.57; 7.43)	0.50	0.58

Data are expressed as mean (SD) or mean difference (SE), median (Q1; Q3) or median difference (Q1; Q3), or percentages. Abbreviations: T1: assessment at hospital discharge; T2: assessment one month after discharge; S: assessment in patients with SCOPD; QF: quadriceps force; HGS: hand grip strength; SPPB: short physical performance battery; LP: low performance; MP: medium performance; HP: high performance; 5STS: five-repetition sit-to-stand test; 4MGS: four-meter gait speed test; 6MWD: six-minute walk distance; PROMs: patient-reported outcome measures; CAT: COPD assessment test; LCADL: London chest activity of daily living; mMRC: modified medical research council; CIS: checklist individual strength; PHQ: patient health questionnaire; PA: physical activity; MVPA: moderate-to-vigorous PA. Indicates a significant difference after Bonferroni correction.*

For the exploration whether peripheral muscle strength, functional capacity, symptoms, and HRQOL at hospital discharge could discriminate patients' risk for exacerbation-related readmission or mortality, we used data of 69 patients who had undergone the assessment at hospital discharge. Twenty-three out of 69 patients with an AECOPD were readmitted or died within six months after hospital discharge. These patients had a significantly worse SPPB total score, SPPB classification and 5STS at T1, than the patients that had no readmission or died (Table 3). After controlling for age, sex, FEV_1%pred and previous hospitalizations, SPPB classification and 5STS remained significant (Figure 2).

Table 3. Comparison of outcomes between patients that were readmitted/death within six months

	Not readmitted/death	**Readmitted/death**	**p-value**
	n = 46	**n = 23**	
Age (yrs)	68 (9)	71 (8)	0.15
Sex (% male)	41	57	0.31
Packyears	36 (22)	43 (29)	0.30
BMI (kg/m^2)	26.1 (5.5)	23.7 (5.5)	0.10
Waist-hip ratio	0.99 (0.09)	0.99 (0.09)	0.76
Lean mass (kg)	41.6 (35.4; 51.6)	45.1 (35.5; 49.6)	0.99
FFMI (kg/m^2)	16.4 (3.5)	15.6 (3.3)	0.38
CCI (total score)	4 (3; 5)	4 (3; 5)	0.83
Comorbidities: mild/moderate/severe (% of patients)	9/63/28	9/65/26	0.98
GOLD stage: I/II/III/IV (% of patients)	2/24/50/24	0/13/48/39	0.40
FEV_1 (%pred)	41.5 (30.4; 52.2)	33.9 (28.1; 45.3)	0.20
FVC (%pred)	65.5 (51.1; 74.6)	64.0 (51.7; 72.6)	0.48
LOS (days)	5 (4; 8)	5 (4; 8)	0.71

Hospitalization in previous 12m (% of patients)	35	57	0.12
Time to event (days)	NA	66 (26; 124)	
Muscle force			
QF (N)	238 (197; 308)	205 (162; 298)	0.13
QF (%pred)	85.2 (24.0)	72.8 (28.0)	0.06
HGS (kg)	29 (9)	28 (10)	0.75
HGS (%pred)	102.7 (19.6)	92.8 (23.7)	0.07
Functional capacity			
SPPB total score (points)	10 (8; 11)	8 (6; 9)	**0.031**
SPPB: LP/MP/HP (% of patients)	20/24/56	26/52/22	**0.019**
5STS (sec)	12.6 (9.7; 16.5)	17.8 (13.2; 60)	**0.002**
4MGS (m/sec)	0.70 (0.24)	0.69 (0.25)	0.76
6MWD (m)	243 (115)	226 (119)	0.55
6MWD (%pred)	51.3 (24.0)	46.4 (24.9)	0.44
6MWD <70%pred (% of patients)	82	87	0.74
PROMs			
CAT total score (points)	22 (7)	22 (7)	0.97
CAT total score ≥18 points (% of patients)	74	70	0.78
LCADL total score (points)	36 (26; 51)	41 (28; 51)	0.64
mMRC dyspnea (grade)	3 (2; 4)	3 (2; 4)	0.95
mMRC ≥2 (% of patients)	87	87	1.00
CIS-fatigue score (points)	48 (42; 54)	40 (31; 51)	0.05
CIS-fatigue ≥36 (% of patients)	85	65	0.12
PHQ-9 score (points)	7 (4; 11)	6 (3; 11)	0.39
PHQ-9 score ≥10 (% of patients)	33	35	1.00
Physical activity	n = 38	n = 15	

Steps (per day)	2309 (959; 3014)	1562 (951; 2080)	0.16
Light intensity PA (min/day)	189 (91)	142 (55)	0.07
MVPA (min/day)	1.09 (0.57; 4.14)	0.57 (0.14; 1.43)	0.11

Data are expressed as mean (SD), median (Q1; Q3), or percentages. Abbreviations: BMI: body mass index; FFMI: fat-free mass index; CCI: Charlson comorbidity index; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; LOS: length of hospital stay; NA: not applicable; QF: quadriceps force; HGS: hand grip strength; SPPB: short physical performance battery; LP: low performance; MP: medium performance; HP: high performance; 5STS: five-repetition sit-to-stand test; 4MGS: four-meter gait speed test; 6MWD: six-minute walk distance; PROMs: patient-reported outcome measures; CAT: COPD assessment test; LCADL: London chest activity of daily living; mMRC: modified medical research council; CIS: checklist individual strength; PHQ: patient health questionnaire; PA: physical activity; MVPA: moderate-to-vigorous PA.

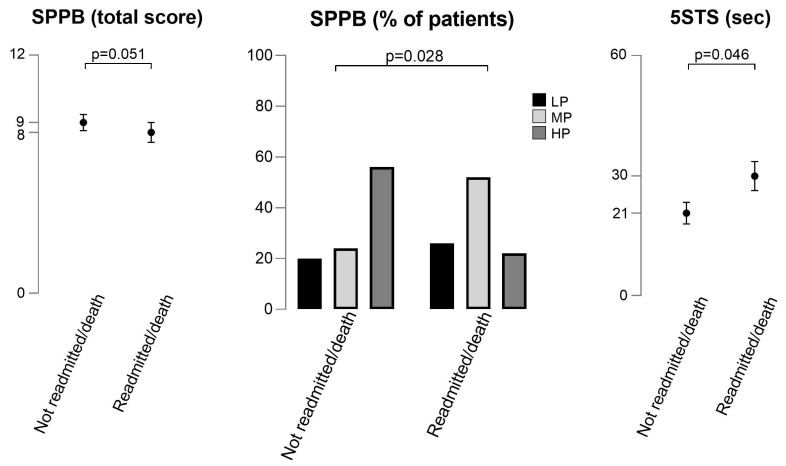

Figure 2. Comparisons of outcomes between readmitted/death patients and without readmission/death within six months. *Adjusted means and standard error reported from ANCOVA, after adjusting for covariates (age, sex, FEV1%pred and previous hospitalizations). Abbreviations: ANCOVA: analysis of covariance; SPPB: short physical performance battery; LP: low performance (SPPB score 0-6); MP: medium performance (SPPB score 7-9); HP: high performance (SPPB score 11-12); 5STS: five-repetition sit-to-stand test.*

At 1-year follow-up, 42 patients were readmitted or died and similar results to the 6 months analysis were found (Table S3 in the Supplementary).

Discussion

This study found that: i) patients during a severe AECOPD show worse functional capacity, HRQOL, performance of ADL and symptoms of dyspnea and fatigue compared to patients

with SCOPD; ii) one month after a severe AECOPD, there is a significant improvement in functional capacity, performance of ADL, and HRQOL, however, patients with severe AECOPD still score worse on the performance of ADL when compared to patients with SCOPD; iii) patients that were readmitted or died within six months have significantly worse scores on the SPPB and 5STS at hospital discharge, independently of age, sex, FEV_1%pred and number of previous hospitalizations.

Contrarily to the findings of Spruit et al.[3], we found that during a severe AECOPD peripheral muscle strength was not different than in patients with SCOPD. Moreover, no significant improvement was found in peripheral muscle strength at one month follow-up, as in the study of Pitta et al.[2]. In contrast, Torres-Sánchez et al. observed a persistent decrease in QF and HGS from hospital admission to one month after discharge[4]. It is worth nothing that our sample had a relatively high peripheral muscle strength at hospital discharge and the standard care provided to our patients included physiotherapy sessions during hospitalization.

Previous studies reported a significant increase in walking time at one month follow-up[2], and an improvement in active time and daily steps at three months follow-up, compared to PA during hospitalization[7]. Due to severe illness and worsening symptoms during a severe AECOPD, patients typically have low levels of PA during hospitalization. To account for this, we assessed PA in the first week following hospitalization. The distribution of the patients over the functional exercise capacity and PA quadrants showed that after one month most patients improved from the “can’t do, don’t do” quadrant to the “can do, don’t do”. Thus, these patients improved in functional exercise capacity but are not physically active. Therefore, PA coaching to primarily enhance PA levels can be a valuable intervention to choose[46]. In addition, according to the step-based classification of PA, both

our patients after a severe AECOPD and patients with SCOPD are markedly inactive with a medium of 2000 and 2600 steps per day, respectively[47]. This is lower than other patients with SCOPD that performed an average of 4500 steps per day[48]. Our sample of SCOPD had a worse FEV_1%pred and exercise capacity compared to previous studies and were highly symptomatic (with 65% of the sample having an mMRC ≥2) which are all determinants of PA[49].

Our findings are consistent with previous research that has shown a recovery in functional exercise capacity and HRQOL one month after a severe AECOPD[2, 5, 50]. One month after experiencing a severe AECOPD, patients' health status was similar to those with SCOPD, indicating that patients tend to recover effectively following a single AECOPD. However, patients' ability to perform ADL did not fully recover. Patients with COPD have been shown to experience increased metabolic demands and higher levels of ventilation during the performance of domestic ADLs. This can lead to a greater perception of symptoms, including dyspnea[51].

Our study showed that the performance on the SPPB and 5STS at hospital discharge for a severe AECOPD is independently related to exacerbation-related readmissions and mortality within six months. Numerous predictive factors for hospital readmissions and mortality among patients with COPD have been identified, including prior exacerbations, comorbidities and more severe COPD[16]. To our knowledge, only a limited number of studies investigated measures of health status during a severe AECOPD and the association with readmissions or mortality. Previous studies showed that frailty on hospital admission, 4MGS on hospital discharge, and the CAT on discharge were associated with readmissions[17-19]. Furthermore, regular PA had a strong association with a nearly 50% decrease in the risk of readmission[52].

Our findings highlight the importance of assessing patients during a severe AECOPD in the hospital setting. The SPPB and 5STS are simple assessments that can be easily administered at hospital discharge. It can facilitate early identification of patients at risk for readmission or death and can guide the implementation of tailored interventions to treat these traits. Early supervised pulmonary rehabilitation can decrease the risk of exacerbations-related readmission or mortality, while leading to substantial and clinically meaningful improvements in functional capacity and HRQOL[53]. Therefore, assessing patients' functional status during hospitalization should be an integral part of the care for patients with COPD.

It is a clear strength of this study that patients with severe AECOPD were matched with patients with SCOPD for relevant covariates. The same assessor performed all measurements, suggesting high reliability of the measurements between patients.

Study limitations

Firstly, due to our study design, it remains uncertain to what extent patients with a severe AECOPD had impairments in physical status before hospitalization. Secondly, after finalization of our study, the ROME proposal suggested an alternative classification of exacerbation severity[54]. However, we have not evaluated the specific parameters utilized in the ROME classification, leaving us uncertain about the prevalence of mild or moderate exacerbations among our patients. Thirdly, we pragmatically chose to use six weeks as a time window to define stable COPD. Yet, health recovery at six weeks may not be completed in a selection of patients. Furthermore, although it is recommended to perform the 6MWT twice in patients with COPD, we only assessed it once, as patients' tolerability was still very limited at the time of hospital discharge. In addition, a score of 60 sec was given to patients unable to perform the 5STS, which can be an underestimation of the

performance. Lastly, due to the small sample size, it was not possible to develop prediction models as a minimum of 20 events per variable is recommended[55].

Conclusions

This study showed that patients during a severe AECOPD experience a significant impairment in functional capacity, HRQOL and symptoms of dyspnea and fatigue compared to patients with SCOPD. Patients after a severe AECOPD showed an improvement in functional capacity and HRQOL one month after hospital discharge. While the distribution of patients across functional exercise capacity and PA quadrants improved, patients still scored worse on the performance of ADL when compared to patients with SCOPD. Moreover, patients who were readmitted or died within six months had significantly worse scores on functional tests at hospital discharge, independently of age, sex, FEV_1%pred and previous hospitalizations. Our findings indicate that simple measures of functional capacity on hospital discharge can be predictive for exacerbation-related readmissions and mortality.

Acknowledgments

The data were partially presented as poster at the European Respiratory Society congress that was held online in 2020 and 2021.

Ana Machado's work was supported by Bijzonder Onderzoeksfonds – Bilaterale Samenwerking (BOF BILA) from Hasselt University (BOF BILA reference: DOC/SCHL-BOSE/190/522). Fabiano Francisco de Lima's work was supported by the São Paulo Research Foundation – FAPESP (Grant: 2019/10744-3). The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

The authors would like to acknowledge the support of all the patients who agreed to participate in this study and their families. We also want to thank the institution and staff involved in the recruitment process.

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