Phenotypic Characteristics of Patients With Chronic Obstructive Pulmonary Disease After Stratification for the Short Physical Performance Battery Summary Score

Peer-reviewed author version

Stoffels, Anouk A.F.; DE BRANDT, Jana; Meys, Roy; van Hees, Hieronymus W.H.; Vaes, Anouk W.; Klijn, Peter; BURTIN, Chris; Franssen, Frits M.E.; van den Borst, Bram; Sillen, Maurice J.H.; Wouters, Emiel F.M.; Janssen, Daisy J.A. & SPRUIT, Martijn A. (2020) Phenotypic Characteristics of Patients With Chronic Obstructive Pulmonary Disease After Stratification for the Short Physical Performance Battery Summary Score. In: Archives of physical medicine and rehabilitation, 101(11), p. 1887-1897.

DOI: 10.1016/j.apmr.2020.05.011
Handle: http://hdl.handle.net/1942/32003

TITLE: Phenotypic characteristics of patients with Chronic Obstructive Pulmonary Disease after stratification for the Short Physical Performance Battery summary score.

RUNNING HEAD: Mobility and balance in COPD.

AUTHORS:

Anouk A.F. Stoffels, MSc,[a,b*] Jana De Brandt, MSc, [c*] Roy Meys, MSc, [b] Hieronymus W.H. van Hees, PhD, [a] Anouk W. Vaes, PhD, [b] Peter Klijn, PhD, [d, e] Chris Burtin, PhD, [c] Frits M.E. Franssen, MD, PhD, [b, f] Bram van den Borst, MD, PhD, [a] Maurice J.H. Sillen, PhD, [b] Emiel F.M. Wouters, MD, PhD, [b] Daisy J.A. Janssen, MD, PhD, [b,g] Martijn A. Spruit, PhD [b,c, f] on behalf of the BASES consortium

AFFILIATIONS:

From the [a]Department of Pulmonary Diseases, Dekkerswald Radboudumc, Nijmegen, the Netherlands; [b]Department of Research and Development, CIRO, Horn, the Netherlands; [c]Reval Rehabilitation Research – Biomedical Research Institute, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium; [d]Department of Pulmonology, Merem pulmonary rehabilitation centre, Hilversum, the Netherlands; [e]Department of Pulmonary, Amsterdam University medical Centre, Amsterdam, the Netherlands; [f]Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht, The Netherlands; and [g]Department of Health Services Research, CAPHRI School for Public Health and Primary Care, Faculty of Health Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands.

*Drs Stoffels and De Brandt contributed equally to the current work.

The BASES consortium is financially supported by Lung Foundation, the Netherlands (#5.1.18.232). Drs. Jana De Brandt is funded by the Flemish government. The Research of FWO Aspirant Jana De Brandt is sponsored by FWO-grant (#11B4718N). Dr. F.M.E. Franssen is supported by grants and personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from GlaxoSmithKline, grants and personal fees from Novartis, personal fees from TEVA, outside the submitted work. Dr. B. van den Borst is supported by personal lecture fees from AstraZeneca and Boehringer Ingelheim bv. Drs. A.A.F. Stoffels, J. De Brandt and R. Meys, Dr. H.W.H. van Hees, A.W. Vaes, P. Klijn, M.J.H. Sillen and D.J.A. Janssen and Prof. Dr. C. Burtin, E.F.M. Wouters and M.A. Spruit declare that they do not have a conflict of interest.

ACKNOWLEDGEMENTS

We would like to thank Prof. Dr. Wim Derave (Ghent University) for his input and collaboration within the BASES-consortium, in the context of which the current manuscript was written.

CORRESPONDENCE TO: Anouk A.F. Stoffels, MSc, Department of Pulmonary diseases, Dekkerswald Radboudumc, Nijmegen, the Netherlands; e-mail: anouk.stoffels@radboudumc.nl.

TITLE: Phenotypic characteristics of patients with Chronic Obstructive Pulmonary Disease after stratification for the Short Physical Performance Battery summary score.

ABSTRACT

Objective: To assess the phenotypic characteristics of patients with Chronic Obstructive Pulmonary Disease (COPD) after stratification for Short Physical Performance Battery (SPPB) summary scores and to determine phenotypic characteristics of the SPPB summary score at the start of pulmonary rehabilitation (PR).

Design: Retrospective, cross-sectional.

Setting: Baseline assessment for PR program.

Participants: 900 patients with COPD (age 65±8 years, 52% male, FEV_1 43 (31-62)% predicted).

Interventions: Not applicable.

Main outcome measure: Patients were stratified according to their SPPB summary scores into low-performance (LP), moderate-performance (MP) or high-performance (HP). Furthermore, lung function, arterial blood gases, body composition, physical capacity, lower-limb muscle strength and endurance and symptoms of anxiety and depression were assessed.

Results: Generally, physical capacity and muscle function were lower and scores for symptoms of anxiety and depression were higher in LP patients compared to MP and HP patients (all values, $p<0.01$). However, 25% of HP patients with COPD scored high on symptoms of anxiety and/or depression (≥10 points) and HP patients still had on average an impaired physical capacity (median 6 minute walk test distance (6MWD) distance of 68% predicted). Furthermore, age and 6MWD (meters) were the only independent predictors in a multivariate regression model, explaining 29% of the variance in SPPB summary score.

Conclusions: In COPD, LP patients have the worst physical and emotional functioning. However, HP patients can still exhibit physical and emotional impairments. As the explained variance in SPPB summary score is low, SPPB should not be considered as a test to discriminate between patients with COPD with a low or preserved physical capacity and emotional status.

Keywords: Pulmonary Disease, Chronic Obstructive; Anxiety; Depression; Postural Balance; Physical Fitness; Physical Functional Performance

ABBREVIATIONS: CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; CWRT = constant work rate test; FFM = fat free mass; HP = high-performance; LP = low-performance; MP = moderate-performance; PR = pulmonary rehabilitation; SPPB = short physical performance battery; Wmax = maximal workload; 4MGS = four meter gait speed; 5STS = five-repetition sit-to-stand; 6MWT = 6 minute walk test

Airflow limitation is a cardinal feature of patients with chronic obstructive pulmonary disease (COPD)[1]. Additionally, evidence shows extra-pulmonary consequences like impairment in balance control and mobility[2-4], which are mainly caused by lower-limb muscle weakness[5]. Mobility and balance deficits may induce more falls[6] and provoke difficulties in performing activities of daily living safely and independently[7-9]. Furthermore, it can be the first sign of further functional decline and, therefore, it is important to identify patients with COPD with reduced balance and mobility to prevent disability in activities of daily living[10-12].

The Short Physical Performance Battery (SPPB) is a commonly used, simple and quick performance measure to evaluate mobility and balance, and is recommended in older patients by the European Medicines Agency[13]. Furthermore, the SPPB score has prognostic value as it might identify a subsequent decline in activities of daily living status, rehospitalization and mortality in elderly, including COPD, after hospital discharge [14]. Individuals can be grouped based on their SPPB summary score into a low-performance (LP), a moderate-performance (MP), and a high-performance (HP) group[11]. Patel *et al.* and Mohan *et al.* were the first to evaluate the physical phenotypic characteristics of the abovementioned SPPB performance groups in patients with COPD[15,16]. Indeed, LP patients with COPD had more functional impairment, loss of muscle mass and structural muscle abnormality compared to HP patients[15]. Furthermore, a longer 6-minute walk test (6MWT) distance, greater quadriceps maximal voluntary contraction strength, lower age, self-reported hypertension and dyspnea, and being married decreased the likelihood of being in the LP group[16]. These data need further corroboration in a non-UK-based settings, as geographic differences in clinical characteristics and management of COPD are known[17].

Symptoms of anxiety and depression are also common in patients with COPD[18], and significantly correlate with mobility and balance in healthy elderly[19,20]. However, it remains unclear whether and to what extent a similar pattern occurs in emotional status (i.e. symptoms

of anxiety and depression) after stratification for SPPB summary scores. Furthermore, it is unclear whether and to what extent physical and emotional impairment is also present in HP patients. This is important to know, as HP patients may give a first impression that they have a normal physical and emotional functioning.

The current study aimed to assess phenotypic characteristics of patients with COPD after stratification for SPPB summary scores and to investigate which phenotypic characteristics determine the SPPB summary score at the start of pulmonary rehabilitation (PR).

METHODS

This retrospective analysis of an observational, cross-sectional study included anonymized data of 953 patients, evaluated during baseline assessment of a comprehensive PR between January 2016 and January 2018 in a specialized PR clinic. All measurements were performed by a highly-trained and skilled team of biomedical engineers and laboratory technicians. The medical ethical committee informed the authors that the Medical Research Involving Human Subjects Act (WMO) does not apply to this retrospective study using de-identified, pre-existing data and that an official approval of this study by our committee is not required (METC 2018-0541). This study was conformed to the principles of the Declaration of Helsinke.

Inclusion criteria were a primary diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[1] and complete data available regarding SPPB. This latter may result in selection bias. Furthermore, patients were excluded from this analysis if they participated in the PR program for the second time during the inclusion period and/or if they were younger than 40 years of age.

Baseline characteristics

Age, gender, weight, body mass index, the degree of dyspnea (modified Medical Research Council; mMRC[21]), health status (COPD Assessment Test; CAT[22]), exacerbation and all-cause hospitalization frequency in the last 12 months, Charlson Comorbidity Index[23] and use of long-term oxygen therapy were systematically assessed. A mMRC dyspnea grade of ≥ 2[1], CAT score of ≥ 10 and ≥ 18 points[24,25] were used to classify patients as highly symptomatic.

Short Physical Performance Battery

Patients performed the SPPB according to the National Institute on Aging protocol[26]. Firstly, the standing balance measurement was performed in which the patient is required to maintain three stances for 10 seconds (feet placed side-by-side, semi-tandem and tandem). The four meter gait speed (4MGS) test assessed the time needed to walk four meter at habitual gait speed from a standing position. This test was performed twice and the best time was used to score the test. In the five-repetition sit-to-stand test (5STS), the time was measured to complete five sit-to-stand maneuvers as quick as possible with arms folded in front of their chest.

Each component was scored from 0 (mobility impairment) to 4 points (no mobility impairment), resulting in a SPPB summary score ranging from 0 to 12 points. The scoring system can be found in e-Table 1. Additionally, patients were classified as LP (0-6 points), MP (7-9 points) or HP (10-12 points)[11].

Phenotypic characteristics

The GOLD classification[27] and arterial blood gases were evaluated. Furthermore, spirometry, static lung volumes and transfer factor for carbon monoxide by single-breath method were executed according to the European Respiratory Society recommendations[28] (MasterScreen PFT/ Body[a]).

Waist circumference was measured and fat-free mass (FFM) and T-scores of the hip (trochanter) and lumbar spine (L2-L4) were evaluated using dual energy x-ray absorptiometry (DEXA) (Lunar iDXA[b])[29]. The FFM index was calculated by dividing FFM by height*height. The reference values of International Diabetes Federation were used for waist circumference[30]. Physical capacity was assessed using the 6 minute walk test (6MWT), maximal incremental cardiopulmonary exercise test and constant work rate test (CWRT). The 6MWT was performed indoor, on a flat and straight walking course of 30 meters, following the ERS/ATS guidelines[31,32]. Reference values from Troosters *et al.*[33] were used and a cutoff value of 350 meters according to Spruit *et al*. was applied to predict respiratory related hospitalization[34]. The maximal cardiopulmonary exercise test was performed on an electromagnetically braked cycle ergometer (Ergoselect[c]) according to the recommended guidelines[35]. The maximal workload (Wmax) was calculated as a percentage of the predicted value[36]. The CWRT was performed on the same ergometer at 75% of the predetermined Wmax. Patients cycled until symptom limitation or until pedaling rate decreased under 60 rpm (with a maximum of 20 minutes)[37].

Isotonic muscle strength was measured by one repetition-maximum leg press, leg extension, upper back and chest press using standard weight training apparatus (Technogym[d]) and was corrected for the FFM of the legs or arms. Isokinetic quadriceps peak torque (Nm) and endurance (total amount of delivered work, J) of the right leg were assessed with a computerized dynamometer (Biodex Multi-joint System 3[e]) and also corrected for the FFM of the legs. Patients performed a set of 30 repetitions at an angular speed of 90°/s.

The Hospital Anxiety and Depression Scale was used as a screening tool to detect symptoms of anxiety and depression. A cutoff point of >10 points was used for each domain[38].

Statistical analyses

Statistical analyses were performed using SPSS, version 25.0[f]. Descriptive data were presented as mean ± SD, median (interquartile) or percentages, as appropriate. Differences between included and excluded patients were tested by an unpaired t-test or Mann-Whitney U test as appropriate. Differences between LP, MP and HP groups were tested by one-way analysis of variance (ANOVA) or Kruskal-Wallis test as appropriate. Categorical data were tested with a Chi-square test. When a statistically significant difference was obtained, a pairwise post-hoc test was performed and Bonferroni post-hoc testing was applied to correct for multiple comparison. Due to the many statistical tests performed in this study, a p-value <0.01 was considered significant.

Univariate and multivariate regression models were used to assess the associations between the phenotypic characteristics and the SPPB summary score, both using the ENTER method. Explanatory variables, based on univariate models, with a p-value <0.20 and not highly correlated with another variable of interest were used to build the multivariate linear regression model. Variables with a p-value <0.05 were considered as independent predictors of SPPB summary score.

RESULTS

Nine hundred of the 953 patients with COPD were analysed. Reasons for exclusion were absence of SPPB data (n=1), being younger than 40 years (n=5), participating in the PR program for the second time (n=20), and erroneous download from the database (n=27). Differences between included and excluded patients are depicted in e-Table 2.

Clinical characteristics

The included patients had a mean age of 65±8 years, 52% were male, 63% of the patients experienced ≥2 exacerbations <12 months and 44% experienced ≥1 hospitalization <12 months.

Furthermore, 87% was highly symptomatic (mMRC ≥2), and 45% of patients were multimorbid. A 6MWT distance <350 meters was found in 38% of patient and the median time-to-exhaustion on the CWRT was 230 (165-334) seconds. The isokinetic quadriceps peak torque was 61±19% of predicted and the total work was 1487±632 J. Furthermore, 30% and 31% of the patients with COPD had a score ≥10 points on symptoms for anxiety and depression, respectively. All details can be found in Tables 1 and 2.

******* Tables 1 and 2 near here *******

Short Physical Performance Battery

The SPPB summary score of the whole group was 9 (8-10) points. Ninety-eight patients (11%) had LP scores, 393 patients (44%) had MP scores, and 409 patients (45%) had HP scores. The frequency distribution of the SPPB summary score can be found in e-Figure 1.

The balance standing test score differed significantly among the levels of performance, with the LP group performing the worst ($p<0.001$). Furthermore, the LP group executed the 4MGS and 5STS (after excluding patients (n=70; whereof n=54 in LP group) who were not able to perform the 5STS test), the slowest in comparison to the MP group and the HP group ($p<0.001$, Table 3). The frequency distribution of the SPPB components can be found in Figure 1.

******* Figure 1 and Table 3 near here *******

Characteristics after stratification for SPPB

According to stratification for SPPB score, patients with LP scores were older, experienced more dyspnoea, had a lower health status, had a higher percentage of ≥2 exacerbations and ≥1 hospitalizations in the past 12 months and were more likely long-term oxygen therapy users

than the MP and HP groups. Furthermore, 89% of the LP group and 79% of the MP group scored ≥18 points on the CAT which was higher than the HP (68%) group (p<0.001, Table 1). The LP group had a higher GOLD classification and lower FEV_1 % predicted than MP and HP. The LP group showed lower arterial oxygen pressures and higher carbon dioxide pressures than the MP and HP group. The FFM of arms was lower (p=0.003) in the LP group in comparison to the HP group. The proportion of patients with a normal bone mineral density, osteopenia and osteoporosis was comparable between groups (Table 2).

Physical capacity was lowest in the LP group and highest in the HP group (all values p<0.001). In the LP group had 96% of the patients a 6MWT distance <350 meters[34]. This proportion was lower in the MP group (46%) and HP group (16%). Furthermore, the LP group had on average a lower CWRT time-to-exhaustion than the MP and HP group.

The muscle strength and endurance differed among the groups, with the LP group performing the worst, even after correcting for FFM (all values p<0.001, Table 2). Additionally, the LP group scored higher on symptoms of anxiety and depression and had a higher proportion of patients scoring ≥10 points on anxiety (46%) and depression (52%) in comparison to the MP and/or HP groups (all values, p<0.001, Table 2).

Even though, the HP group scored better on physical capacity and emotional status, still 8% of patients needed ≥1 stop during the 6MWT, the median Wmax on the maximal incremental cycle test was 54 (40-71)% of the predicted value and one-fourth of the patients had symptoms of anxiety and/or depression (Table 2).

Determinants of SPPB summary score

Almost all absolute phenotypic characteristics were univariate predictors of SPPB summary score (e-Table 3). Explanatory predictors without a high correlation with another variable of interest were entered in a multivariate linear regression model. This model (F(15,508)=13.673,

p<0.001) explained 29% of the variance in SPPB summary score. Age (B=-0.085, p=0.043) and 6MWT (meters) (B=0.454, p<0.001) were the only significant independent predictors (e-Table 4).

DISCUSSION

The present study shows that the phenotypic characteristics differ between patients with COPD after stratification for SPPB summary scores, with the worst values reported in the LP group. Moreover, patients with a SPPB summary score ≥10 points (HP group) can still exhibit impairments in physical capacity and emotional traits. Age and 6MWT (meters) were the only independent predictors in a multivariate regression model, explaining only 29% of the variance of SPPB summary score.

In this study, 55% of the COPD patients scored <10 points on the SPPB at the pre-PR assessment, indicating a reduced functional capacity and increased risk of developing mobility and/or activities of daily living[11,39].

The LP group performed worse on all SPPB subtests in comparison to the MP and HP group. Furthermore, a lower quadriceps strength and 6MWT is reported in the LP group, this may, at least partly, explain the reduced SPPB performance. Recently, associations between the isometric quadriceps muscle strength, 6MWT, SPPB summary score and SPPB subtests scores have been reported which confirms our results[15,16,40].

Patients performed the 5STS worst of all SPPB subtests, which is consistent with the study of Larsson *et al.*[41]. Bernabeau-Mora *et al.* reported only an association between CAT and the 5STS (partial R^2=0.073, p<0.001) in the multivariable regression model, and not with the other subtests. This supports the concept that the 5STS is a better screening tool for poor health

status[40] than the other SPPB subtests. One possible reason is that ventilatory demands during 5STS are higher than during the standing balance tests and 4MGS[41,42] and is therefore more sensitive in obtaining differences between the performance group.

Overall, the phenotypic characteristics are worse in the LP group in comparison to the MP and HP group. The reduced lung function in the LP group is in accordance with other studies as an impaired lung function is known to contribute to mobility and balance deficits[13]. Furthermore, Eisner *et al.* suggested that lung functional impairment may contribute to muscle weakness in the upper and lower extremity of COPD patients, which is consistent with systemic involvement from the disease[43].

The body composition, physical capacity and quadriceps muscle strength and endurance were worse in the LP group, which is consistent with the studies of Patel *et al.* and Mohan *et al.*[15,16]. They reported lower quadriceps strength and bulk, physical activity, exercise capacity and performance in the LP and/or MP group in comparison to the HP group[15] and decreased odds of being in a lower category for the SPPB summary score for a longer 6MWT and greater quadriceps maximal voluntary contraction strength[16]. Additionally, a decrease in FFM is correlated with a decline in postural stability and mobility[44,45]. A possible explanation can be that a reduction in muscle mass is related to a loss in muscle function and strength[46], which are both necessary to maintain balance and mobility and execute functional activities[7,47-49].

The emotional status differed between the three performance groups with the highest prevalence of anxiety and depression symptoms present in the LP group. The difference in anxiety between LP group and MP and HP group and in depression between LP and HP group reaches the minimal important difference[50]. Other studies have already reported associations between anxiety, depression and mobility and balance which might explain the higher prevalence of symptoms of anxiety and depression in the LP group[19,20,51]. A suggestion could be the increased

risk of falls due to the inattention to potential environmental hazards in people with depression[52] or due to greater fear of falls in patients exhibiting anxiety or depression[9]. Contradictory, physical activity is known to improve one's self-esteem and reduce depressive and anxiety symptoms and less active patients may therefore develop more often emotional impairment[53]. Future studies are needed to determine the exact causal relationship and evaluate emotional status more extensively.

Even though the values for phenotypic characteristics were the highest in the HP group, still 16% of the patients had a 6MWT distance <350 meters, which is a risk factor for respiratory related hospitalization[34]. Additionally, one out of four HP patients experienced symptoms of anxiety and/or depression. These results indicate that even the HP patients with COPD at the start of PR can exhibit impairments in physical capacity and emotional status which cannot be determined by the SPPB alone. This emphasizes the importance of additional assessment in patients with COPD during baseline assessment in PR as SPPB alone cannot identify all patients at risk and/or in need for PR.

Many phenotypic factors were univariate predictors of the SPPB summary score, but age and 6MWT were the only independent predictors in a multivariate regression model. This finding is consistent with the literature[15,16,40] and highlights the importance of age and physical capacity in maintaining balance and mobility.

Methodological considerations

The strengths of the study are the large sample size of COPD patients with well-defined and well-characterized data which provides for the first time an extensive overview on phenotypic characteristics per SPPB performance of patients with COPD in a non-UK PR setting. The study

confirms the high prevalence of physical and emotional impairment among all performance groups.

Obviously, the cross-sectional design prevents us from establishing causality between patients' phenotypic factors and mobility and balance. Secondly, the data is obtained retrospectively from one location, which reduces the generalizability of the results. Current studies also need corroboration in the primary care setting.

CONCLUSIONS

In COPD, patients with a LP SPPB summary score have the worst physical and emotional functioning. However, HP patients can still exhibit physical and emotional impairments. As the explained variance in SPPB summary score is low, the SPPB should not be considered as a screening tool to discriminate between COPD patients with a low or preserved physical capacity and emotional status.

REFERENCES

1. Lopez-Campos JL, Soler-Cataluna JJ, Miravitlles M. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2019 Report: Future Challenges. *Arch Bronconeumol.* 2020;56(2):65-67.
2. Wouters EF. Chronic obstructive pulmonary disease. 5: systemic effects of COPD. *Thorax.* 2002;57(12):1067-1070.
3. Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* 2008;5(4):549-555.
4. Vanfleteren L, Spruit MA, Wouters EFM, Franssen FME. Management of chronic obstructive pulmonary disease beyond the lungs. *Lancet Respir Med.* 2016;4(11):911-924.
5. Ozge A, Atis S, Sevim S. Subclinical peripheral neuropathy associated with chronic obstructive pulmonary disease. *Electromyogr Clin Neurophysiol.* 2001;41(3):185-191.
6. Beauchamp MK, Hill K, Goldstein RS, Janaudis-Ferreira T, Brooks D. Impairments in balance discriminate fallers from non-fallers in COPD. *Respir Med.* 2009;103(12):1885-1891.
7. Katz PP, Gregorich S, Eisner M, et al. Disability in valued life activities among individuals with COPD and other respiratory conditions. *J Cardiopulm Rehabil Prev.* 2010;30(2):126-136.
8. Bernabeu-Mora R, Medina-Mirapeix F, Llamazares-Herran E, Garcia-Guillamon G, Gimenez-Gimenez LM, Sanchez-Nieto JM. The Short Physical Performance Battery is a discriminative tool for identifying patients with COPD at risk of disability. *Int J Chron Obstruct Pulmon Dis.* 2015;10:2619-2626.
9. Crisan AF, Oancea C, Timar B, Fira-Mladinescu O, Tudorache V. Balance impairment in patients with COPD. *PLoS One.* 2015;10(3):e0120573.
10. Eisner MD, Iribarren C, Blanc PD, et al. Development of disability in chronic obstructive pulmonary disease: beyond lung function. *Thorax.* 2011;66(2):108-114.
11. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med.* 1995;332(9):556-561.
12. Studenski S, Perera S, Wallace D, et al. Physical performance measures in the clinical setting. *J Am Geriatr Soc.* 2003;51(3):314-322.
13. Agency EM. Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials. *EMA/CHMP/778709/2015.* 2018.
14. Volpato S, Cavalieri M, Sioulis F, et al. Predictive value of the Short Physical Performance Battery following hospitalization in older patients. *J Gerontol A Biol Sci Med Sci.* 2011;66(1):89-96.
15. Patel MS, Mohan D, Andersson YM, et al. Phenotypic characteristics associated with reduced short physical performance battery score in COPD. *Chest.* 2014;145(5):1016-1024.
16. Mohan D, Benson VS, Allinder M, et al. Short Physical Performance Battery: What Does Each Sub-Test Measure in Patients with Chronic Obstructive Pulmonary Disease? *Chronic Obstr Pulm Dis.* 2020;7(1):13-25.
17. Miravitlles M, Murio C, Tirado-Conde G, et al. Geographic differences in clinical characteristics and management of COPD: the EPOCA study. *Int J Chron Obstruct Pulmon Dis.* 2008;3(4):803-814.
18. Cleutjens F, Spruit MA, Ponds R, et al. Cognitive impairment and clinical characteristics in patients with chronic obstructive pulmonary disease. *Chron Respir Dis.* 2018;15(2):91-102.
19. Lenze EJ, Schulz R, Martire LM, et al. The course of functional decline in older people with persistently elevated depressive symptoms: longitudinal findings from the Cardiovascular Health Study. *J Am Geriatr Soc.* 2005;53(4):569-575.
20. Stuck AE, Walthert JM, Nikolaus T, Bula CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Soc Sci Med.* 1999;48(4):445-469.

21. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax.* 1999;54(7):581-586.
22. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J.* 2009;34(3):648-654.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.
24. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT) scores. *BMC Pulm Med.* 2011;11:42.
25. Smid DE, Franssen FME, Gonik M, et al. Redefining Cut-Points for High Symptom Burden of the Global Initiative for Chronic Obstructive Lung Disease Classification in 18,577 Patients With Chronic Obstructive Pulmonary Disease. *J Am Med Dir Assoc.* 2017;18(12):1097 e1011-1097 e1024.
26. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* 1994;49(2):M85-94.
27. Global Initiative for Chronic Obstructivie Lung Disease. 2017; https://goldcopd.org/wp-content/uploads/2016/12/wms-GOLD-2017-Pocket-Guide.pdf. Accessed 11-03, 2020.
28. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl.* 1993;16:5-40.
29. Coin A, Sergi G, Minicuci N, et al. Fat-free mass and fat mass reference values by dual-energy X-ray absorptiometry (DEXA) in a 20-80 year-old Italian population. *Clin Nutr.* 2008;27(1):87-94.
30. IDF. The IDF consensus worldwide definition of the metabolic syndrome. *International Diabetes Federation (IDF).* 2006.
31. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J.* 2014;44(6):1428-1446.
32. Hernandes NA, Wouters EF, Meijer K, Annegarn J, Pitta F, Spruit MA. Reproducibility of 6-minute walking test in patients with COPD. *Eur Respir J.* 2011;38(2):261-267.
33. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J.* 1999;14(2):270-274.
34. Spruit MA, Polkey MI, Celli B, et al. Predicting outcomes from 6-minute walk distance in chronic obstructive pulmonary disease. *J Am Med Dir Assoc.* 2012;13(3):291-297.
35. Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev.* 2019;28(154).
36. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis.* 1985;131(5):700-708.
37. van 't Hul A, Gosselink R, Kwakkel G. Constant-load cycle endurance performance: test-retest reliability and validity in patients with COPD. *J Cardiopulm Rehabil.* 2003;23(2):143-150.
38. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370.
39. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci.* 2000;55(4):M221-231.
40. Bernabeu-Mora R, Gimenez-Gimenez LM, Montilla-Herrador J, Garcia-Guillamon G, Garcia-Vidal JA, Medina-Mirapeix F. Determinants of each domain of the Short Physical Performance Battery in COPD. *Int J Chron Obstruct Pulmon Dis.* 2017;12:2539-2544.

41. Larsson P, Borge CR, Nygren-Bonnier M, Lerdal A, Edvardsen A. An evaluation of the short physical performance battery following pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. *BMC Res Notes.* 2018;11(1):348.
42. Ozalevli S, Ozden A, Itil O, Akkoclu A. Comparison of the Sit-to-Stand Test with 6 min walk test in patients with chronic obstructive pulmonary disease. *Respir Med.* 2007;101(2):286-293.
43. Eisner MD, Iribarren C, Yelin EH, et al. Pulmonary function and the risk of functional limitation in chronic obstructive pulmonary disease. *Am J Epidemiol.* 2008;167(9):1090-1101.
44. McIntosh EI, Smale KB, Vallis LA. Predicting fat-free mass index and sarcopenia: a pilot study in community-dwelling older adults. *Age (Dordr).* 2013;35(6):2423-2434.
45. Mainenti MR, Rodrigues Ede C, Oliveira JF, Ferreira Ade S, Dias CM, Silva AL. Adiposity and postural balance control: correlations between bioelectrical impedance and stabilometric signals in elderly Brazilian women. *Clinics (Sao Paulo).* 2011;66(9):1513-1518.
46. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc.* 2002;50(5):889-896.
47. Organisation WH. *International Classification of Functioning, Disability, and Health.* Geneva: World Health Organisation;2002.
48. van de Ven-Stevens LA, Graff MJ, Peters MA, van der Linde H, Geurts AC. Construct validity of the canadian occupational performance measure in participants with tendon injury and Dupuytren disease. *Phys Ther.* 2015;95(5):750-757.
49. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. *J Hand Surg Am.* 1984;9(2):222-226.
50. Curtis M, Kon S, Canavan J, et al. The minimum important difference of the hospital anxiety and depression scale in COPD. *European Respiratory Journal.* 2014;44(Suppl 58):4829.
51. Maurer J, Rebbapragada V, Borson S, et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest.* 2008;134(4 Suppl):43S-56S.
52. Rubenstein LZ, Josephson KR. Falls and their prevention in elderly people: what does the evidence show? *Med Clin North Am.* 2006;90(5):807-824.
53. Anderson E, Shivakumar G. Effects of exercise and physical activity on anxiety. *Front Psychiatry.* 2013;4:27.

SUPPLIERS

A. MasterScreen PFT/ Body; Jaeger, Würzburg, Germany

B. Lunar iDXA; DEXAtech Benelux BV, Ridderkerk, the Netherlands

C. Ergoselect; Ergoline, Bitz, Germany

D. Technogym, Cesena, Italy

E. Biodex Multi-joint System 3; Biometrics Motion B.V., Groningen, the Netherlands

F. IBM North America, 590 Madison Ave, New York, NY 10022.

LEGENDS OF FIGURES

Figure 1. Percentages (%) of patients of low-, moderate-, and high-performance group that scored 0 to 4 on the (a) standing balance tests, (b) four meter gait speed (4MGS), and (c) five sit-to-stand test (5STS).

e-Figure 1. The distribution (%) of the SPPB summary score within patients with COPD starting pulmonary rehabilitation.

Table 1. Characteristics of patients with COPD stratified for SPPB summary score.

Baseline characteristics	Patients with COPD (n=900)	Short Physical Performance Battery levels			p-value
		Low-Performance (n=98)	Moderate-Performance (n=393)	High-Performance (n=409)	
General Characteristics					
Age (years)	65 ± 8	69 ± 8	66 ± 8	64 ± 8	<0.001 *,#,†
Gender (male, %)	52	44	52	53	0.240
Weight [a] (kg)	74 ± 20	76 ± 25	74 ± 19	73 ± 19	0.604
BMI [a] (kg/m^2)	26.2 ± 6.3	27.3 ± 7.8	26.3 ± 6.1	25.7 ± 5.9	0.055
mMRC [b] (grade)	2 (2-3)	4 (3-4)	3 (2-3)	2 (2-3)	<0.001 *,#,†
mMRC ≥ 2 [b] (% patients)	87	100	92	79	<0.001 *,#,†
CAT [c] (points)	21 ± 7	25 ± 6	22 ± 6	20 ± 7	<0.001 *,#,‡
CAT ≥ 10 [c] (% patients)	95	100	96	93	0.009
CAT ≥ 18 [c] (% patients)	75	89	79	68	<0.001 #,†
Exacerbations in the past 12 months [d]: 0/1/2/3/4/>4	20/17/20/14/8/21	6/17/10/23/5/39	22/16/19/14/9/20	23/18/24/11/8/16	<0.001 *,#
≥ 2 exacerbations in the past 12 months [d] (% patients)	63	77	63	59	0.006 *,#
Hospitalizations in the past 12 months [e]: 0/1/2/3/4/>4	55/25/9/5/2/4	36/26/12/12/4/10	55/26/10/4/1/4	61/23/6/5/3/2	<0.001 *,#
≥ 1 hospitalization in the past 12 months [e] (% patients)	44	64	45	39	<0.001 *,#
CCI (points)	1 (1-2)	2 (1-3)	1 (1-2)	1 (1-2)	0.012
CCI ≥ 2 (% patients)	45	55	46	41	0.028
Long-term O_2 use [f] (yes, % patients)	22	42	22	16	<0.001 *,#

*Data is presented as mean ± SD, median (IQR), or percentages. * indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 7-9. # indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 10-12. † indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 7-9 and SPPB 10-12. ‡ indicates no significant difference after Bonferroni post-hoc testing. Alphabetic characters in superscript indicates a sample size deviant from n = 900 with the following: a. n=897 (low, moderate, and high resp. 98, 390, 409), b. n=899 (low, moderate, and high resp. 98, 393, 408), c. n=844 (low, moderate, and high resp. 87, 374, 383), d. n=895 (low, moderate, and high resp. 98, 390, 407), e. n=897 (low, moderate, and high resp. 96, 392, 409), f. n=883 (low, moderate, and high resp. 95, 387, 401). Abbreviations: BMI: Body Mass Index, CAT: COPD Assessment Test, COPD: chronic obstructive pulmonary disease, CCI: Charlson Comorbidity Index, kg: kilogram, m: meters, mMRC: Modified Medical Research Council, n: numbers, O_2: oxygen, SPPB: Short Physical Performance Battery.*

Table 2. Phenotypic characteristics of patients with COPD stratified for SPPB summary scores.

Phenotypic characteristics	Patients with COPD (n=900)	Short Physical Performance Battery			p-value
		Low-Performance (n=98)	Moderate-Performance (n=393)	High-Performance (n=409)	
Lung function and arterial blood gasses					
GOLD I/II/III/IV (% patients)	9/29/38/24	2/30/31/38	11/27/39/23	10/30/39/22	0.007 *,#
GOLD A/B/C/D [a] (% patients)	5/24/8/63	0/15/0/85	3/27/5/66	9/24/13/54	<0.001 *,#,†
FEV_1 (% predicted)	43 (31-62)	35 (24-54)	43 (31-62)	44 (32-63)	0.001 *,#
FEV_1 (L)	1.07 (0.76-1.54)	0.81 (0.53-1.22)	1.05 (0.73-1.58)	1.13 (0.84-1.59)	<0.001 *,#
FEV_1/FVC	0.35 (0.28-0.47)	0.34 (0.25-0.46)	0.36 (0.28-0.49)	0.35 (0.27-0.47)	0.283
TL_{CO} SB [b] (% predicted)	50.1 ± 17.1	42.7 ± 16.3	49.7 ± 17.4	51.9 ± 16.6	<0.001 *,#
RV-BB [c] (% predicted)	165.5 ± 55.7	181.0 ± 72.2	161.4 ± 56.5	166.0 ± 49.8	0.012
TLC-BB [d] (% predicted)	117.3 ± 19.7	116.5 ± 24.7	115.3 ± 19.9	119.6 ± 17.9	0.013
paO_2 [e] (kPa)	9.1 (8.3-10)	8.6 (7.7-9.8)	9.0 (8.2-10.1)	9.3 (8.4-10.1)	0.001 *,#
$paCO_2$ [f] (kPa)	5.3 (4.9-5.9)	5.8 (5.1-6.8)	5.3 (4.9-5.9)	5.2 (4.9-5.7)	<0.001 *,#
Saturation [g] (%)	94 (92-95)	92 (90-95)	93 (92-95)	94 (93-95)	0.181
Body composition					
FFMI [h] (kg/m^2)	16.6 ± 2.5	16.3 ± 2.8	16.6 ± 2.6	16.7 ±2.4	0.444
FFM of the arms [j] (kg)	5.1 (3.9-6.5)	4.5 (3.6-6.0)	5.1 (3.9-6.3)	5.2 (4.2-6.7)	0.003 #
FFM of the legs [k] (kg)	15.1 (12.2-17.9)	14.0 (11.7-17.0)	15.0 (12.1-17.8)	15.4 (12.5-18.0)	0.020
Waist circumference [l] (cm)	97.8 ± 17.1	101.3 ± 20.2	98.6 ± 16.9	96.2 ± 16.4	0.015
Waist circumference above predicted values [l] (% patients)	74	76	76	72	0.276
T-score L2L4 [m]	-0.79 ± 1.72	-0.60 ± 1.90	-0.80 ± 1.69	-0.83 ± 1.70	0.495
T-score trochanter [n]	-1.76 ± 1.02	-1.95 ± 0.95	-1.81 ± 1.02	-1.66 ± 1.03	0.018
Normal bone mineral density/ osteopenia/ osteoporosis [o] (% patients)	20/47/32	17/45/38	19/47/34	22/49/29	0.467
Physical capacity					
6MWT [p] (m)	389 (300-459)	194 (139-259)	360 (288-421)	441 (381-492)	<0.001 *,#,†
6MWT < 350 m [p] (% patients)	38	96	46	16	<0.001 *,#,†
6MWT [q] (% predicted)	62 (50-72)	33 (24-46)	58 (49-67)	69 (59-78)	<0.001 *,#,†
6MWT: Patients with ≥ 1 stop [r] (% patients)	16	52	16	8	<0.001 *,#,†
Wmax [s] (W)	59 (43-80)	36 (23-53)	56 (41-76)	66 (49-90)	<0.001 *,#,†
Wmax [t] (% of predicted)	49 (35-67)	31 (17-63)	46 (34-62)	54 (40-71)	<0.001 *,#,†
CWRT TTE [u] (s)	230 (165-334)	145 (111-260)	213 (160-310)	254 (187-355)	<0.001 *,#,†

Table 2 (continued).

Physical status	Patients with COPD (n=900)	Short Physical Performance Battery			p-value
		Low-performance (n=98)	Moderate-performance (n=393)	High-performance (n=409)	
Isotonic muscle strength (1-RM)					
Leg press [v] (kg)	70 (50-100)	40 (20-60)	60 (40-90)	80 (60-110)	<0.001 *,#,†
Leg extension [w] (kg)	28 (20-38)	18 (10-25)	25 (20-35)	30 (25-40)	<0.001 *,#,†
Upper back [x] (kg)	23 (15-35)	15 (10-20)	20 (15-30)	25 (20-35)	<0.001 *,#,†
Chest press [y] (kg)	23 (15-33)	18 (10-23)	20 (15-30)	25 (18-35)	<0.001 *,#,†
Isotonic muscle strength corrected for FFM					
Leg press [z]	4.83 ± 2.26	3.16 ± 1.98	4.40 ± 2.05	5.56 ± 2.20	<0.001 *,#,†
Leg extension [za]	1.91 ± 0.70	1.36 ± 0.59	1.76 ± 0.66	2.15 ± 0.65	<0.001 *,#,†
Upper back [zb]	4.67 ± 1.68	3.37 ± 1.60	4.47 ± 1.65	5.13 ± 1.56	<0.001 *,#,†
Chest press [zc]	4.63 ± 1.68	3.58 ± 1.43	4.41 ± 1.69	5.04 ± 1.59	<0.001 *,#,†
Isokinetic muscle strength/endurance (BIODEX)					
Peak torque [zd] (Nm)	86 ± 33	60 ± 31	83 ± 33	93 ± 30	<0.001 *,#,†
Peak torque [ze] (% predicted)	61 ± 19	46 ± 18	59 ± 19	65 ± 17	<0.001 *,#,†
Total work [zd] (J)	1487 ± 632	889 ± 550	1400 ± 635	1648 ± 571	<0.001 *,#,†
Isokinetic muscle strength/endurance corrected for FFM					
Peak torque [zf] (Nm/kg)	5.57 ± 1.40	4.01 ± 1.45	5.36 ± 1.37	5.97 ± 1.21	<0.001 *,#,†
Peak torque [zg] (%/kg)	4.06 ± 1.17	3.22 ± 1.23	3.94 ± 1.18	4.28 ± 1.08	<0.001 *,#,†
Total work [zf] (J/kg)	95.5 ± 29.8	60.1 ± 29.5	89.8 ± 29.5	105.4 ± 24.4	<0.001 *,#,†
Emotional status					
HADS anxiety [zh] (points)	7.5 ± 4.2	9.2 ± 4.6	7.7 ± 4.1	6.9 ± 4.1	<0.001 *
HADS anxiety ≥ 10 [zh] (% patients)	30	46	32	24	<0.001 #
HADS depression [zh] (points)	7.4 ± 4.0	9.0 ± 4.4	7.8 ± 3.8	6.7 ± 4.0	<0.001 *,#,†
HADS depression ≥ 10 [zh] (% patients)	31	52	31	25	<0.001 #,†

*Data is presented as mean ± SD, median (IQR), or percentages. * indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 7-9. # indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 10-12. † indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 7-9 and SPPB 10-12. Alphabetic characters in superscript indicates a sample size deviant from n = 900 with the following: a. n=892 (low, moderate, and high resp. 96, 390, 406), b. n=835 (low, moderate, and high resp. 72, 363, 400), c. n=864 (low, moderate, and high resp. 90, 370, 404), d. n=865 (low, moderate, and high resp. 90, 371, 404), e. n=843 (low, moderate, and high resp. 81, 370, 392), f. n=843 (low, moderate, and high resp. 82, 370, 391), g. n=124 (low, moderate, and high resp. 13, 57, 54), h. n=891 (low, moderate, and high resp. 95, 389, 407), i. n=889 (low, moderate, and high resp. 95, 387, 407), j. n=892 (low, moderate, and high resp. 95, 390, 407), k. n=892 (low, moderate, and high resp. 96, 389, 407), l. n=897 (low, moderate, and high resp. 96, 393, 408), m. n=881 (low, moderate, and high resp. 94, 384, 403),*

n. n=875 (low, moderate, and high resp. 91, 381, 403), o. n=888 (low, moderate, and high resp. 94, 388, 406), p. n=893 (low, moderate, and high resp. 95, 390, 408), q. n=893 (low, moderate, and high resp. 94, 390, 409), r. n=895 (low, moderate, and high resp. 95, 391, 409), s. n=822 (low, moderate, and high resp. 64, 359, 399), t. n=819 (low, moderate, and high resp. 64, 356, 399), u. n=796 (low, moderate, and high resp. 57, 347, 392), v. n=865 (low, moderate, and high resp. 87, 373, 405), w. n=834 (low, moderate, and high resp. 79, 366, 389), x. n=801 (low, moderate, and high resp. 80, 343, 378), y. n=794 (low, moderate, and high resp. 77, 342, 375), z. n=858 (low, moderate, and high resp. 85, 370, 403), za. n=828 (low, moderate, and high resp. 78, 363, 387), zb. n=796 (low, moderate, and high resp. 79, 341, 376), zc. n=789 (low, moderate, and high resp. 76, 340, 373), zd. n=690 (low, moderate, and high resp. 53, 285, 352), ze. n=689 (low, moderate, and high resp. 53, 285, 351), zf. n=684 (low, moderate, and high resp. 53, 281, 350), zg. n=683 (low, moderate, and high resp. 53, 281, 349). zh. n=843 (low, moderate, and high resp. 87, 374, 382). Abbreviations: BB: Body Box, COPD: chronic obstructive pulmonary disease, CWRT: Constant Work Rate Test, FEV_1: Forced Expiratory Volume in the first second, FFM: Fat Free Mass, FFMI: Fat Free Mass index, FVC: Forced Vital Capacity, GOLD: Global Initiative for Chronic Obstructive Lung Disease, HADS: Hospital Anxiety and Depression Scale, J: Joule, kg: kilogram, L: liters, L2-L4: Lumbar spine (L2-L4), m: meters, Nm: Newton-meter, $paCO_2$: Partial pressure of arterial carbon dioxide, paO_2: Partial pressure of arterial oxygen, SPPB: Short Physical Performance Battery, SB: single-breath, RV: Residual Volume, TLC: Total Lung Capacity, TL_{CO}: Diffusion capacity for carbon monoxide, TTE: time-to-exhaustion, Wmax: maximal wattage, W: wattage, 1-RM: One-Repetition Maximum, 6MWT: Six-Minute Walk Test..

Table 3. Short Physical Performance Battery (SPPB) results of patients with COPD stratified for SPPB summary scores.

SPPB score	Patients with COPD (n=900)	Short Physical Performance Battery levels			p-value
		Low-Performance (n=98)	Moderate-Performance (n=393)	High-Performance (n=409)	
Balance side-by-side (s)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	<0.001 *,#
Balance semi-tandem (s)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	<0.001 *,#
Balance tandem (s)	10.0 (10.0-10.0)	0.0 (0.0-5.5)	10.0 (7.3-10.0)	10.0 (10.0-10.0)	<0.001 *,#,†
4MGS (s)	3.8 (3.2-4.7)	6.3 (4.9-7.9)	4.2 (3.6-5.0)	3.4 (3.0-3.9)	<0.001 *,#,†
4MGS [a] (m/s)	1.04 ± 0.28	0.62 ± 0.20	0.98 ± 0.24	1.19 ± 0.23	<0.001 *,#,†
5STS (s) – all patients	15.0 (12.3-18.4)	0 (0.0-22.0)	18.2 (16.0-21.4)	13.1 (11.6-14.7)	<0.001 *,†
5STS [b] (s) – only patients able to perform the test	15.4 (12.9-18.8)	23.3 (19.3-31.4)	18.4 (16.6-21.6)	13.1 (11.6-14.7)	<0.001 *,#,†
Total SPPB score (points)	9 (8-10)	5 (4-6)	9 (8-9)	11 (10-11)	<0.001 *,#,†

*Data is presented as mean ± SD or median (IQR). * indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 7-9. # indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 10-12. † indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 7-9 and SPPB 10-12. Alphabetic characters in superscript indicates a sample size deviant from n = 900 with the following: a. n=884 (low, moderate, and high resp. 82, 393, 409), b. n=830 (low, moderate, and high resp. 44, 377, 409). Abbreviations: COPD: Chronic Obstructive Pulmonary Disease, m: meters, s: seconds, SPPB: Short Physical Performance Battery, 4MGS: Four-Meter Gait Speed, 5STS: Five Sit-To-Stand.*

Supplemental Table S2. Differences in patients' characteristics between included and excluded patients.

Patients' characteristics	Included (n=900)	Excluded (n=53)	P Value
Age (y), mean ± SD	65±8	63±12	.140
Sex (male, % of patients)	52	55	.397
Weight (kg), mean ± SD [a]	74±20	75±16	.728
BMI (kg/m^2), mean ± SD [a]	26.2±6.3	26.4±5.7	.806
mMRC (grade), median (IQR) [b]	2 (2-3)	3 (2-4)	<.001
CAT (points), mean ± SD [c]	21±7	23±6	.047
Exacerbations in the past 12 mo: 0/1/2/3/4/>4 (% of patients) [d]	20/17/20/14/8/21	11/10/17/13/6/43	.006
Hospitalizations in the past 12 mo: 0/1/2/3/4/>4 (% of patients) [e]	55/25/9/5/2/4	39/26/13/20/2/0	.001
CCI (points), median (IQR)	1 (1-2)	1 (1-2)	.600
Long-term O_2 use (yes, % patients) [f]	22	37	.015
Lung function and arterial blood gases			
FEV_1 (L), median (IQR) [g]	1.07 (0.76-1.54)	0.86 (0.69-1.47)	.070
paO_2 (kPa), median (IQR) [h]	9.1 (8.3-10.0)	9.3 (8.1-11.1)	.270
$paCO_2$ (kPa), median (IQR) [i]	5.3 (4.9-5.9)	5.2 (4.8-5.7)	.180
Saturation (%), median (IQR) [h]	94 (92-95)	94 (91-97)	.247
Body composition			
FFM of the arms (kg), median (IQR) [j]	5.1 (3.9-6.5)	4.6 (3.8-6.0)	.081
FFM of the legs (kg), median (IQR) [j]	15.1 (12.2-17.9)	14.3 (11.3-16.8)	.061
Waist circumference (cm), mean ± SD [k]	97.8±17.1	96.1±14.9	.504
T score lumbar spine (L2-L4), mean ± SD [l]	-0.79±1.72	-1.11±1.56	.198
T score hip (trochanter), mean ± SD [m]	-1.76±1.02	-1.85±1.15	.522
Physical capacity and exercise tolerance			
6MWT (m), median (IQR) [n]	389 (300-459)	351 (259-428)	.049
Wmax (W), median (IQR) [o]	59 (43-80)	56 (42-80)	.694
CWRT TTE (s), median (IQR) [p]	230 (165-334)	184 (151-237)	.044
Isotonic muscle strength			
Leg press (kg), median (IQR) [q]	70 (50-100)	50 (30-90)	.027
Leg extension (kg), median (IQR) [r]	28 (20-38)	20 (15-39)	.053
Upper back (kg), median (IQR) [s]	23 (15-35)	30 (15-35)	.509
Chest press (kg), median (IQR) [t]	23 (15-33)	25 (13-30)	.428
Isokinetic muscle strength/endurance			
Peak torque (Nm), mean ± SD [u]	86±33	75±28	.041
Total work (J), mean ± SD [u]	1487±632	1197±529	.009
Emotional status			
HADS anxiety (points), mean ± SD [v]	7.5±4.2	8.5±4.5	.106
HADS depression (points), mean ± SD [v]	7.4±4.0	7.4±3.9	.952
Short Physical Performance Battery			

Balance tests score, median (IQR)	4 (4-4)	4 (3-4)	.300
4MGS score, median (IQR)	4 (4-4)	4 (3-4)	.001
5STS score, median (IQR) [w]	2 (1-3)	1 (1-3)	.010
SPPB total score, median (IQR) [w]	9 (8-10)	8 (7-11)	.009

Alphabetic characteristics in superscript indicates a sample size deviant from n = 953 with the following: a = 927 (included = 897 and excluded = 31), b = 952 (included = 899 and excluded = 53), c = 894 (included = 844 and excluded = 50), d = 948 (included = 895 and excluded = 53), e = 910 (included = 864 and excluded = 46), f = 935 (included = 884 and excluded 51), g = 951 (included = 899 and excluded = 52), h = 881 (included = 840 and excluded = 41), i = 882 (included = 841 and excluded = 41), j = 935 (included = 885 and excluded = 50), k = 949 (included 891 and excluded = 50), l = 923 (included = 874 and excluded = 49), m = 916 (included = 868 and excluded = 48), n = 916 (included = 875 and excluded = 41), o = 832 (included = 796 and excluded = 36), p = 858 (included = 822 and excluded = 36), q = 909 (included = 865 and excluded = 44), r= 878 (included = 834 and excluded = 44), s = 825 (included = 801 and excluded = 24), t = 830 (included = 794 and excluded = 36), u = 720 (included = 687 and excluded = 33), v = 892 (included = 843 and excluded = 49), w = 952 (included = 900 and excluded 52). Abbreviations: BMI, Body Mass Index; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; CWRT, Constant Work Rate Test; FEV_1, Forced Expiratory Volume in the first second; FFM, Fat-Free Mass; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; mMRC, Modified Medical Research Council; $paCO_2$, Partial Pressure of arterial carbon dioxide; paO_2, Partial pressure of arterial oxygen; O_2, oxygen; SD, standard deviation; SPPB, Short Physical Performance Battery; TTE, time-to-exhaustion; Wmax, maximal workload; 4MGS, 4-M Gait Speed; 5STS, 5-repetition Sit-To-Stand; 6MWT, 6-Minute Walk Test.

Supplemental Table S3. Univariate regression models of patients' characteristics and the SPPB summary score.

Patients' characteristics	Model	ANOVA		Coefficient		P Value
	Adjusted R^2	F-value	Df	Beta	CI	
Age (y)	0.056	54.415	898	-0.060	-0.076- -0.044	<.001
Sex (Female/Male)	0.001	2.017	898	-0.196	-0.468- 0.075	.156
Weight (kg)	-0.001	0.459	895	-0.002	-0.009- 0.005	.498
BMI (kg/m^2)	0.003	3.928	895	-0.022	-0.044- 0.000	.048
mMRC (grade)	0.200	225.840	897	-0.920	-1.040- -0.799	<.001
CAT (points)	0.058	52.603	843	-0.075	-0.095- -0.055	<.001
Exacerbations in the past 12 months	0.031	29.277	893	-0.207	-0.282- -0.132	<.001
Hospitalizations in the past 12 months	0.033	31.642	895	-0.300	-0.404- -0.195	<.001
CCI (points)	0.011	11.262	898	-0.179	-0.283- -0.074	.001
Long-term O_2 use (yes/no)	0.042	39.922	881	1.047	0.722- 1.372	<.001
Lung function and arterial blood gases						
FEV_1 (L)	0.026	24.938	898	0.523	0.318-0.729	<.001
paO_2 (kPa)	0.012	11.482	841	0.160	0.067-0.253	.001
$paCO_2$ (kPa)	0.046	41.178	841	-0.498	-0.651- -0.346	<.001
Saturation (%)	0.009	2.111	122	0.096	-0.035-0.226	.149
Body composition						
FFM of the arms (kg)	0.012	11.815	890	0.142	0.061-0.223	.001
FFM of the legs (kg)	0.009	9.524	890	0.053	0.019-0.087	.002
Waist circumference (cm)	0.007	7.152	895	-0.011	-0.019- -0.003	.008
T score lumbar spine (L2-L4)	0.000	0.643	879	-0.033	-0.112-0.047	.423
T score hip (trochanter)	0.006	5.973	873	0.167	0.033-0.300	.015
Physical capacity and exercise tolerance						
6MWT (m)	0.422	653.200	891	0.012	0.011-0.013	<.001
Wmax (W)	0.097	89.162	820	0.017	0.014-0.021	<.001
CWRT TTE (s)	0.023	20.127	794	0.001	0.001-0.002	<.001
Isotonic muscle strength						
Leg press (kg)	0.110	107.639	863	0.016	0.013-0.019	<.001
Leg extension (kg)	0.114	107.754	832	0.048	0.039-0.057	<.001
Upper back (kg)	0.075	66.264	799	0.041	0.031-0.051	<.001
Chest press (kg)	0.061	52.926	792	0.038	0.028-0.048	<.001
Isokinetic muscle strength/endurance						
Peak torque (Nm)	0.090	69.351	688	0.018	0.014-0.022	<.001
Total work (J)	0.130	103.696	688	0.001	0.001-0.001	<.001
Emotional status						
HADS anxiety (points)	0.026	23.885	841	-0.081	-0.113- -0.048	<.001
HADS depression (points)	0.039	34.742	841	-0.102	-0.136- -0.068	<.001

Abbreviations: BMI, Body Mass Index; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; CI, Confidence Interval; CWRT, Constant Work Rate Test; DF, Degrees of Freedom; FEV_1, Forced Expiratory Volume in the first second; FFM, Fat Free Mass; HADS, Hospital Anxiety and Depression Scale; mMRC, Modified Medical Research Council; $paCO_2$, Partial Pressure of arterial carbon dioxide; paO_2, Partial pressure of arterial oxygen; O_2, oxygen; SPPB, Short Physical Performance Battery; TTE, time-to-exhaustion; Wmax, maximal workload; 6MWT, 6-Minute Walk Test.

Supplemental Table S4. Multivariate regression model using the enter method to predict the SPPB summary score.

Independent variable	Estimate	Standard error	B standardized	P Value	Partial R^2
Age (y)	**-0.016**	**0.008**	**-0.085**	**.043**	**-0.090**
mMRC (grade)	-0.023	0.075	-0.015	.757	-0.014
CAT (points)	-0.007	0.010	-0.029	.519	-0.029
Exacerbations in the past 12 months	0.039	0.039	0.045	.316	0.045
Hospitalizations in the past 12 months	-0.014	0.060	-0.010	.810	-0.011
CCI (points)	-0.061	0.049	-0.049	.212	-0.055
Long-term O_2 use (yes/no)	-0.084	0.168	-0.020	.617	-0.022
paO_2 (kPa)	-0.004	0.041	-0.004	.917	-0.005
$paCO_2$ (kPa)	0.045	0.078	0.025	.563	0.026
Waist circumference (cm)	-0.006	0.004	-0.072	.141	-0.065
T score hip (trochanter)	-0.066	0.061	-0.045	.282	-0.048
6MWT (m)	**0.007**	**0.001**	**0.454**	**<.001**	**0.342**
CWRT TTE (s)	>0.001	0.000	-0.001	.979	-0.001
Total work (J)	0.000	0.000	0.056	.292	0.047
HADS depression (points)	-0.019	0.016	-0.048	.249	-0.051

Abbreviations: B, Beta; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; CWRT, Constant Work Rate Test; HADS, Hospital Anxiety and Depression Scale; mMRC, Modified Medical Research Council; $paCO_2$, Partial Pressure of arterial carbon dioxide; paO_2, Partial pressure of arterial oxygen; O_2, oxygen; SPPB, Short Physical Performance Battery; TTE, time-to-exhaustion; 6MWT, 6-Minute Walk Test.

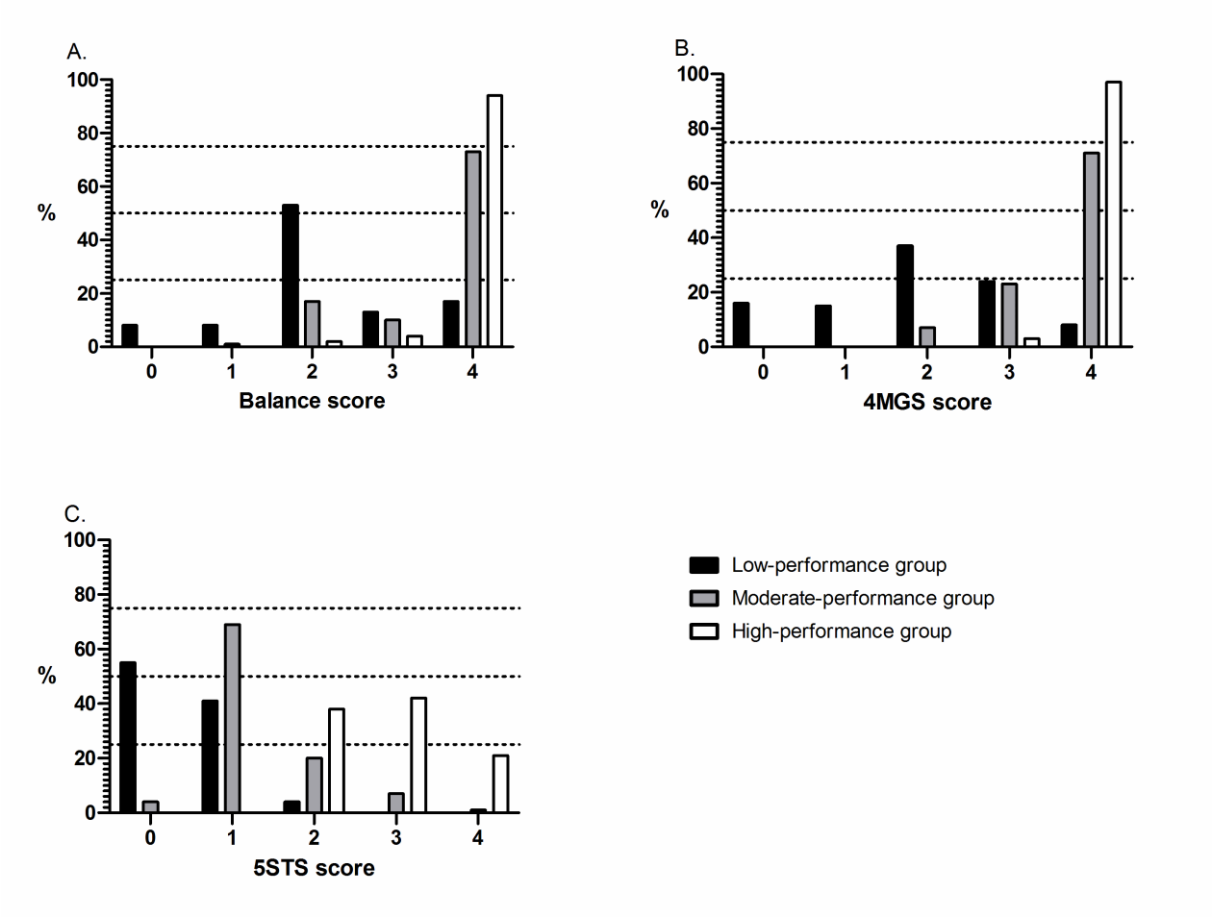
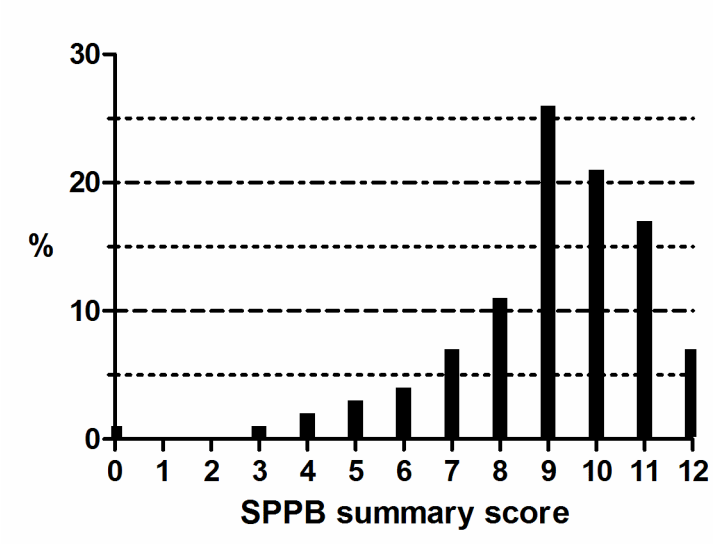


Figure 1



Supplemental fig S1

Supplemental Table S1. The scoring system of the standing balance, 4-m gait speed (4MGS) and 5-repetition sit-to-stand (5STS) tests.

	Balance: Side by side	**Balance: semitandem**	**Balance: tandem**	**4MGS**	**5STS**
Scores	**Seconds**	**Seconds**	**Seconds**	**Seconds**	**Seconds**
4				< 4.82	< 11.20
3				4.82 – 6.20	11.20 – 13.69
2			10.00	6.21 – 8.70	13.70 – 16.69
1	10.00	10.00	3.00-9.99	> 8.70	16.7 – 60
0	< 10.00	< 10.00	< 3.00	Not able to perform test	Not able to perform test