



**UHASSELT**

KNOWLEDGE IN ACTION

## **Faculteit Revalidatiewetenschappen**

master in de revalidatiewetenschappen en de kinesietherapie

### **Masterthesis**

***The difference in SPPB between patients with severe exacerbations and a stable COPD population***

**Jana Peeters**

**Jonas Stas**

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesietherapie, afstudeerrichting revalidatiewetenschappen en kinesietherapie bij inwendige aandoeningen

### **PROMOTOR :**

De heer Chris BURTIN



**UHASSELT**

KNOWLEDGE IN ACTION

[www.uhasselt.be](http://www.uhasselt.be)  
Universiteit Hasselt  
Campus Hasselt:  
Martelarenlaan 42 | 3500 Hasselt  
Campus Diepenbeek:  
Agoralaan Gebouw D | 3590 Diepenbeek

**2018**  
**2019**



# **Faculteit Revalidatiewetenschappen**

master in de revalidatiewetenschappen en de kinesietherapie

## ***Masterthesis***

***The difference in SPPB between patients with severe exacerbations and a stable COPD population***

**Jana Peeters**

**Jonas Stas**

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesietherapie, afstudeerrichting revalidatiewetenschappen en kinesietherapie bij inwendige aandoeningen

## **PROMOTOR :**

De heer Chris BURTIN



## **Acknowledgement**

We would like to express our gratitude to our promotor Dr. Chris Burtin and research assistant Kirsten Quadflieg for their help when writing this master thesis. We would like to thank Kirsten Quadflieg in particular for her help with attaining the data of the unstable COPD patients.

We would like to thank Dr. Daenen for screening and referring the stable COPD patients, eligible for our study. Likewise, we would like to thank Filipa Machado for helping with statistics and reading our thesis. For the material used for our testings, we would like to thank REVAL. We would like to thank Ziekenhuis-Oost-Limburg for letting us use the facilities for the testings. Furthermore, we would like to thank all the patients who participated in the study.

Kreemersstraat 76, 3660 Oudsbergen, 03/06/2019

P.J.

Pastorijstraat 65a, 2460 Kasterlee, 03/06/2019

S.J



## Research context

In this study the focus will be on patients with Chronic obstructive pulmonary disease (COPD). Patients with COPD can experience acute exacerbations (AE). This is an acute worsening of respiratory symptoms that results in additional therapy. An upcoming exacerbation can be predicted by using simple testings, assessing the risk factors of an exacerbation. These testings can be performed by a physiotherapist or a doctor. Testings used to measure functional status in this study are: the Short Physical Performance Battery (SPPB), quadriceps muscle strength measurements and lung function tests (FEV<sub>1</sub>%). The main interest was whether there is a difference in the SPPB score between stable patients and patients with AECOPD. Moreover, the aim was to investigate which subtest is responsible for a possible difference in score and whether this difference is due to muscle function or lung function.

This study is a part of our two years master 'rehabilitation sciences and physiotherapy' at the University of Hasselt (UHasselt) in Diepenbeek, Belgium. This duo-master thesis can be framed within the research domain 'Rehabilitation of internal disorders'. The thesis is situated within a current research study (Eudract/B-nr: B371201732540). In this overall study, the aim is to investigate the predictability of an AE (acute exacerbation) within a COPD population by functional parameters. Also, the study aimed to identify the impact of an AECOPD on the functional status.

The literature study of this master thesis was done in our first master year at the UHasselt. The title of this literature study was: "*What are predictive factors of hospitalizations for COPD exacerbations?*". The second part, the measurements, were performed in the nearby hospital 'Ziekenhuis Oost-Limburg (ZOL)' in Genk, Belgium under the supervision of post-doctoral researcher Chris Burtin and with help of the research assistant Kirsten Quadflieg. We tested the patients in the department 'lung function'.

Before the patients were included in the study, they needed to sign the written informed consent. Ethical approval was obtained by the ethical committee of the UHasselt and ZOL. Definitive favourable opinion was given on the 17<sup>th</sup> of July, 2017 (Eudract/B-nr: B371201732540). The research design was similar to the existing study and selected by promotor C. Burtin. The two master students (P.J and S.J.) specified the research question according to what they wanted to investigate, this with approval from the promotor. The promotor determined which testings were done. This was analogous with the existing study.

The recruitment of patients was done by the promotor and research assistant, who screened the patients at ziekenhuis Oost-Limburg upon their medical files. The patients were informed after the recruitment by the promotor, research assistant or one of the two students. Moreover, Dr. Daenen did the screening of stable COPD patients.

This year, and a year earlier, the students participated in some measurements to practice the testings. These were testings of stable COPD patients. These data were also used in this study.

The stable COPD patients were tested by a master student and the research assistant.

The research assistant tested the unstable COPD patients with help of a master student.

The statistical methodology and data analysis were done by the master students and were checked by the promotor. The central format was implemented for this thesis. The writing of the text was performed by both master students.

## Table of contents

1	Abstract.....	7
2	Introduction .....	9
3	Methods.....	11
3.1	Study design.....	11
3.2	Participants.....	11
3.3	Procedure .....	12
3.4	Data analysis.....	15
4	Results.....	17
4.1	Subjects.....	17
4.2	Between group comparison of SPPB subtests.....	18
4.3	Association between FEV1%, quadriceps muscle strength and SPPB score .....	19
5	Discussion.....	21
5.1	Interpretation of results .....	21
5.2	Comparison with other literature .....	22
5.3	Limitations and strengths .....	25
6	Conclusion.....	27
7	Reference list .....	29
8	Appendices.....	33





## 1 Abstract

**Background:** Patients with chronic obstructive pulmonary disease (COPD) often experience functional limitations. The Short Physical Performance Battery (SPPB) is a quick and simple functional test that has proven to be important in the assessment of patients with stable COPD. However, no studies have explored the use of the SPPB in a population with severe exacerbations.

**Objectives:** This study aimed to compare the performance of patients with stable COPD and patients with severe exacerbations for each subtest of the SPPB; and to explore the relationship between the SPPB, quadriceps muscle strength and FEV<sub>1</sub>% in both groups.

**Participants:** A cross-sectional study was conducted in patients with stable COPD and patients with severe exacerbations recruited and assessed in 'Ziekenhuis Oost-Limburg (ZOL)', Belgium.

**Measurements:** FEV<sub>1</sub>%, quadriceps muscle strength and the SPPB, which is composed of the 4 meter gait test (4MGT), 5 repetitions sit to stand (5STS) and balance test, were collected.

**Results:** 28 patients with stable COPD (gender: 15 male and 13 female; mean age: 65.93 ± 8.24 years; mean FEV<sub>1</sub>%, 52.73 ± 17.20) and 22 patients with a severe exacerbation (gender: seven male and 15 female; mean age: 67.23 ± 10.49 years; mean FEV<sub>1</sub>%, 39.20 ± 12.04) participated. In patients with stable COPD and patients with a severe exacerbation, the correlation between the quadriceps muscle strength and SPPB score was strong and very strong respectively (r=0.428; r=0.774). A very weak correlation was found between the FEV<sub>1</sub>% and the SPPB score in both groups (r=0.025; r=0.154). Patients with severe exacerbations performed significantly worse on the SPPB, namely on the 5STS (p=0.002) and 4MGT (p=0.002). Balance tests were similar in both groups (p=0.078).

**Conclusion:** Patients with more muscle weakness perform worse on the SPPB. During a severe exacerbation, the 5STS and 4MGT are even more impaired. These aspects should be focussed on during rehabilitation.



## 2 Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. (Global Initiative for chronic Obstructive Lung Disease[GOLD], 2018).

The chronic airflow limitation that is characteristic in COPD is caused by a mixture of small airway diseases (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions vary from person to person (GOLD, 2018). Patients with COPD can experience functional limitations, which can be a threat for daily life activities (Eisner et al., 2008); (Bernabeu-Mora et al., 2015). For this reason it is important to identify patients with COPD at risk for disability progression in the near future, particularly in routine clinical care (Bernabeu-Mora et al., 2015). According to Eisner et al. (2008) more functional limitations occur with a lower FEV<sub>1</sub> and a lower quadriceps muscle strength. Besides lung dysfunction and functional limitation it is also known that COPD is accompanied with a lower Cross Section Area (CSA) of the quadriceps muscle compared to healthy subjects (Bernard et al., 1998). Patients with COPD can experience acute exacerbations (AE), this is defined as “an acute worsening of respiratory symptoms that results in additional therapy” (GOLD, 2018). These acute exacerbations are a frequent cause of hospital admission, which are defined as severe exacerbations. They are also associated with significant morbidity, disease progression, mortality, high readmission rates and high resource utilization (GOLD, 2018). Furthermore, exacerbations and hospital admissions determine a great part of the medical cost of COPD (Jakovljevic et al., 2013). People with severe exacerbations show a significant decrease in peripheral muscle force, similar or greater to that of stable COPD patients (Spruit et al., 2003). To our knowledge no research is done investigating a link between functional status, FEV<sub>1</sub>% and quadriceps muscle strength in AECOPD patients.

A broadly used functional test is the SPPB. This test is a quick and simple test for the assessment of lower extremity function that only requires a short course, a chair and a stopwatch (Guralnik JM, et al.,1994). The SPPB is composed of three tests: the four meter gait test (4MGT), five-repetition sit-to-stand-test (5STS) and a balance test. To our knowledge, the utility of the SPPB in stable patients with COPD (Bernabeu-Mora et al., 2015) and hospitalized older patients without COPD is well known (Fisher, Ottenbacher, Goodwin, Graham, and Ostir,

2009). However, no studies analysed the SPPB in an unstable COPD population. For this reason it is the primary aim to assess whether the unstable patients score differently on each subtest of the SPPB than stable patients with COPD. The hypothesis is that unstable COPD patients score worse on the 5STS than stable COPD patients and have similar results on the other subtests. Because of the important role of the quadriceps in the 5STS (Bernabeu-Mora et al. 2017) , we assume this test will be specifically lower in AECOPD patients.

A second aim is to investigate how the SPPB is related with quadriceps muscle strength and the FEV<sub>1</sub>% in both a stable and unstable population. Analogous with the results of Spruit et al. (2003) that show a lower quadriceps muscle strength in AECOPD patients, the first hypothesis is that quadriceps weakness is correlated to a greater extent with a poor SPPB score in unstable COPD patients than patients with stable COPD. Despite the lack of research about the SPPB in an unstable COPD population, our second hypothesis is that lower FEV<sub>1</sub>% will be related to a greater extent to a low SPPB score in patients with AECOPD than in a stable COPD population.

### 3 Methods

#### 3.1 Study design

This study has an observational, cross-sectional design where stable COPD patients and patients who experienced a severe exacerbation were measured. Measurements were analysed for each group and also a between group comparison was made. Ethical approval was obtained by the ethical committee of the University of Hasselt and ZOL. Final approval was given 17 July, 2017 (Eudract/B-nr: B371201732540).

#### 3.2 Participants

Patients with stable COPD and patients admitted to the hospital 'Ziekenhuis Oost-Limburg (ZOL)' in Genk, Belgium for an AECOPD were recruited and assessed under the supervision of post-doctoral researcher Chris Burtin. If they met the selection criteria, patients needed to sign the written informed consent before participating in the study. Overall inclusion criteria were: diagnosis of COPD (post-bronchodilator  $FEV_1/FVC < 0.7$ ) and an age older than 40 years. Patients with stable COPD were either screened and referred to the study by a pulmonologist or recruited by phone calls conducted by the research assistant to ask about their willingness to participate in the study. Usually, stable patients' assessments were made on the same day they were reassessed by their pulmonologist. Stable patients were assessed at the lung function department. These patients were included if they did not experience an exacerbation in the previous four weeks. The patients with AECOPD were recruited by the research assistant who visited the patient in their hospital room in the pulmonology department. During their stay in the hospital, patients received standard medical care which included physiotherapy. Physiotherapy sessions were performed daily during 20 to 30 minutes and included airway clearance and mobilisation exercises, as required. Unstable patients were assessed in the pulmonology department. Specific inclusion criteria for patients with AECOPD were: non previous exacerbation in the previous four weeks, diagnosis of exacerbation based on the GOLD criteria, AECOPD resulting in hospital admission.

Patients who were sedated, underwent mechanical ventilation or had signs of cognitive deterioration, ongoing cancer, cardiac problems primary to COPD, other respiratory diseases besides COPD and patients who had musculoskeletal problems that impaired their performance of the tests, were all excluded from the study.

### 3.3 Procedure

The outcome measures of this study are the SPPB, quadriceps muscle strength and the lung function test (FEV<sub>1</sub>%). The SPPB is composed of three tests: the 4MGT, the 5STS and a balance test. Each of these three tests gets a score from 0 to 4. Because of this, 12 is the maximum score of the SPPB. The higher the score, the better (Guralnik JM, et al.,1994).

For the 4MGT the protocol described by Kon et al. (2013) was followed. The patients had to walk four meter at their normal walking speed, the use of a daily walking aid was allowed. A flat, quiet and unobstructed course of more than six meters was provided. Four meter was marked with tape on the floor. First, a walk was demonstrated by the researcher. Second, the patient was positioned with the toes just touching the starting line. The following instruction was given: *“This is our walking course. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street to go to the shops. Walk all the way past the other end of the tape before you stop”*. The time needed to walk the four meter was measured with a stopwatch. The stopwatch was started when the patient started to move and was stopped when the first foot completely crossed the four meter line. The 4MGT was repeated once without rest. The fastest repetition was used for analysis in meters/seconds (m/s). Similar to other papers, the quantity speed was used (4MGS). According to Kon et al. (2013), for the 4MGT, the interobserver reliability for a COPD population as well as test-retest reliability is excellent, with ICC values of 0.99 (95% CI 0.98 to 0.99) and 0.97 (95% CI 0.95 to 0.98), respectively.

The protocol of Jones et al. (2013) was used for the 5STS. The patient had to sit on a 43-47 cm high straight-backed, armless chair with a hard seat. We placed the chair against the wall for safety. The arms were folded across the chest and the feet were fully on the ground. The patient was asked to stand up straight from the chair and to sit down again. This was repeated five times as fast as possible. The following instruction was given: *“Stand up all the way and sit down landing firmly, as fast as possible, five times without using the arms”*. The time was

measured with a stopwatch and started when the researcher gave the “start command”. The time stopped when the patient ended the fifth stand. The measured time was used for analysis. No retest was performed unless there was a clear submaximal effort. For a COPD population, the 5STS showed excellent test-retest with an ICC of 0.97 (95% CI 0.95 to 0.99) and excellent interobserver reliability with an ICC of 0.99 (95% CI 0.99 to 1.00) according to Jones et al. (2013).

The last part of the SPPB is the balance test. The protocol of Guralnik et al. (2000) was used. The patient was asked to stand up straight and hold the three different positions for 10 seconds. These three positions were: stand up straight with the feet together (side by side stand), stand up with the feet in semi tandem, and to stand up with the feet in tandem position. The patient must be able to stand unassisted without the use of a cane or walker. The researcher may help the patient to get into the right position. First, the semi tandem stand was performed. The researcher stood next to the patient for helping him/her into the right position and also for safety. However, patients should not be fully supported by the researcher. The following instruction was giving: *“Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you”*. The time was measured with a stopwatch and began when the patient was in the correct position. If the patient is unable to do semi tandem stand for 10 seconds, the side by side stand was performed. When the patient was able to perform the semi tandem for 10 seconds, the tandem stand was the next position that was tested. The previous procedure was used for all the positions. For analysis we used the score zero or one. When the patient was able to hold the position for 10 seconds the score one was used, zero when he was not. According to Medina-Mirapeix et al. (2016) the balance test has a questionable reliability with ICC values of 0.33 (95% CI 0.42 to 0.68). The SPPB is a valid tool to estimate mobility limitations in a COPD population with AUC = 0.75 (>0.7), (95% CI 0.66–0.85) (Bernabeu-Mora et al., 2015). Medina-Mirapeix et al. (2016) state that the inter-observer reliability is good with ICC values of 0.92 (95% CI 0.62 to 0.91) for the total SPPB in a COPD population.

To assess the isometric quadriceps muscle strength, we used a hand-held dynamometer (Microfet2, Biometrics, NL). The hand-held dynamometer has an excellent inter and intra-operator reproducibility (ICC 0.95 and 0.99) for the measurement of quadriceps muscle strength in patients with COPD (Beaumont et al., 2017). The used protocol was the “UZ Leuven



protocol". Before the test was performed, the Microfet2 device has to be calibrated with standardized weight and the battery needs to be checked. The patient had to sit on the edge of the treatment table in the upright position without backrest, with their feet not touching the ground and the knee cavities not against the table. The knees and hips were in 90° flexion. The hands were lying pronated on the thighs. First, the intended movement was shown to the patient by passively moving the leg. Secondly, there was a submaximal practice trial. Next, the make test was performed on the right then left side, meaning that the researcher did not break through the resistance of the patients so the patient performed an isometric contraction. The following instruction was given: *"You need to extend your leg as powerful as possible. I will apply counterpressure using the device and will prevent any movement."* The treatment table was placed close to a wall, so that the researcher could seek support against the wall while giving resistance to the patient. The test was repeated three times on both sides. After each trial, the device was reset. Variability should be preferably <5% between the two highest values, if not an extra trial was performed. The highest score in Newton was used for analysis.

We used normative values to compare the isometric muscle strength measurements, obtained with a hand-held dynamometer. We calculated percentage predicted of the quadriceps muscle strength using the equation, stated in the paper of Andrews, Thomas, & Bohannon (1996).

The values of FEV<sub>1</sub>% were measured following the ERS standards (Miller et al., 2005). They were measured by a nurse at the department 'lung function' and the data of each subject were included in the study by consulting their medical files.

### 3.4 Data analysis

Data analysis was performed using IBM SPSS statistics 25 program (IBM Corp., 2017). Data are reported as mean  $\pm$  standard deviation, median [interquartile range] or number (percentage). A p-value lower than 0.05 was contemplated as statistically significant. Descriptive statistics were used to characterize the patients. All data were tested for normality, afterwards an independent t-test for normally distributed data or Mann–Whitney U test for not normally distributed data was used to compare the stable patients with COPD and subjects with severe exacerbations. Nominal comparisons were done with Chi-square tests.

For our first part of the study, we investigated whether the unstable patients scored differently on each subtest of the SPPB than a stable population of patients with COPD. For this aim, an independent t-test for the 4MGS and a Mann–Whitney U test for the SPPB, 5STS and the balance total score were used to compare the results between the two populations. A secondary aim was to evaluate the predictive value of the FEV<sub>1</sub>% and quadriceps muscle strength on the SPPB score in both a stable and unstable population of patients with COPD. The continuous explanatory variables (x-variable) were the FEV<sub>1</sub>% and quadriceps muscle strength. The response variable (y-variable) was the SPPB score, which was ordinal. First, the Kolmogorov-Smirnov normality test and Pearson's linear correlation were used for the data analysis. All of the assumptions of the statistical method were respected, including the absence of multicollinearity among the independent variables. Multiple linear regression models by the enter method were used for this first part.



## 4 Results

### 4.1 Subjects

A total of 50 participants were included in the cohort study. Data were collected of 28 stable patients with COPD and 22 patients with a severe exacerbation from June 2017 until May 2019.

Table 1 summarizes the characteristics of both samples. The stable population had a mean age of  $65.93 \pm 8.24$  years, similar to that of the population of patients with severe exacerbations ( $67.23 \pm 10.49$  years). Furthermore, FFMI ( $p= 0.133$ ), CAT ( $p= 0.262$ ), mMRC dyspnoea ( $p= 0.167$ ), GOLD stage ( $p= 0.129$ ) and GOLD group ( $p= 0.209$ ) were similar in both groups. The stable group had a population of 15 male and 13 female subjects in contrast to seven male and 15 female subjects with severe exacerbations. Gender was not significantly different between both groups ( $p= 0.158$ ). The stable group had a statistically significant higher FEV<sub>1</sub>%, 6MWD, handgrip strength and reported different smoking behaviour ( $p<0.05$ ). Different missing data were reported. In the stable COPD population there were three missing values for FFMI, two missing CAT and two missing MRC dyspnoea scores. Nine missing data for the FEV<sub>1</sub>% were reported. Four data, regarding the GOLD stage and GOLD group were missing. Lastly, one measurement of handgrip strength and two data about smoking history were reported to be missing in the stable COPD subjects. In the group of patients with severe exacerbations, there were six missing data about the GOLD group and six missing values for the FEV<sub>1</sub>%.

#### 4.2 Between group comparison of SPPB subtests

First, the difference between groups of stable patients and patients with severe exacerbations was investigated. A significant difference in total SPPB score between stable subjects and subjects with severe exacerbation was found ( $p=0.019$ ). With a median score of 11.00 and 8.00 respectively (Table 2). This difference in total score was mainly due to the difference in 5STS and 4MGS. Figure 1 shows similar median scores (4.00) for the balance part of the SPPB in a population of stable subjects and subjects with severe exacerbations ( $p=0.078$ ).

Figure 2 and 3 depict a statistically significant difference ( $p=0.002$ ) in 4MGS and 5STS with a mean 0.99m/s and median 11.57s in the stable population in contrast to 0.73m/s and 15.16s in subjects with severe exacerbations. These results are similar to the difference in quadriceps muscle strength percentage of the predicted value for age, gender and weight of the individual subjects (Table 2).

#### 4.3 Association between FEV<sub>1</sub>%, quadriceps muscle strength and SPPB score

Figure 4 presents the linear correlation ( $r$ ) between the explanatory variable quadriceps muscle strength and the total SPPB score in both stable patients and patients with severe exacerbations. We found a moderate correlation in the stable sample ( $r=0.428$ ) and a strong correlation ( $r=0.774$ ) was found between the quadriceps muscle strength and SPPB score in patients with severe exacerbations.

Figure 5 shows the linear correlation ( $r$ ) between FEV<sub>1</sub>% and the SPPB score. There was a very weak correlation between the FEV<sub>1</sub>% and the SPPB score in stable patients ( $r=0.025$ ) and in patients with severe exacerbations as well ( $r=0.154$ ). Linear regression models to predict SPPB scores with FEV<sub>1</sub>% and either quadriceps muscle strength or quadriceps muscle strength percentage predicted were calculated. Table 3 shows the models for stable patients with COPD. The model using quadriceps muscle strength and FEV<sub>1</sub>% had an R-squared value of 0.186. Table 4 depicts the same models for patients with severe exacerbations. The model with quadriceps muscle strength and FEV<sub>1</sub>% had an R-squared value of 0.630.

Moreover, Table 5 shows the same models for a population of both stable COPD patients and patients with severe exacerbations. In this case, the second model using quadriceps muscle strength percentage predicted and FEV<sub>1</sub>% has a bigger R-squared value (0.512) than the one using quadriceps muscle strength (0.472).



## 5 Discussion

### 5.1 Interpretation of results

To the author's best knowledge, this is the first study comparing SPPB subtests in stable COPD patients and patients with severe exacerbations. Patients with severe exacerbations scored worse on the 4MGS and 5STS than stable patients with COPD. Balance scores were similar between groups, as hypothesised. This subtest analysis suggests that quadriceps muscle strength and functional status might be an even greater key factor in rehabilitation of patients with severe exacerbations. Future research should confirm this difference between patients with stable COPD and patients with severe exacerbations.

Furthermore, this is the first study exploring the relationship between quadriceps muscle strength, FEV<sub>1</sub>% and SPPB score in a COPD sample with severe exacerbations as well as a stable COPD population. As predicted, quadriceps muscle weakness was more related to a poor SPPB score in patients with unstable COPD. In contrast to the hypothesis, low FEV<sub>1</sub>% had a very weak correlation with a poor SPPB score, in both a stable and an unstable COPD population.



## 5.2 Comparison with other literature

In this study, patients with severe exacerbations presented a significant decrease in quadriceps muscle strength, greater than the one observed in stable patients with COPD. These results are in line with Spruit et al. (2003) where patients with severe exacerbations had similar or greater decreases in peripheral muscle strength than patients with stable COPD. Hyatt, Whitelow, Bhat, Scott & Maxwell (1990) studied the association between muscle strength and functional status in elderly people and stated muscle strength correlated with several measures of functional status. It has been shown that quadriceps muscle weakness is associated with deficits in balance and gait speed. Additionally, it is also an extremely important factor to stand up from a chair, as in the 5STS (Moxley Scarborough, Krebs, & Harris, 1999; Hughes, Myers & Schenkman 1996). Therefore, quadriceps muscle strength has been related to all three domains of the SPPB in patients with COPD (Bernabeu-Mora et al. 2017). Likewise, a low quadriceps muscle strength related to a poor SPPB total score (Patel et al., 2014).

On the basis of our results, we dare to claim that the SPPB is a useful tool to investigate functional limitations in patients with severe exacerbations. Earlier, the same has been proven in stable patients with COPD and older hospitalized patients without COPD (Bernabeu-Mora et al., 2015; Fisher, Ottenbacher, Goodwin, Graham, and Ostir, 2009). Because of the very important role of quadriceps muscle strength in patients with severe exacerbations, Puhan et al. (2013) suggests measuring how many times a person can stand up from a chair in one minute. This paper investigates functional tests in relation with mortality in COPD. It is stated that this test could be an even more important test and puts a greater emphasis on endurance than the tests within the SPPB (Puhan et al., 2013). We calculated quadriceps muscle strength percentage predicted for gender, age and weight. This gives a better look at the muscle strength of an individual patient with COPD. Furthermore the R-squared value of the general linear regression model (Table 3) was higher when we used quadriceps muscle strength percentage predicted instead of muscle strength. Although, we think the use of percentage predicted value might be less accessible to work with in everyday practice. Moreover, the separate models for stable patients (Table 4) and patients with severe exacerbations (Table 5) did not improve when using the percentage predicted value. We suggest, the percentage predicted might be more useful in a mixed population of stable patients and patients with

exacerbations. Certainly in a more professional setting where data and formulas for this calculation can be easily applied.

FEV<sub>1</sub>% was not related to SPPB score in both stable and patients with severe exacerbations. Controversial results were found in older studies like Eisner et al. (2008). Furthermore Medina-Mirapeix et al. (2018) found that low FEV<sub>1</sub>% is related to poor SPPB score in an older population (60-80 years). Nevertheless, recent studies show similar results as our study and counter the relationship between the FEV<sub>1</sub>% and the SPPB score (Karpman, DePew, LeBrasseur, Novotny & Benzo, 2014; Patel et al., 2014) or any of the three domains of the SPPB in patients with COPD (Bernabeu-Mora et al. 2017).

Furthermore, when we take a closer look at Table 1, CAT score is significantly higher in patients with severe exacerbations. According to Bernabeu-Mora et al. (2017) health score, measured by CAT score was associated with the 5STS but not with the other two tests of the SPPB. Cignarella et al. (2018) referred to the CAT as a significant predictor of severe exacerbations in veterans. We hypothesize that if we add CAT score to our linear regression models with quadriceps and FEV<sub>1</sub>% for both populations, the predictive models could be even better than the ones in this study.

Additionally, the 6MWD was higher in a population of stable COPD patients (Table 1). According to Bernabeu-Mora et al. (2017) the 6MWT was negatively associated with the 4MGS and 5STS. We hypothesize that if we add 6MWD to our linear regression the same way as the CAT score, the predictive models could also improve. Moreover, we think the 6MWT might be a more important functional test in patients with stable COPD than other functional tests. In stable patients, physical endurance is a more important aspect. Therefore, stable patients are more likely to be able to perform the 6MWT and to walk longer distances. We advise the addition of 6MWD and CAT in predictive models of SPPB score in future research.

We noticed that the balance part of the SPPB was not significantly different between both groups. This is probably because balance is a complex skill that also relies on other determinants, such as the integration and coordination of musculoskeletal systems and neural systems (Beauchamp et al., 2012; Vittinghoff & McCulloch 2007). We do not expect that these systems are more affected in patients with severe exacerbations. Besides, its reliability was questionable (Medina-Mirapeix et al. 2016). The balance test might be the least specific and therefore least important part of the SPPB. In this study, most of the patients had a maximum score on the balance test (Figure 1). This ceiling effect could make it harder to find differences

between individual patients with COPD. Further research should investigate the validity and reliability of the SPPB within patients with severe exacerbations.

Our initial plan was to subdivide the results of the SPPB describing the grade of restriction, i.e. >9; 4-9; and <3 according to the protocol of Guralnik et al. (2000). However, when we finished data collection, we found that the patients in both groups had scores in only the two highest categories which would mean binomial data. Thus, we decided to keep the ordinal value in order to perform a more thorough and comprehensive analysis of the data.

Altogether, the SPPB is useful in clinical practice to evaluate the functional status of COPD patients, both stable and unstable. Moreover, this test has a good correlation with quadriceps muscle strength and is less expensive than the hand-held dynamometer or Cybex II which can be interesting in a more professional clinical setting. Additionally, the SPPB test demands less time than the 6MWD for instance.

### 5.3 Limitations and strengths

This study has some limitations. For example, stable patients were tested at the same day of health examinations in an outpatient pulmonary service. Only cross-sectional strategies were used in this paper. Thus, causal relationships could not be explored. Patients with severe exacerbations received physiotherapy in the hospital (20-30 min). Some stable patients also went to physiotherapy sessions in the hospital. However, we did not keep track of these data in our study. Further, any use of medication as well as pack years were not reported along with the characteristics in Table 1.

Another limitation is the difference in smoking behaviour between the two groups. We also had a relatively small sample size. For future research, it would be interesting to have a larger sample size and a longitudinal study to examine the effect all outcomes on future exacerbations. Missing data were reported, namely the high amount of missing data of the FEV<sub>1</sub>% can be a bias when interpreting our results. We measured quadriceps muscle strength with a hand-held dynamometer instead of an isokinetic dynamometer, such as the Cybex II (Lumex, Inc., New York, New York). Although, these devices can provide better isolation of muscle groups and more information about muscle dynamics, they are expensive and require specialized training to use. In contrast, dynamometers are more feasible in terms of both cost (+/- €1000) and ease of use. On the one hand, hand-held dynamometers correlate strongly with isokinetic dynamometers and provide valid and reliable results (Agre et al., 1987). On the other hand, the skill of the researcher plays an important role in these kind of testings. All of the researchers were well-trained and followed a strict protocol that was described in our methods. However, four different researchers carried out measurements in this study, this might have an influence on the results. Besides, Visser et al. (2003) state that measurements with forces above 250N, a hand-held dynamometer might be less sensitive, due to limited strength of the tester.

One of the strengths of the current study is the clear method section, which makes it easy for other researchers to replicate a study with a similar protocol. Likewise, clear inclusion- and exclusion criteria were described. Another strength is that multiple functional tests and measurements were performed, so different data can easily be compared. More importantly, the study contained a sample of both unstable COPD patients and patients with severe exacerbations. Our study was unique in a way that it compared the subtests of the SPPB in

both groups. It also examined the relationship of values with the total SPPB score with the aim of investigating the utility of the SPPB. This in a population of patients with severe exacerbations in comparison with a stable COPD population. Additionally, we aimed to make suggestions concerning tests that might be more important in either patients with severe exacerbations or patients with COPD. In this way, we try to contribute to a more comprehensive approach of COPD rehabilitation. Finally an extensive comparison was made between the findings of this study and already existing literature.

## **6 Conclusion**

We conclude that the SPPB is a useful tool in patients with severe exacerbations as well as patients with stable COPD. Patients with severe exacerbations score worse on the SPPB due to a poor 4MG and 5STS. Future research should confirm this difference in patients with stable COPD and investigate the validity and reliability of the SPPB in patients with severe exacerbations. Furthermore, in our study, quadriceps muscle strength was moderately correlated to SPPB score in a stable population and had a very strong correlation in patients with severe exacerbations. Future research should investigate the correlation of CAT and 6MWD with SPPB score in patients with severe exacerbations. Lastly, more research should be done concerning the predictive value of functional tests, its subtests, muscle strength and predictive models with these values on future exacerbations.



## 7 Reference list

- Agre, J. C., Magness, J. L., Hull, S. Z., Wright, K. C., Baxter, T. L., Patterson, R., & Stradel, L. (1987). Strength testing with a portable dynamometer: reliability for upper and lower extremities. *Arch Phys Med Rehabil*, *68*(7), 454-458.
- Andrews, A. W., Thomas, M. W., & Bohannon, R. W. (1996). Normative values for isometric muscle force measurements obtained with hand-held dynamometers. *Phys Ther*, *76*(3), 248-259. doi:10.1093/ptj/76.3.248
- Beauchamp, M. K., Sibley, K. M., Lakhani, B., Romano, J., Mathur, S., Goldstein, R. S., & Brooks, D. (2012). Impairments in systems underlying control of balance in COPD. *Chest*, *141*(6), 1496-1503. doi:10.1378/chest.11-1708
- Beaumont, M., Kerautret, G., Peran, L., Pichon, R., Le Ber, C., & Cabillic, M. (2017). [Reproducibility of strength and endurance measurements of the quadriceps in patients with COPD]. *Rev Mal Respir*, *34*(9), 1000-1006. doi:10.1016/j.rmr.2016.11.004
- Bernabeu-Mora, R., Gimenez-Gimenez, L. M., Montilla-Herrador, J., Garcia-Guillamon, G., Garcia-Vidal, J. A., & Medina-Mirapeix, F. (2017). Determinants of each domain of the Short Physical Performance Battery in COPD. *Int J Chron Obstruct Pulmon Dis*, *12*, 2539-2544. doi:10.2147/copd.S138402
- Bernabeu-Mora, R., Medina-Mirapeix, F., Llamazares-Herran, E., Garcia-Guillamon, G., Gimenez-Gimenez, L. M., & Sanchez-Nieto, J. M. (2015). The Short Physical Performance Battery is a discriminative tool for identifying patients with COPD at risk of disability. *Int J Chron Obstruct Pulmon Dis*, *10*, 2619-2626. doi:10.2147/copd.S94377
- Bernard, S., LeBlanc, P., Whittom, F., Carrier, G., Jobin, J., Belleau, R., & Maltais, F. (1998). Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, *158*(2), 629-634. doi:10.1164/ajrccm.158.2.9711023
- Cignarella, A. G., Shiva, P. B., Tovar, K., Urdaneta, G., Vital, I., Holt, G., . . . Campos, M. A. (2018). COPD Assessment test (CAT) Score as a predictor of severe exacerbations in veterans. In: Eur Respiratory Soc.
- Eisner, M. D., Iribarren, C., Yelin, E. H., Sidney, S., Katz, P. P., Ackerson, L., . . . Blanc, P. D. (2008). Pulmonary function and the risk of functional limitation in chronic obstructive pulmonary disease. *Am J Epidemiol*, *167*(9), 1090-1101. doi:10.1093/aje/kwn025



- Fisher, S., Ottenbacher, K. J., Goodwin, J. S., Graham, J. E., & Ostir, G. V. (2009). Short Physical Performance Battery in hospitalized older adults. *Aging Clin Exp Res, 21*(6), 445-452.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of COPD. 2018 report
- Guralnik, J. M., Ferrucci, L., Pieper, C. F., Leveille, S. G., Markides, K. S., Ostir, G. V., . . . Wallace, R. B. (2000). 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, 55*(4), M221-231.
- Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., . . . Wallace, R. B. (1994). A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol, 49*(2), M85-94.
- Hughes, M. A., Myers, B. S., & Schenkman, M. L. (1996). The role of strength in rising from a chair in the functionally impaired elderly. *J Biomech, 29*(12), 1509-1513.
- Hyatt, R. H., Whitelaw, M. N., Bhat, A., Scott, S., & Maxwell, J. D. (1990). Association of muscle strength with functional status of elderly people. *Age Ageing, 19*(5), 330-336. doi:10.1093/ageing/19.5.330
- Jakovljevic, M. B., Lazic, Z., Verhaeghe, N., Jankovic, S., Gajovic, O., & Annemans, L. (2013). Direct medical costs of COPD diagnosis and treatment, Eastern vs Western European country – examples of Serbia and Belgium. *Farmeconomia. Health economics and therapeutic pathways; Vol 14, No 4 (2013)DO - 10.7175/fe.v14i4.676*
- Jones, S. E., Kon, S. S., Canavan, J. L., Patel, M. S., Clark, A. L., Nolan, C. M., . . . Man, W. D. (2013). The five-repetition sit-to-stand test as a functional outcome measure in COPD. *Thorax, 68*(11), 1015-1020. doi:10.1136/thoraxjnl-2013-203576
- Karpman, C., DePew, Z. S., LeBrasseur, N. K., Novotny, P. J., & Benzo, R. P. (2014). Determinants of gait speed in COPD. *Chest, 146*(1), 104-110. doi:10.1378/chest.13-2017
- Kon, S. S., Patel, M. S., Canavan, J. L., Clark, A. L., Jones, S. E., Nolan, C. M., . . . Man, W. D. (2013). Reliability and validity of 4-metre gait speed in COPD. *Eur Respir J, 42*(2), 333-340. doi:10.1183/09031936.00162712

- Medina-Mirapeix, F., Bernabeu-Mora, R., Llamazares-Herran, E., Sanchez-Martinez, M. P., Garcia-Vidal, J. A., & Escolar-Reina, P. (2016). Interobserver Reliability of Peripheral Muscle Strength Tests and Short Physical Performance Battery in Patients With Chronic Obstructive Pulmonary Disease: A Prospective Observational Study. *Arch Phys Med Rehabil*, *97*(11), 2002-2005. doi:10.1016/j.apmr.2016.05.004
- Medina-Mirapeix, F., Bernabeu-Mora, R., Sanchez-Martinez, M. P., Montilla-Herrador, J., Bernabeu-Mora, M., & Escolar-Reina, P. (2018). Mobility limitations related to reduced pulmonary function among aging people with chronic obstructive pulmonary disease. *PLoS One*, *13*(5), e0196152. doi:10.1371/journal.pone.0196152
- Miller, M. R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., . . . Wanger, J. (2005). Standardisation of spirometry. *Eur Respir J*, *26*(2), 319-338. doi:10.1183/09031936.05.00034805
- Moxley Scarborough, D., Krebs, D. E., & Harris, B. A. (1999). Quadriceps muscle strength and dynamic stability in elderly persons. *Gait Posture*, *10*(1), 10-20
- Patel, M. S., Mohan, D., Andersson, Y. M., Baz, M., Samantha Kon, S. C., Canavan, J. L., . . . Polkey, M. I. (2014). Phenotypic characteristics associated with reduced short physical performance battery score in COPD. *Chest*, *145*(5), 1016-1024. doi:10.1378/chest.13-1398
- Puhan, M. A., Siebeling, L., Zoller, M., Muggensturm, P., & ter Riet, G. (2013). Simple functional performance tests and mortality in COPD. *Eur Respir J*, *42*(4), 956-963. doi:10.1183/09031936.00131612
- Spruit, M. A., Gosselink, R., Troosters, T., Kasran, A., Gayan-Ramirez, G., Bogaerts, P., . . . Decramer, M. (2003). Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax*, *58*(9), 752-756
- Visser, J., Mans, E., de Visser, M., van den Berg-Vos, R. M., Franssen, H., de Jong, J. M., . . . de Haan, R. J. (2003). Comparison of maximal voluntary isometric contraction and hand-held dynamometry in measuring muscle strength of patients with progressive lower motor neuron syndrome. *Neuromuscul Disord*, *13*(9), 744-750.

Vittinghoff, E., & McCulloch, C. E. (2007). Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*, 165(6), 710-718. doi:10.1093/aje/kwk052

## 8 Appendices

Table 1: Baseline characteristics

Table 2: Difference between groups

Table 3: Linear regression models to predict SPPB Score in a population of stable COPD

Table 4: Linear regression models to predict SPPB Score in a patients with severe exacerbations

Table 5: Linear regression models to predict SPPB Score

Figure 1: Balance test

Figure 2: Five repetition sit to stand

Figure 3: Four meter gait speed

Figure 4: Quadriceps muscle strength and SPPB correlation

Figure 5: FEV<sub>1</sub>% and SPPB correlation



Table 1

## Baseline characteristics

Baseline characteristics	Stable (n=28)	Exacerbation (n=22)	p-value
Age (yr), <i>M ± SD</i>	65.93 ± 8.24	67.23 ± 10.49	0.626
FFMI (kg/m <sup>2</sup> ), <i>M ± SD</i>	8.52 ± 2.34	10.06 ± 4.11	0.133
FEV <sub>1</sub> (%), <i>M ± SD</i>	52.73 ± 17.20	39.20 ± 12.04	0.012 *
CAT, <i>M ± SD</i>	17.27 ± 6.74	19.32 ± 5.56	0.262
6MWD (m) , <i>Median</i> <i>[interquartile range]</i>	405.50 [323.00; 539.25]	272.50 [123.00; 316.75]	0.000 *
Handgrip strength, <i>M ± SD</i>	37.41 ± 14.65	26.59 ± 10.09	0.005 *
Gender, <i>N(%)</i>			0.158
male	15 (53.6)	7 (31.8)	
female	13 (46.4)	15 (68.2)	
GOLD stage, <i>N(%)</i>			0.129
I	1 (3.6)		
II	17 (60.7)	6 (33.3)	
III	6 (21.4)	9 (50.0)	
IV	4 (14.3)	3 (16.7)	
GOLD group, <i>N(%)</i>			0.209
A	6 (24.0)		
B	6 (24.0)	4 (25.0)	
C	3 (12.0)	2 (12.5)	
D	10 (40.0)	10 (62.5)	
Smoking, <i>N(%)</i>			0.034 *
never	1 (3.8)	1 (4.5)	
current	6 (23.1)	0 (0.0)	
former	19 (73.1)	21 (95.5)	
mMRC dyspnoea, <i>Median</i> <i>[interquartile range]</i>	2.00 [1.00; 3.00]	2.00 [1.75; 3.25]	0.167

*Note. Abbreviations:* M=mean, SD=standard deviation, N=number, yr=years, FFMI=Fat Free Mass Index cm=centimetres, kg/m<sup>2</sup>=kilograms per meter square, FEV<sub>1</sub>%=forced expiratory volume in the first second, m=metres, CAT=COPD assessment test, 6MWD=six minute walking distance, mMRC=modified Medical Research Council Dyspnoea Scale

\**p-value* < 0.05

Table 2

Difference between groups

Outcome	Stable	Exacerbation	p-value
Quadriceps%pred, <i>M ± SD</i>	97.63 ± 24.55	79.42 ± 28	0.022 *
4MGS, <i>M ± SD</i>	0.99 ± 0.25	0.73 ± 0.28	0.002 *
Balance test, <i>Median [interquartile range]</i>	4.00 [4.00; 4.00]	4.00 [2.00; 4.00]	0.078
5STS, <i>Median [interquartile range]</i>	11.57 [9.90; 14.22]	15.16 [12.13; 19.69]	0.002 *
SPPB, <i>Median [interquartile range]</i>	11.00 [9.00; 12.00]	8.00 [6.00; 10.50]	0.019 *

*Note. Abbreviations:* M=mean, SD=standard deviation, Quadriceps%pred=Quadriceps muscle strength percentage predicted, 4MGS=four meter gait speed, 5STS=five repetition sit to stand, SPPB=Short Physical Performance Battery

\**p-value* <0.05

Table 3

Linear regression models to predict SPPB Score in a population of **stable COPD**

SPPB Score			
Predictive models	Explanatory Variables	R <sup>2</sup>	R <sup>2</sup> adjusted
Model 1	Quadriceps strength, FEV <sub>1</sub> %	0.186	0.078
Model 2	Quadriceps strength % predicted, FEV <sub>1</sub> %	0.126	0.002

*Note. Abbreviations:* FEV<sub>1</sub>%=forced expiratory volume in the first second percentage predicted

Table 4

Linear regression models to predict SPPB Score in patients with **severe exacerbations**

SPPB Score			
Predictive models	Explanatory Variables	R <sup>2</sup>	R <sup>2</sup> adjusted
Model 1	Quadriceps strength, FEV <sub>1</sub> %	0.630	0.568
Model 2	Quadriceps strength % predicted, FEV <sub>1</sub> %	0.593	0.525

*Note. Abbreviations:* FEV<sub>1</sub>%=forced expiratory volume in the first second percentage predicted

Table 5

Linear regression models to predict SPPB Score

SPPB Score			
Predictive models	Explanatory Variables	R <sup>2</sup>	R <sup>2</sup> adjusted
Model 1	Quadriceps strength, FEV <sub>1</sub> %	0.472	0.438
Model 2	Quadriceps strength % predicted, FEV <sub>1</sub> %	0.512	0.478

*Note. Abbreviations:* FEV<sub>1</sub>%=forced expiratory volume in the first second percentage predicted



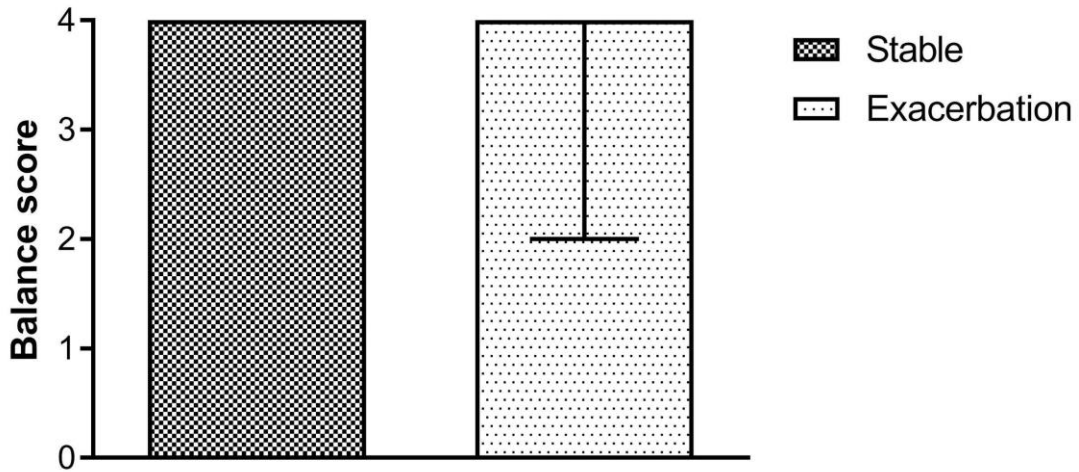


Figure 1: Balance test

\**p-value* <0.05

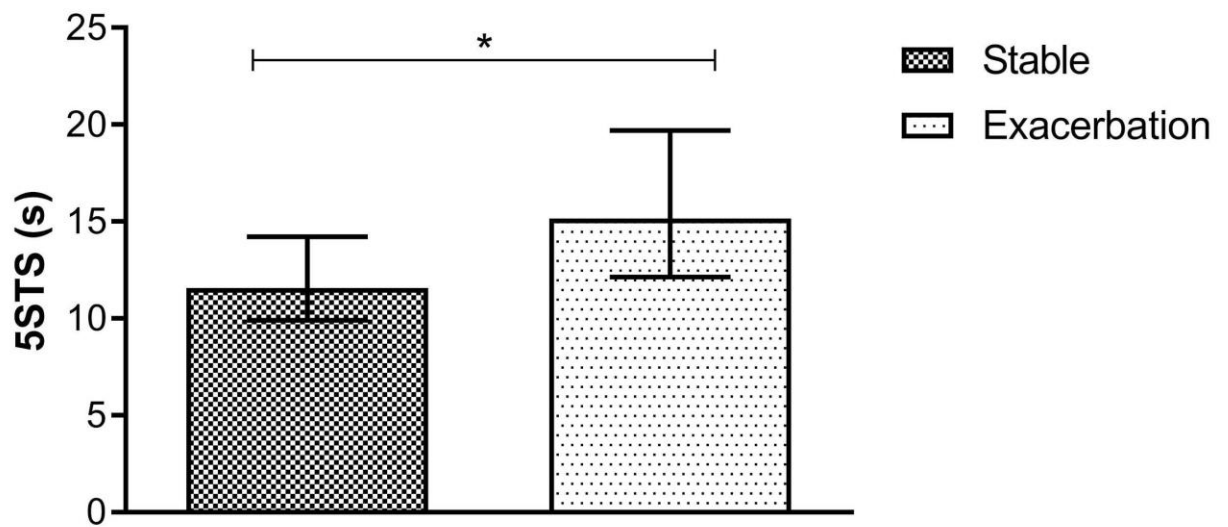


Figure 2: Five repetition sit to stand

Note. Abbreviations: 5STS=5 repetition sit to stand, s=second

\**p-value* <0.05

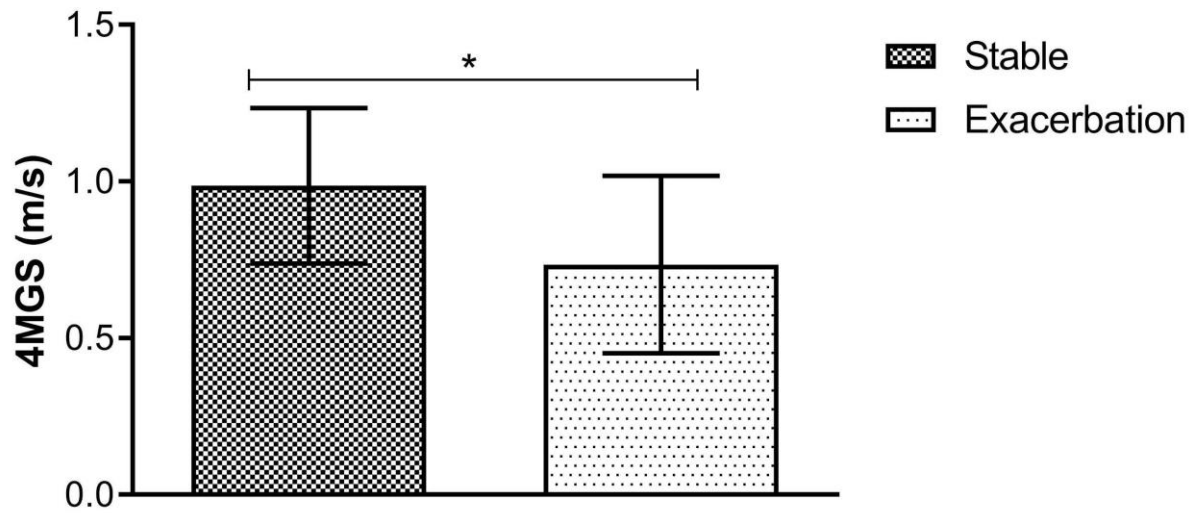


Figure 3: Four meter gait speed

Note. Abbreviations: 4MGS=four meter gait speed, m/s=meters per second

\**p*-value <0.05

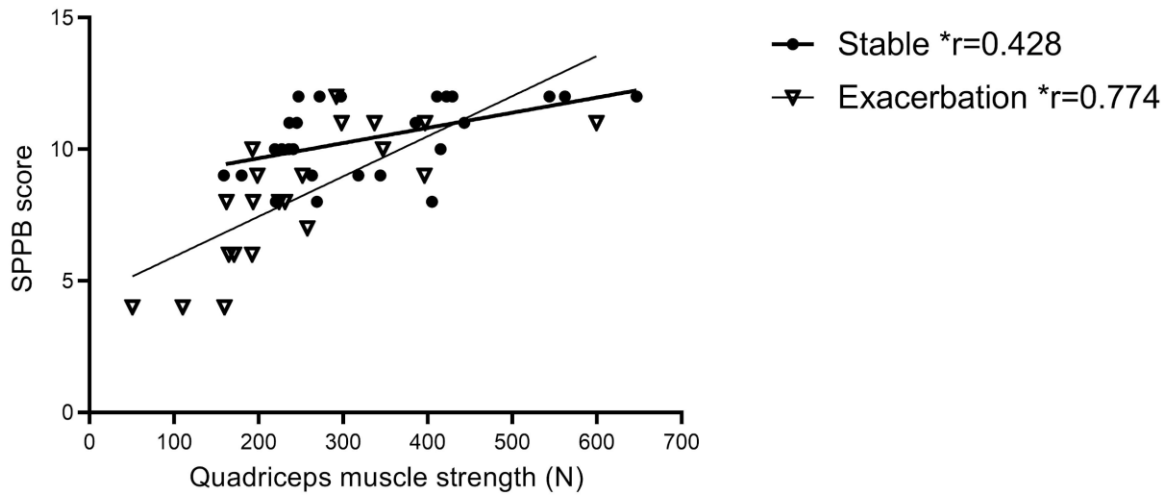


Figure 4: Quadriceps muscle strength and SPPB correlation

Note. Abbreviations: SPPB=Short Physical Performance Battery, N=Newton

\*p-value <0.05

Stable \*p=0.038; Exacerbation \*p=0.000

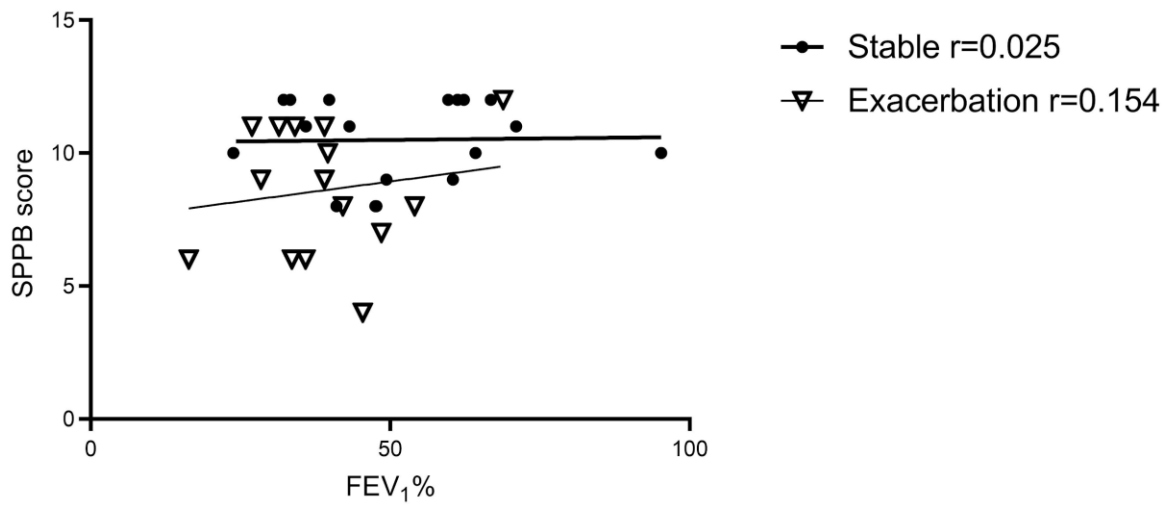


Figure 5: FEV1% and SPPB correlation

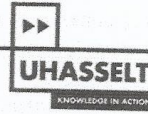
Note. Abbreviations: SPPB=Short Physical Performance Battery, FEV1%=forced expiratory volume in the first second percentage predicted

\*p-value <0.05

Stable p=0.398; Exacerbation p=0.292

Voortgangsformulier wetenschappelijke stage deel 2

www.uhasselt.be  
 Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt  
 Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek  
 T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be



INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
27/09/2018	stageperiodes, verloop van de thesis in grote lijnen, het maken van enkele afspraken	Promotor: Copromotor/Begeleider: Student(e): Student(e):
04/12/2018	onderzoeksvraag + hypothese	Promotor: Copromotor/Begeleider: Student(e): Student(e):
15/02/2019	onderzoeksvraag + hypothese	Promotor: Copromotor/Begeleider: Student(e): Student(e):
15/05/2019	overlopen tekst tot en met data analyse + bespreking data analyse	Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):