University of Porto

Faculty of Sport

Research Center in Physical Activity, Health and Leisure

_____

Emergent measures and patterns of recovery during acute exacerbations of Chronic Obstructive Pulmonary Disease

_____

Thesis submitted in fulfillment of the requirements for the degree of Doctor in Physiotherapy by the Faculty of Sport of the University of Porto, under the Law 74/2006 from March 24th.

Supervisor: Dr. Alda Sofia Pires de Dias Marques
School of Health Sciences, University of Aveiro, Aveiro

Co-supervisor: Dr. José Alberto Ramos Duarte
Faculty of Sport, University of Porto, Porto

Ana Oliveira

Porto, 2019

Funding

If you focus on the hurt, you will continue to suffer.

If you focus on the lesson, you will continue to grow.

Author Unknown

Acknowledgments

I would like to acknowledge several people without whom the development of this research work would not have been possible.

Firstly, I would like to thank all physicians, nurses and physiotherapists who have supported my research and all patients and families who participated and allowed me to briefly enter their lives in the course of my studies.

I would like to express my sincere gratitude to my supervisor Doctor Alda Marques. She has taught me, both consciously and unconsciously, how to grow as a human being and as a researcher. I would also like to thank my co-supervisor Doctor José Alberto Duarte for all his support.

I would like to thank Doctor João Rodrigues and Doctor Vera Afreixo for their insightful comments and encouragement which encouraged me to widen my research from various perspectives.

I owe a special thanks to Filipa Machado for her help in collecting data and to Cátia Pinho for her help in computerised respiratory sounds analysis.

To my fellow labmates of Lab3R, I thank them for the stimulating discussions, companionship and for providing a pleasure working atmosphere.

To all great researchers and health professionals I had the pleasure to meet and discuss my work with during the course of my studies. Their questions deeply enriched my vision and critical thinking about science.

To my closer friends, I express my gratitude for their unconditional friendship, support and patience throughout these years.

Last, but not least, I would like to thank to my parents, Albino and Armanda, my grandmother, Alice and my husband, João, for their unconditional support, encouragement and love, without which I would not have come this far.

Table of contents

List of figures

List of tables

List of appendices

Resumo

As exacerbações agudas da doença pulmonar obstrutiva crónica (EADPOC) são eventos frequentes e onerosos. Contudo, o conhecimento acerca da sua avaliação e curso de evolução é limitado. Este trabalho de investigação teve como objetivo compreender a avaliação e os padrões de recuperação das EADPOC geridas em contexto de ambulatório. Especificamente, pretendeu-se: i) aprofundar o conhecimento acerca das medidas de avaliação mais utilizadas na avaliação de doentes com EADPOC e ii) explorar os padrões de recuperação durante as EADPOC utilizando diferentes medidas de avaliação. Foram realizados seis estudos. A Revisão Sistemática e os Estudos empíricos I e II responderam ao primeiro objetivo específico deste trabalho de investigação, sintetizando e explorando a fiabilidade, validade, capacidade de resposta e interpretabilidade de medidas de avaliação comummente utilizadas e de fácil acesso para a avaliação de doentes com EADPOC em contexto de ambulatório. Os resultados revelaram que apesar de existirem poucas medidas de avaliação com as suas propriedades métricas adequadamente estudadas, os seus valores de interpretabilidade parecem semelhantes aos estabelecidos em fases estáveis da DPOC. O segundo objetivo específico deste trabalho de investigação foi alcançado através de três Estudos empíricos (Estudos III, IV e V) que demonstraram que a recuperação de uma EADPOC é influenciada pelas características dos doentes no momento inicial da exacerbação. Estes Estudos mostraram ainda que as medidas reportadas pelos doentes e as medidas clínicas diferem nos seus padrões e tempos de recuperação durante as EADPOC. Os resultados deste trabalho de investigação constituem nova evidência acerca das medidas de avaliação e dos momentos mais adequados para avaliar, monitorizar e interpretar alterações no curso de EADPOC. É necessário realizar mais investigação com metodologias padrão, amostras maiores e desenhos de estudo longitudinais com avaliações pré e pós exacerbação de forma a consolidar estes resultados preliminares e aumentar o conhecimento acerca do curso de evolução das EADPOC geridas em contexto de ambulatório.

Palavras-chave: DPOC, EXACERBAÇÕES, MEDIDAS DE RESULTADOS, PROPRIEDADES DE MEDIDA, RECUPERAÇÃO, EVOLUÇÃO.

Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are frequent and burdensome events. However, knowledge about their assessment and course of evolution is limited. This research work focused on understanding the assessment and recovery pattern of AECOPD managed on an outpatient setting. Specifically, it aimed to: i) gain more insight on the outcome measures most used to assess patients with AECOPD and their measurement properties and ii) explore patterns of recovery of different outcomes and outcome measures during these events. Six studies were conducted. The Systematic Review and empirical Studies I and II addressed the first specific aim of this research work by synthetising and exploring the reliability, validity, responsiveness and interpretability of outcome measures commonly used and easily available to assess outpatients with AECOPD. Findings showed that although few outcome measures exist which measurement properties have been properly studied in patients with AECOPD, their interpretability values seem to be similar to those in stable patients. The second specific aim of this research work was addressed with three empirical Studies (Studies III, IV and V) which showed that the recovery from AECOPD is influenced by patients' characteristics assessed at the onset of the exacerbation. These Studies further evidenced different patterns and timings of recovery among patient-reported and clinical outcome measures. The findings of this research work constitute new evidence on the most adequate outcome measures and timings to assess, monitor and interpret changes during the course of AECOPD managed on an outpatient setting. Further research with standardised methodologies, larger samples and longitudinal pre-/post exacerbation designs is warranted to consolidate these preliminary findings and increase the scope of knowledge on the time course of AECOPD treated on an outpatient basis.

Key words: COPD, EXACERBATIONS, OUTPATIENTS, OUTCOME MEASURES, MEASUREMENT PROPERTIES, RECOVERY, EVOLUTION.

List of abbreviations and symbols

5STS	5 times sit-to-stand test
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
ARS	Adventitious respiratory sounds
AUC	Area under the curve
BDI/TDI	Baseline dyspnoea index and transition dyspnoea index
BMI	Body mass index
CAT	COPD assessment test
CCI	Charlson comorbidity index
CCQ	Clinical COPD questionnaire
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CORSA	Computerised respiratory sound analysis
COSMIN	COnsensus-Based Standards for the selection of health status Measurement INstruments
CRQ	Chronic respiratory disease questionnaire
DALYs	Disability adjusted life years
CRS	Computerised respiratory sounds
d_z	Cohen's d effect size
EXACT-PRO	EXAcerbations of Chronic Pulmonary Disease Tool–Patient-Reported Outcome
F50	Median frequency
FEV_1	Forced expiratory volume in one second
GEE	Generalised estimating equation
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GOLD+SSI	Global Initiative for Chronic Obstructive Lung Disease plus symptom severity index
ICC	Intraclass correlation coefficient
Imax	Maximum intensity
LCADL	London chest activities of daily living scale

mBorg	Modified Borg scale
MBS	Modified Borg scale
MCDI	Minimal clinically important difference
MDC	Minimal detectable change
MDD	Minimal detectable difference
MESH	Medical subject headings
MID	Minimal important difference
mMRC	Modified British Medical Research Council questionnaire
NRS	Numeric rating scale
NS	Numeric scale
P	p-value
PEF	Peak expiratory flow
PImax	Maximum inspiratory pressure
PROM	Patient-reported outcome measures
QMS	Quadriceps muscle strength
r	Pearson correlation coefficient
ROC	Receiver operating characteristic
r_s	Spearman's rank correlation
SD	Standard deviation
SEM	Standard error of measurement
SGRQ	St George respiratory questionnaire
SN	Sensitivity
SP	Specificity
SpO_2	Peripheral oxygen saturation
%Wh	Occupation rate of wheezes
α	Alpha
κ	Cohen's kappa
$\sum$	Sum

Introduction

_____

General Introduction

Chronic respiratory diseases, defined as chronic conditions affecting the airways and the other structures of the lungs (World Health Organization, 2007), are rated by the World Health Organization as one of the four major chronic diseases of mankind (World Health Organization, 2008). Currently, more than one billion people suffer from chronic respiratory diseases worldwide (Forum of International Respiratory Societies, 2013) and, in Europe, the total annual cost of respiratory diseases amounts to more than €380 billion (European Respiratory Society, 2013). In Portugal, respiratory diseases are the 3rd leading cause of death and direct costs related to hospitalisations (in 2013 - €213 millions) (Direção-Geral da Saúde, 2016). These facts lead chronic respiratory diseases to represent a major health, societal and economic burden worldwide (World Health Organization, 2007).

Chronic obstructive pulmonary disease (COPD) is defined as a "*common, preventable and treatable disease that is characterised 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 gase*s" (The Global Initiative for Chronic Obstructive Lung Disease, 2019). Currently, COPD is one of the five major respiratory diseases (Forum of International Respiratory Societies, 2013), affecting 384 million people worldwide (Adeloye et al., 2015) and 800.000 people in Portugal (Araújo, 2016). Attention to diagnosis and management of COPD has been growing, with an increase of 241% new diagnosed cases from 2011 to 2016, in Portugal (Direção-Geral da Saúde, 2017). Nevertheless, according to the Portuguese national health regulator, COPD is still underdiagnosed (Direção-Geral da Saúde, 2017). Diagnosis of COPD should be considered in any patient who suffers from dyspnoea, chronic cough or sputum production, and/or has a history of exposure to risk factors for the disease, such as tobacco smoke, air pollution and occupational exposures (The Global Initiative for Chronic Obstructive Lung Disease, 2019). Although COPD prevalence is noted from the 40 decade of life onwards, it presents the highest prevalence

among those older than 60 years old (The Global Initiative for Chronic Obstructive Lung Disease, 2019). In these patients, COPD is currently the 3rd leading cause of Disability Adjusted Life Years (DALYs) lost worldwide (GBD 2015 DALYs and HALE Collaborators, 2016), being acute exacerbations of COPD (AECOPD) one of the events that most contribute to patients' disability in the long term (Chabot et al., 2014; Kerkhof, Freeman, Jones, Chisholm, & Price, 2015).

AECOPD, defined as an "*acute worsening of respiratory symptoms that result in additional therapy*" (The Global Initiative for Chronic Obstructive Lung Disease, 2019), are frequent events during the course of COPD (Wedzicha et al., 2017) with mean rates from 0.85 to 4 per patient/year (Boer et al., 2018; Hurst et al., 2010). AECOPD may be triggered or potentiated by several risk factors, such as smoking, severe airflow limitation, bronchiectasis, bacterial and viral infections and comorbidities (Kim & Aaron, 2018) and result in significant personal, societal, clinical and economic impacts (Anzueto, 2010; Guarascio, Ray, Finch, & Self, 2013; Kessler et al., 2006; Miravitlles, Anzueto, Legnani, Forstmeier, & Fargel, 2007; Patel, Nagar, & Dalal, 2014; Toy, Gallagher, Stanley, Swensen, & Duh, 2010). On an individual level, AECOPD are known to impair patients' health-related quality of life, psychological well-being and daily activities, with about 50% of patients being prevented from performing any activity during exacerbations (Kessler et al., 2006; Miravitlles et al., 2007). These effects have adverse consequences on patients' personal and family relationships, leading to isolation and avoidance of social activities (Kessler et al., 2006). In addition, periodic AECOPD often require treatment on an outpatient or inpatient basis, resulting in absence from work (Patel et al., 2014). Clinically, patients with more frequent exacerbations present more pronounced decreases in their lung function and exercise performance and are associated with increased morbidity and mortality (Anzueto, 2010). The upper mentioned adverse effects culminate in a substantial economic burden with individual costs per patient/exacerbation varying from $88 to $7.757 worldwide (Guarascio et al., 2013; Toy et al., 2010) and corresponding to 50% of all COPD-related costs (Celli & MacNee, 2004).

These epidemiologic and clinical data indicate that chronic respiratory diseases, namely COPD and its exacerbations, are posing tremendous challenges on health systems and societies (Price, Freeman, Cleland, Kaplan, & Cerasoli, 2011; Wilkinson, Donaldson, Hurst, Seemungal, & Wedzicha, 2004). Thus, their timely assessment and management have lately become a priority for researchers and health regulators (Direção-Geral da Saúde, 2015; Wilkinson et al., 2004), leading to several efforts to reach an in-depth understanding of the time course of AECOPD and the most effective interventions to accelerate recovery (Oliveira et al., 2017; Viniol & Vogelmeier, 2018; Wedzicha et al., 2017).

Due to the significant contribution of AECOPD to the progression of the disease (Halpin, Miravitlles, Metzdorf, & Celli, 2017) and direct economic costs (Anzueto, 2010), the time course of AECOPD requiring patients' hospitalisation has been widely studied. These studies have unravelled the behaviour of AECOPD treated at a hospital-basis and the response to treatment of relevant outcomes, such as dyspnoea, impact of the disease and patients' respiratory and peripheral muscle strength (Feliz-Rodriguez et al., 2013; Koutsokera et al., 2009; Mesquita, Donaria, Genz, Pitta, & Probst, 2013; Nishimura et al., 2018; Parker, Voduc, Aaron, Webb, & O'Donnell, 2005; Seemungal, Donaldson, Bhowmik, Jeffries, & Wedzicha, 2000; Seemungal et al., 1998; Spruit et al., 2003; Zhou et al., 2018). Thus, contributing to better plan and manage these patients' treatments on a hospital-basis. However, conflicting results have been reported on the behaviour of some outcomes, namely lung function (Mesquita et al., 2013; Parker et al., 2005; Seemungal et al., 2000), and on the effects of specific interventions with established evidence in the treatment of stable patients with COPD, such as pulmonary rehabilitation (Puhan, Gimeno-Santos, Cates, & Troosters, 2016; Wedzicha et al., 2017; Wilson et al., 2018). These inconsistencies among studies may occur due to the wide variety of outcomes and outcome measures used and/or due to the lack of appropriate measurement properties (i.e., reliability, validity and responsiveness) of these outcome measures used during exacerbation periods. Therefore, knowledge on the outcome measures used to assess a particular outcome and evidence on the

measurement properties of those instruments in patients with AECOPD is needed (research question I).

Secondly, although most research has been conducted in hospitalised patients, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), more than 80% of the AECOPD are managed on an outpatient basis (The Global Initiative for Chronic Obstructive Lung Disease, 2019), and failure in their treatment may lead to patients' prolonged disability and hospitalisations (Adams, Melo, Luther, & Anzueto, 2000; Macfarlane, Colville, Guion, Macfarlane, & Rose, 1993; Miravitlles, Murio, & Guerrero, 2001). Hospitalised patients differ from outpatients not only in their management but also in the severity of their exacerbation (The Global Initiative for Chronic Obstructive Lung Disease, 2019), which may influence their pattern of recovery. Thus, understanding outpatients' recovery during AECOPD seems crucial to timely manage and appropriately plan their follow-ups (research question II).

This document is presented in five chapters. An introduction (**Chapter I**) is first provided with an overview of the two research questions and research objectives. This chapter is followed by **Chapter II** – background – which introduces research question I by presenting a **Systematic review** of the outcome measures used to assess the effects of pulmonary rehabilitation in patients with AECOPD and synthesising their measurement properties. **Chapter III** is composed of five empirical studies developed to address the two research questions within the timeframe of this research work**.**

Research question I integrates two empirical studies – **Studies I** and **II,** that were built on the findings of the systematic review and explored the measurement properties of outcome measures to be used in patients with AECOPD. **Study I** explored the reliability, validity and minimal detectable difference (MDD) of computerised respiratory sounds in patients with COPD. **Study II** estimated the minimal important difference (MID) and MDD of the modified Borg scale (MBS), modified British Medical Research Council questionnaire (mMRC), peripheral oxygen saturation (SpO_2), computerised

6

respiratory sounds and forced expiratory volume in one second (FEV_1) in outpatients with AECOPD.

Research question II started to be addressed in **Study III**, where the changes in computerised adventitious respiratory sounds of patients with AECOPD managed on an outpatient basis were explored. Considering the same time period (i.e., AECOPD), **Study IV** evaluated the changes in patient-reported symptoms and its relationships with the clinical outcome measures previously studied, whereas **Study V** evaluated the time course of different clinical, physiological and functional outcome measures, as well as the factors influencing patients' recovery. An integrated discussion of the main findings, overall limitations and implications for future research and clinical practice follows in **Chapter IV**. **Chapter V** outlines the main conclusions of this research work and provides directions for further research in the field. Finally, **Chapter VI** presents the references used to support the General Introduction and General Discussion chapters. Figure 1 provides a graphic presentation of the rationale for this research work.
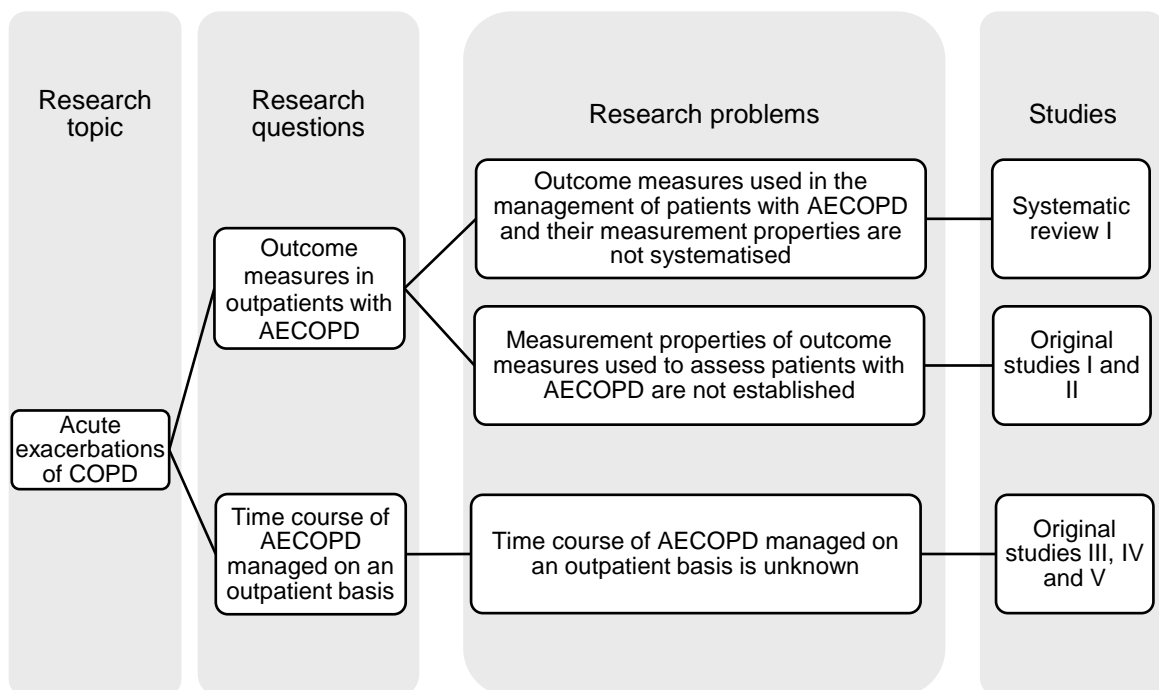
Figure 1. Graphic representation of the rationale for this research work.

Research question I

AECOPD are highly heterogeneous, presenting an extensive range of clinical presentations (Oliveira et al., 2017). Thus, management of these events is challenging, and in the last decade strong research efforts have been conducted to increase the pharmacological and non-pharmacological approaches available to these patients (Evensen, 2010; National Clinical Guideline Centre, 2010; Puhan et al., 2016; Viniol & Vogelmeier, 2018; Wedzicha et al., 2017). The most recent European Respiratory Society/American Thoracic Society guideline aimed to provide the basis for rational decisions in the treatment of AECOPD, however, due to the sparse evidence and inconsistency among the results of studies, the majority of recommendations were of conditional strength and moderate to very low quality (Wedzicha et al., 2017). The consequences of this guideline are of particular importance for non-pharmacological interventions, such as pulmonary rehabilitation, a high-quality evidence-based intervention for stable patients with COPD, which implementation in acute exacerbations has been recommended against. However, this recommendation mainly focuses in AECOPD managed on inpatient settings and no recommendations were made regarding those managed on outpatient settings, which account for more than 80% of all AECOPD (The Global Initiative for Chronic Obstructive Lung Disease, 2019). Additionally, the recommendations made were largely based on outcomes related with future exacerbations, hospitalisations, treatment failure and adverse events. But, as recently stressed by Wilson et al. (2018), several outcomes of interest, such as patient-reported symptoms, muscle strength and exercise tolerance were not taken into account. Thus, as pointed out in a previous European Respiratory Society/American Thoracic Society statement of 2015 (Celli et al., 2015), a question emerges on which outcomes and outcome measures are of relevance to assess the effects of treatments in patients with COPD, also during AECOPD. The selection of outcome measures in a clinical trial is of paramount importance as it can directly affect the success in capturing the impact of an intervention, or ultimately, mislead the true results (Coster, 2013; Ioannidis et al., 2014). Selecting unsuitable or poor-quality outcome measures

may lead to a waste of resources and even be unethical because participants contribute little to the body of knowledge but still suffer the burdens and risks of the study (Ioannidis et al., 2014). Thus, knowledge regarding new management strategies for outpatients with AECOPD should be built on sound evidence-based research using outcome measures that have demonstrated to be valid for the purpose and population in study, sensitive to small but clinically important changes and highly reproducible. These important psychometric properties of validity, reliability and responsiveness may also need to be balanced against some more practical considerations, such as costs and ease of use (Jerosch-Herold, 2005). Aiming at contributing to increase the knowledge on the measurement properties of outcome measures used to assess patients with AECOPD, a Systematic review was conducted. This **Systematic review** identified patient-reported and clinical (non-patient-reported) outcome measures commonly used to assess the effects of pulmonary rehabilitation in patients with AECOPD and that can be easily applied in an outpatient setting (i.e., not expensive, not invasive, and quickly implemented). Additionally, it also synthesised the measurement properties of the identified outcome measures, if available in the literature.

The **Systematic review** informed about some outcome measures which measurement properties have been tested in patients with AECOPD, such as computerised respiratory sounds. Computerised respiratory sounds are a simple, objective and non-invasive clinical measure (Bohadana, Izbicki, & Kraman, 2014) that can be acquired using electronic devices, such as digital stethoscopes and microphones, and classified/analysed using computerised technology based on specific signal characteristics of the respiratory sounds (Hadjileontiadis, 2018; Kahya, 2018; Pramono, Bowyer, & Rodriguez-Villegas, 2017). As its acquisition and analysis do not require significant resources, beyond those typical used in a patient-health professional encounter, computerised respiratory sounds have been indicated as an emergent measure to provide information on the function of the respiratory system (Bohadana et al., 2014).

Computerised respiratory sounds are generally classified as normal or adventitious (Sovijärvi et al., 2000). Normal respiratory sounds are nonmusical sounds produced from breathing and heard over the trachea (i.e., normal tracheal sounds) and chest wall (i.e., normal lung sounds) (Sovijärvi et al., 2000). These sounds are generated by the airflow in the respiratory tract and characterised by broad spectrum noise (Sovijärvi et al., 2000). Adventitious respiratory sounds are superimposed on normal respiratory sounds and can be discontinuous and explosive (crackles) or continuous and musical (wheezes) (Sovijärvi et al., 2000). Both normal and adventitious respiratory sounds have been found to be directly related to movement of air, changes within lung morphology and presence of secretions (Bohadana et al., 2014; Kiyokawa & Pasterkamp, 2002). Therefore, changes in airway and/or alveolar mechanisms may be primarily detected by changes in the frequency/intensity of normal respiratory sounds and by the presence of adventitious respiratory sounds (i.e., crackles and wheezes) (Gavriely, Nissan, Cugell, & Rubin, 1994). This theoretical potential of computerised respiratory sounds to be used as an outcome measure has been motivating research on their characteristics and measurement properties (Jácome & Marques, 2015).

Jácome and Marques (2015) have found adequate within-day reliability of computerised respiratory sounds in patients with stable COPD. However, other measurement properties, such as between-days reliability and validity, need to be studied in stable patients with COPD before the use of these measures can be recommended for assessing respiratory function in both patients with stable and exacerbated COPD (Terwee et al., 2007). Thus, **Study I** explored computerised respiratory sounds repeatability during stable phases (i.e., between-day reliability) and its usefulness to assess lung function (validity) in stable patients with COPD.

According to the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN), reliability, validity and responsiveness are the three main domains of measurement properties (Mokkink et al., 2010).

10

Nevertheless, to provide useful information about the effects of an intervention, the changes observed in a given outcome measure should also be easily interpreted (Cook, Paul, & Wyatt, 2014). Interpretability is defined as *the degree to which one can assign qualitative meaning – that is, clinical or commonly understood connotations – to an instrument's quantitative scores or change in scores,* and although is not considered a measurement property (Mokkink, Prinsen, Bouter, Vet, & Terwee, 2016), it is recognised by the COSMIN as an important characteristic of a measurement instrument (Mokkink et al., 2016). A number of methods have been purposed to establish the interpretability of a measure, however the MID has been indicated has the most adequate method (Terwee et al., 2007). The MID has been defined as *the smallest difference in score in the domain of interest which patients perceive as beneficial and would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management (Jaeschke, Singer, & Guyatt, 1989).* In interventions involving patients with AECOPD, MIDs have mainly been established for patient-reported outcome measures (PROM), e.g., the COPD assessment test (CAT) and the chronic respiratory disease questionnaire (CRQ) (Weldam, Schuurmans, Liu, & Lammers, 2013), and in inpatients (Kon et al., 2014; Tsai et al., 2008). This limited knowledge impairs the management of patients treated on an outpatient basis and the interpretation of changes in other important and widely used clinical respiratory measures, such as SpO_2 and lung function. **Study II** estimated MIDs and MDDs, i.e., the minimal change in a specific measure that falls outside the measurement error (de Vet et al., 2006), for clinical respiratory measures in outpatients with AECOPD following pharmacological treatment.

Research question II

Early identification and timely management of AECOPD has been shown to reduce hospital admissions and recovery time, while improving patients' health-related quality of life (Wilkinson et al., 2004). Nevertheless, most exacerbations are still not timely treated or adequately monitored, which may be

related with the symptom-based diagnosis and monitoring of AECOPD (The Global Initiative for Chronic Obstructive Lung Disease, 2019). Although this symptom-based approach of AECOPD presents some advantages, as it targets the primary concern of the patients and caregivers, it is highly subjective (Kim & Aaron, 2018). Patients' recognition and management of their symptoms during AECOPD are influenced by their personal beliefs, perceptions regarding seriousness of the disease, knowledge of exacerbations and former experiences (Korpershoek, Vervoort, Nijssen, Trappenburg, & Schuurmans, 2016). This subjectivity poses difficulties for the patient and for the clinician to decide if a patient's symptoms are "increased more than usual" and require additional management, leading to unreported exacerbations and, consequently, to an under-estimation of patient exacerbation rates (Kim & Aaron, 2018). Hence, a large amount of research has been dedicating to find objective, reliable, easy to obtain and simple markers of AECOPD (Guerra, Gaveikaite, Bianchi, & Puhan, 2017).

Physiologically, AECOPD are characterised by an increase in airway inflammation and obstruction, abnormal bronchial mucus production and marked air trapping (The Global Initiative for Chronic Obstructive Lung Disease, 2019), which results in changes in lung acoustics. As respiratory sounds are directly related to the movement of air within the tracheobronchial tree (Gavriely et al., 1994), the changes in respiratory mechanics related with AECOPD may be primarily detected by changes in respiratory sounds, such as adventitious respiratory sounds. Recent studies have shown respiratory sounds ability to differentiate between groups of patients with stable and exacerbated COPD (Jácome, Oliveira, & Marques, 2017) and to characterise AECOPD into two phenotypes, based on computerised analysis (Fernandez-Granero, Sanchez-Morillo, & Leon-Jimenez, 2018; Sanchez Morillo, Astorga Moreno, Fernandez Granero, & Leon Jimenez, 2013). Nevertheless, little information is available on respiratory sounds changes before, at the onset and during the recovery from an AECOPD within the same group of patients. This information may advance the diagnosis and monitoring of patients with COPD across all clinical and non-

clinical settings, as respiratory sounds are non-invasive, population-specific and nearly universally available by simple means (Bohadana et al., 2014). **Study III** evaluated adventitious respiratory sounds changes during the course of an AECOPD.

AECOPD result in significant short and long-term clinical, physiological and functional deteriorations (Anzueto, 2010; Spruit et al., 2003), being symptoms and lung function the parameters most studied, due to their key role in the diagnosis and monitoring of COPD (Feliz-Rodriguez et al., 2013; Koutsokera et al., 2009; Parker et al., 2005; Seemungal et al., 2000; Seemungal et al., 1998).

Dyspnoea has been identified as the primary symptom in AECOPD, followed by increased cough, sputum production and fatigue (Miravitlles et al., 2007; Parker et al., 2005; Seemungal et al., 2000; Seemungal et al., 1998). Regarding to lung function, modest but inconsistent reductions in peak expiratory flow, FEV_1 and forced vital capacity, associated with lung hyperinflation (i.e., an elevated total lung capacity, functional residual capacity and residual capacity) have been reported at the onset of AECOPD (Aaron et al., 2002; Niewoehner, Collins, & Erbland, 2000; Parker et al., 2005; Seemungal et al., 2000). Nevertheless, the recovery period of these symptoms and signs is poorly understood and time intervals between 5 to 90 days have been reported (Feliz-Rodriguez et al., 2013; Parker et al., 2005; Seemungal et al., 2000; Spencer, Calverley, Sherwood Burge, & Jones, 2001) with approximately 7 to 20% of patients never fully recovering to their baseline status (Seemungal et al., 2000; The Global Initiative for Chronic Obstructive Lung Disease, 2019).

Additionally, although it is well-established that AECOPD in patients not admitted to the hospital may result in prolonged incapacity and hospitalisations (Adams et al., 2000; Macfarlane et al., 1993; Miravitlles et al., 2001), little information is still available on its effects on functional parameters, such as muscle strength, activities of daily living and impact of the disease, and their recovery process. Spruit et al. (2003) and Mesquita et al. (2013) reported decreases in quadriceps muscle strength and no improvements in respiratory

muscle strength during hospitalisations of AECOPD. However, it is known that hospitalised patients differ from outpatients not only in their management but also in the severity of their exacerbation (The Global Initiative for Chronic Obstructive Lung Disease, 2019), which may influence their pattern of recovery. Thus, understanding outpatients' clinical, physiological and functional recovery seems crucial to timely manage and appropriately plan their follow-ups. **Study IV** and **Study V** characterised patients' symptoms, lung function, SpO_2, muscle strength, impact of the disease and functionality during the time course of AECOPD managed on an outpatient basis.

Summary

AECOPD are highly heterogeneous with an extensive range of clinical presentations and recovery patterns, thus significant research and clinical efforts are being conducted to improve the diagnosis, management and monitoring of these events. Noteworthy improvements have been achieved on the monitoring of inpatients with AECOPD, however studies are scarce on patients treated on an outpatient basis, which correspond to more than 80% of all exacerbations. In outpatients with AECOPD, uncertainty remains regarding to what are the most adequate outcome measures to use, the interpretability of those measures and how they evolve during these events. This chapter presents the most recent literature in the diagnosis, management and monitoring of AECOPD, the current challenges in these matters and the contribution of the studies developed within the scope of this research work to enhance knowledge on outcome measures and monitoring of outpatients with AECOPD.

Chapter II

Background

_____

Systematic review

_____

Outcome measures used in pulmonary rehabilitation in patients with acute exacerbation of chronic obstructive pulmonary disease: A systematic review

Oliveira A, Marques A

Abstract

Background: Conflicting results about the effects of community-based pulmonary rehabilitation in acute exacerbations of chronic obstructive pulmonary disease (AECOPD) exist, possibly because the variety of outcome measures used and the lack of appropriate measurement properties hinder the development of pulmonary rehabilitation guidelines.

Purpose: The purpose of this study was to identify and review the measurement properties of patient-reported outcome measures (PROMs) and clinical outcome measures of AECOPD that are used in pulmonary rehabilitation and that can be easily applied in a community setting.

Data Sources: PubMed, Web of Science, Scopus, and CINAHL were searched up to July 1, 2016.

Study Selection: Phase 1 identified outcome measures used in pulmonary rehabilitation for AECOPD. Phase 2 reviewed the measurement properties of the identified outcome measures.

Data Extraction: One reviewer extracted the data and 2 reviewers independently assessed the methodological quality of the studies and the measurement properties of the outcome measures by using the Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) recommendations.

Data Synthesis: Twenty-three PROMs and 18 clinical outcome measures were found. The outcome measures most used were the St George Respiratory Questionnaire (n=15/37 studies) and the 6-minute walk test (n=21/37 studies). Thirty-two studies described the measurement properties of 22 PROMs and 7 clinical outcome measures. The methodological quality of the studies was mostly poor, and the measurement properties were mostly indeterminate. The outcome measure exhibiting more robust properties was the COPD Assessment Test.

Limitations: A number of studies were not found with the validated search strategy used and were included *a posteriori*; the fact that 3 studies presented combined results— for patients who were stable and patients with exacerbation— affected the conclusions that can be drawn.

Conclusions: A large variety of outcome measures have been used; however, studies on their measurement properties are needed to enhance the understanding of community pulmonary rehabilitation for AECOPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is frequently punctuated by acute exacerbations (AECOPD) (Anzueto, 2010). Currently, more than 80% of these events are recommended to be managed within the community since it can shorten the length of hospital stays and/or avoid hospital admittance (The Global Initiative for Chronic Obstructive Lung Disease, 2017)

Pulmonary rehabilitation is a well-established, evidenced-based intervention, possible to be applied within the community (i.e., in nonspecialised community health services, in community centers, or at the patient's home) (Cambach, Chadwick-Straver, Wagenaar, van Keimpema, & Kemper, 1997; Cecins, Landers, & Jenkins, 2017; Lacasse, Goldstein, Lasserson, & Martin, 2006; Neves, Reis, & Goncalves, 2016) and with potential to prevent and decrease the harmful effects of acute exacerbations (Holland, 2014). Costs associated with AECOPD in the United States are estimated in $7100 per patient/per exacerbation (Guarascio, Ray, Finch, & Self, 2013) and recent economic studies have shown that, compared with usual care, community-based pulmonary rehabilitation provides cost savings of $1098 per patient (Xie, Schaink, Wang, & Krahn, 2015).

Nevertheless, conflicting results regarding the clinical effects of pulmonary rehabilitation in AECOPD have been reported (Puhan, Gimeno-Santos, Cates, & Troosters, 2016; Wedzicha et al., 2017) and less than 10% of patients discharged from AECOPD are being referred for pulmonary rehabilitation thus, its implementation is not a common practice. This inconsistency among studies may occur due to the wide variety of outcomes and outcome measures used and/or due to the lack of appropriate measurement properties (i.e., reliability, validity and responsiveness) of the outcome measures used in exacerbation periods. It is known that the measurement properties of any outcome measure are population specific (De Vet, Terwee, Mokkink, & Knol, 2011) and that patients at distinct phases of their chronic disease (stable/exacerbation) differ in the physiologic and ventilatory mechanisms of their lungs (Papi, Luppi, Franco, & Fabbri, 2006).

Therefore, it can be hypothesised that instrument measurement properties will also vary in stable and exacerbation periods.

Nevertheless, studies involving pulmonary rehabilitation in patients with AECOPD have been choosing their outcome measures based on the measurement properties established for stable patients with COPD (Borges & Carvalho, 2014; Puhan et al., 2012), which may hinder the development of pulmonary rehabilitation guidelines and lead instead to publication of recommendations which lack rigorous underpinning evidence in exacerbation periods.

Additionally, attending to patient's level of fragility during exacerbations, the specificities of implementing a pulmonary rehabilitation programme in a nonspecialised center and some practical issues, such as the need for specific equipment and sufficient space and time required to complete testing, especially when more than 1 test at baseline is required, may also influence the selection of the outcome measure (Holland, 2014).

Thus, the 2 aims of this systematic review were to identify patient-reported outcome measures (PROMs) and clinical (non–patient-reported) outcome measures that are used to assess the effects of pulmonary rehabilitation interventions in patients with AECOPD and that can be easily applied in the community (i.e., not expensive, not invasive, and quickly implemented) and to synthesise/evaluate their measurement properties.

Methods

This systematic review (PROSPERO registration no. CRD42015023736) was conducted in 2 phases. Phase 1 identified outcome measures used to assess outcomes of pulmonary rehabilitation interventions in patients with AECOPD and that can be easily applied in community-based practice. Phase 2 aimed to assess the measurement properties of the identified outcome measures.

Phase 1: Measures Used in Pulmonary Rehabilitation

Data sources and searches.

The effects of pulmonary rehabilitation interventions in patients with AECOPD have been largely reviewed (Hill, Patman, & Brooks, 2010; McCrory, Brown, Gelfand, & Bach, 2001; Osadnik, McDonald, Jones, & Holland, 2012; Puhan et al., 2016; Tang, Taylor, & Blackstock, 2010; Wedzicha et al., 2017), thus a first search limited to literature reviews was conducted from May to June 2016 in PubMed, Web of Knowledge, Scopus, and CINAHL. The original papers included in these reviews were extracted and searched for the outcome measures.

The latest available literature review on this theme was dated from 2012 and thus, a second search using the same keywords and databases but limited to original studies published from 2010 to June 2016 was also performed to identify all outcome measures most recently used by physiotherapists. An interval of 2 years until the most recent review in the theme seemed appropriate, as studies indicate that time from submission to publication can go up to 2 years (Björk & Solomon, 2013). In both searches, the reference lists of the identified studies were scanned for other potential eligible studies. Additionally, a weekly update was conducted until July 2016. The full search strategy can be found in eAppendix 1 (available at: https://academic.oup.com/ptj).

Study selection.

Selection of studies was performed by 1 reviewer (A.L.O.) and checked by a second reviewer (A.S.M.). After removing duplicates, 1 reviewer (A.L.O.) performed the initial screening of articles based on type of publication and relevance for the scope of the review. Selection of studies was checked by a second reviewer (A.S.M.).

First, title and abstract were screened, and if the articles were considered relevant, full text was analysed. Studies were included if they met the following 3 criteria: aimed to assess pulmonary rehabilitation or one of its components; assessed patients with an AECOPD within 3 weeks of the onset as this is the

mean time needed for recovery (Seemungal, Donaldson, Bhowmik, Jeffries, & Wedzicha, 2000; Spruit et al., 2013; The Global Initiative for Chronic Obstructive Lung Disease, 2017); and were written in English, Spanish, French, or Portuguese. Studies were excluded if they were conducted in animals; patients requiring emergency intubation, intensive care unit management, and/or mechanical ventilation; patients with compromised neurological status or hemodynamic instability; patients performing self-management programmes only; and patients assessed only after discharge for AECOPD. Book chapters, abstracts of communications or meetings, letters to the editor, commentaries to studies, unpublished work and study protocols were excluded.

Data extraction

Data extraction focused on PROMs and clinical outcome measures used to assess pulmonary rehabilitation interventions and that can be easily applied in community-based practice. Thus, data regarding measures not suitable for this setting (e.g., arterial blood gases, cardiopulmonary exercise testing, body plethysmography studies, sputum weight and analysis; penetration index of inhaled radioparticles and hospital length of stay) were not extracted. Data extracted were: outcomes, outcome measures, patient characteristics (i.e., age and percentage of predicted forced expiratory volume in 1 second (FEV_1) at stability or in acute exacerbation), treatment setting, time from AECOPD to intervention and duration of intervention).

Phase 2: Properties of Measures

Data sources and searches

A systematic electronic literature search was conducted from June to July 2016 on PubMed, Web of Science, Scopus, and CINAHL. A validated sensitive search filter (sensitivity=97.4%; precision=4.4%) for finding studies on measurement properties of outcome measures was used (Terwee, Jansma, Riphagen, & de Vet, 2009). Only outcome measures included in phase 1 were searched in phase 2, however, if new outcome measures feasible to be used in community practice emerged from the search, they were also included.

Reference lists of the identified studies were scanned for other potential eligible studies and a weekly update was conducted until September 2016. The full search strategy can be found in eAppendix 2 (available at: https://academic.oup.com/ptj).

Study selection

Selection of studies was performed by 1 reviewer (A.L.O.) and checked by a second reviewer (A.S.M.). Inclusion and exclusion criteria were as in phase 1. Additionally, studies were included if information was reported regarding 1 or more measurement properties (i.e., reliability – internal consistency, reliability, measurement error; validity – content validity, construct validity and criterion validity, responsiveness and interpretability). Studies were excluded if reported on measurement properties of outcome measures not feasible to use in community-based pulmonary rehabilitation programmes, separated items of an outcome measure and did not included the full measure.

Data extraction and quality assessment

Data was extracted by 1 reviewer (A.L.O.) using 2 standardised tables, one for PROMs and another for clinical outcome measures. Data extracted were: outcome, outcome measure, author and year of publication, measurement property assessed, quality of the study, quality of the measurement property and costs.

Two independent reviewers (A.L.O. and A.S.M.) evaluated the quality of the included studies using the Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) checklist (i.e., poor, fair, good, excellent) (Terwee et al., 2012). A consensus method was used to solve disagreements between reviewers.

The quality of the outcome measures reported was determined using the rating system for measurement properties proposed by Terwee et al. (2007). For each measurement property a criterion is defined for positive, negative and indeterminate rating.

25

Data synthesis and analysis

Data on PROMs and clinical outcome measures were separately analysed. For each measurement property (i.e., reliability, validity, responsiveness and interpretability), a synthesis of the quality of the study, using the COSMIN criteria (Terwee et al., 2012), and of the quality outcome measure, using the system of Terwee et al. (2007) was performed.

The consistency of the quality assessment performed by the 2 reviewers was explored with an interrater agreement analysis using the Cohen kappa for each box of the COSMIN criteria. The Cohen kappa value ranges from 0 to 1 and can be categorised as slight (<0.2), fair (0.21–0.4), moderate (0.41–0.6), substantial (0.61–0.8), or almost perfect (>0.81) agreement (Landis & Koch, 1977).

Results

Phase 1: Measures Used in Pulmonary Rehabilitation

Study selection

A total of 220 literature reviews were found. After duplicates were removed (n=66) and exclusions were made on the basis of abstract and title screenings (n=22), 132 full texts were screened and 15 literature reviews that reported on pulmonary rehabilitation interventions in patients with AECOPD were included. Additionally, 24 original studies included in the 15 reviews were extracted and searched for outcome measures not reported in the reviews.

The search conducted for original studies published after 2010 retrieved 257 original studies. After duplicates were removed (n=134) and exclusions were made on the basis of abstract and title screenings (n=23), 100 full texts were screened and 13 original studies were included. Thus, a total of 37 original studies were searched for outcome measures. A flow diagram concerning the literature reviews and original studies search and reasons for studies exclusions can be found in the eFigure (available at: https://academic.oup.com/ptj).

Study characteristics

The 37 studies included were conducted in 19 different countries. A steady increase in the number of studies investigating pulmonary rehabilitation in patients with AECOPD was observed, with only 7 papers published from 1964 to 2000 and 37 by 2016. Most studies were randomised control trials (n=31) (Aggarwal, Shaphe, George, & Vats, 2010; Babu, Noone, Haneef, & Samuel, 2010; Basoglu, Atasever, & Bacakoglu, 2005; Behnke, Jorres, Kirsten, & Magnussen, 2003; Behnke et al., 2000; Borges & Carvalho, 2014; Carr, Hill, Brooks, & Goldstein, 2009; Chaplin et al., 2013; Cross et al., 2012; Deepak, Mohapatra, Janmeja, Sood, & Gupta, 2014; Eaton et al., 2009; Giavedoni et al., 2012; Goktalay et al., 2013; Greening et al., 2014; He, Yu, Wang, Lv, & Qiu, 2015; Kirsten, Taube, Lehnigk, Jorres, & Magnussen, 1998; Ko et al., 2011; Kodric et al., 2009; Liao, Chen, Chung, & Chien, 2015; Man, Polkey, Donaldson, Gray, & Moxham, 2004; Martín-Salvador et al., 2016; Murphy, Bell, & Costello, 2005; Osadnik et al., 2014; Petersen, Esmann, Honcke, & Munkner, 1967; Puhan et al., 2012; Seymour et al., 2010; Sonia & Gupta, 2012; Tang, Blackstock, Clarence, & Taylor, 2012; Torres-Sanchez et al., 2016; Troosters et al., 2010; Yohannes & Connolly, 2003), conducted with inpatients (n=27) (Aggarwal et al., 2010; Babu et al., 2010; Basoglu et al., 2005; Borges & Carvalho, 2014; Carr et al., 2009; Chaplin et al., 2013; Clini et al., 2009; Cross et al., 2012; Eastwood, Jepsen, Coulter, Wong, & Zeng, 2016; Eaton et al., 2009; Giavedoni et al., 2012; Goktalay et al., 2013; He et al., 2015; Kirsten et al., 1998; Kodric et al., 2009; Liao et al., 2015; Martín-Salvador et al., 2016; Meglic, Sorli, Kosnik, & Lainscak, 2011; Ngai, Jones, Hui-Chan, Ko, & Hui, 2013; Osadnik et al., 2014; Petersen et al., 1967; Puhan et al., 2012; Sonia & Gupta, 2012; Tang et al., 2012; Torres-Sanchez et al., 2016; Troosters et al., 2010; Yohannes & Connolly, 2003), followed by hospital outpatient departments (n=6) (Carr et al., 2009; Deepak et al., 2014; Eaton et al., 2009; Ko et al., 2011; Puhan et al., 2012; Seymour et al., 2010), community settings (n=3) (Man et al., 2004; Oliveira & Marques, 2016; Oliveira, Pinho, & Marques, 2017) and patients' homes (n=1) (Murphy et al., 2005) (Tabs. 1 and 2).

Outcomes and outcome measures

Twenty-three PROMs and 18 clinical outcome measures were identified. The most common patient-reported outcomes assessed were dyspnoea (n=24), using the modified Borg Scale (mBorg) (Behnke et al., 2003; Clini et al., 2009; Eaton et al., 2009; He et al., 2015; Kirsten et al., 1998; Ko et al., 2011; Kodric et al., 2009; Liao et al., 2015; Martín-Salvador et al., 2016; Oliveira & Marques, 2016; Oliveira et al., 2017; Seymour et al., 2010; Sonia & Gupta, 2012; Torres-Sanchez et al., 2016) (n=14), and health-related quality of life (n=23), using the St George Respiratory Questionnaire (SGRQ) (Basoglu et al., 2005; Borges & Carvalho, 2014; Carr et al., 2009; Clini et al., 2009; Cross et al., 2012; Deepak et al., 2014; Greening et al., 2014; Ko et al., 2011; Kodric et al., 2009; Man et al., 2004; Martín-Salvador et al., 2016; Meglic et al., 2011; Murphy et al., 2005; Osadnik et al., 2014; Seymour et al., 2010) (n=15). The most common clinical outcomes assessed were functional exercise capacity (n=24), using the 6-minute walk test (Babu et al., 2010; Behnke et al., 2003; Behnke et al., 2000; Borges & Carvalho, 2014; Carr et al., 2009; Clini et al., 2009; Cross et al., 2012; Deepak et al., 2014; Eaton et al., 2009; Goktalay et al., 2013; He et al., 2015; Kirsten et al., 1998; Ko et al., 2011; Liao et al., 2015; Oliveira & Marques, 2016; Osadnik et al., 2014; Troosters et al., 2010) (n=21), and lung function (n=13), using the FEV_1 (Behnke et al., 2000; Borges & Carvalho, 2014; Eastwood et al., 2016; Kirsten et al., 1998; Ko et al., 2011; Kodric et al., 2009; Murphy et al., 2005; Ngai et al., 2013; Tang et al., 2012; Torres-Sanchez et al., 2016) (n=10). Other outcomes assessed were anxiety and depression, fatigue, cough, physical activity, strength, activities of daily living, lung function, peripheral blood gases, subjective airway clearance, and body composition.

Tables 1 and 2 show the patient-reported and clinical outcomes and outcome measures reported.

Table 1. Patient-reported outcomes used in pulmonary rehabilitation of patients with acute exacerbation (AE) of chronic obstructive pulmonary disease (COPD).

Outcome	Outcome Measure	Patient Characteristics					Intervention Setting	Intervention Timing	Intervention Duration
		No. of Patients	Age (y)	FEV_1pp (%)	FEV_1ppAE (%)	FEV_1ppST (%)			
Dyspnoea	BDI/TDI	26–30	62.3–69		34.1–60		Inpatient and home	4–8 d after hospital presentation	11 d–18 mo
	VAS	1–27	68.4–74	NS			Inpatient	At hospital presentation to 2 d after hospital presentation	45 min–2 mo
	Borg Scale	26–110	61–75			35–42	Inpatient and home	At hospital presentation to hospital discharge	Until hospital discharge to 6 wk
	mBorg	19–1826	45–78.8		34.1–69.4	50.5–56	Inpatient, hospital outpatient department, and community	At hospital presentation to 3 wk after discharge	60 min–19 mo
	MRC	19–94	58.4–73.9		38–53.3	29–56	Inpatient, hospital outpatient department, and home	At hospital presentation to 2 wk after discharge	Until hospital discharge to 12 wk
	mMRC	19–97	56.8–73.8 (mean)		35–69.4	37.3–44.4	Inpatient, hospital outpatient department, and community	At hospital presentation to 3 wk after discharge	Until hospital discharge to 12 wk
	NYHA	38	61	NS			Inpatient	As soon as stable	Until hospital discharge
	ADLDS	94	69.2–73.9		38–39		Inpatient	2 d after hospital presentation	Until hospital discharge
HRQL	Diary	26	64–69		34.9–37.5		Inpatient and home	4–7 d after admission	19 mo

	CRQ	19–97	64–73.9		34.1–52	36.7–42.7	Inpatient, hospital outpatient department, community, and home	As soon as stable to 3.7 wk after hospital presentation	Until hospital discharge to 18 mo
	SGRQ	19–1,826	58.4–78.8		35.6–56.1	29–56	Inpatient, hospital outpatient department, community, and home	As soon as stable to 2 wk after hospital presentation	Until hospital discharge to 12 wk
	SF-36	24–97	69.6–73.8		35–56.1	36.7–41.7	Inpatient, hospital outpatient department, and community	After discharge to 3 wk after hospital presentation	8 wk
	EQ-5D	16–526	65–73.7		52	38–42	Inpatient, hospital outpatient department, and home	As soon as stable to 1 wk after hospital discharge	Until hospital discharge to 8 wk
	CAT	11–94	69.2–78		34–39		Inpatient	1–2 days after hospital presentation	2 d to until hospital discharge
	FACIT fatigue	19	71			29	Inpatient	Immediately at hospital presentation	6 wk
	Feeling thermometer	19	67.5			42.7	Inpatient or hospital outpatient department	2 wk after hospital presentation	12 wk
Anxiety and depression	HADS	49–97	69.7–73.7	35–41			Inpatient and hospital outpatient department	As soon as stable to immediately after discharge	Until hospital discharge to 8 wk
Fatigue	mBorg	60	65–67	52			Hospital outpatient department	1 wk after discharge	8 wk
Sputum	VAS sputum	11–61	68–78		34–39		Inpatient	As soon as stable	2–4 d
General symptoms	BCSS	11–90	56.8–78		34–69.4	37.3–44.4	Inpatient and community	At hospital presentation to 72 h after hospital presentation	60 min to until hospital discharge

ADL	Barthel Index	21–110	68–75		45.1–46.1	35–38	Inpatient	At hospital presentation to 72 h after hospital presentation	Until hospital discharge
	LCADL	44	77.4–78.8		41.8–41.4		Inpatient	As soon as stable	8–9 d
Composite measure	BODE Index	50–97	65.1–73.9		35–39	37.3–44.4	Inpatient and hospital outpatient department	At hospital presentation to 2 d after hospital presentation	Until hospital discharge to 8 wk

ADL = activities of daily living; ADLDS = Activity of Daily Living Dyspnoea Scale; AE = acute exacerbation; BCSS = Breathlessness, Cough, and Sputum Scale; BDI/TDI = Baseline Dyspnoea Index and Transition Dyspnoea Index; BODE = body mass index, airflow obstruction, dyspnoea, and exercise capacity; CAT = COPD Assessment Test; CRQ = Chronic Respiratory Disease Questionnaire; EQ-5D = EuroQol 5D; FACIT = Functional Assessment of Chronic Illness Therapy; FEV_1pp = percentage predicted forced expiratory volume in 1 s; HADS = Hospital Anxiety and Depression Scale; HRQL = Health-Related Quality of Life; LCADL = London Chest Activities of Daily Living Scale; mBorg = modified Borg Scale; MRC = Medical Research Council; mMRC = modified MRC; NS = not stated; NYHA = New York Heart Association Functional Classification; SF-36 = Short Form (36-Item) Health Survey; SGRQ = St George Respiratory Questionnaire; ST = stable; VAS = visual analog scale.

Please note that for clarification purposes, references of the outcome measures were removed from the table and can be found in the original published article.

Table 2. Clinical outcomes used in pulmonary rehabilitation of patients with acute exacerbation (AE) of chronic obstructive pulmonary disease (COPD).

Outcome	Outcome Measure	Patient Characteristics					Intervention Setting	Intervention Timing	Intervention Duration
		No. of Patients	Age (y)	FEV$_1$pp (%)	FEV$_1$ppAE (%)	FEV$_1$ppST (%)			
Functional exercise capacity	6MWT	28–1826	61–73.9		34.1–69.4	50.5	Inpatient, hospital outpatient department, community, and home	At hospital presentation to 3 wk after discharge	4 d–18 mo
	ISWT	26–196	65–71.1		52	36.7–51.9	Inpatient, hospital outpatient department, community, and home	Immediately to 10 d after discharge	6–8 wk
	ESWT	20–196	65–70.1		52	39.8–51.9	Inpatient, hospital outpatient department, and home	At hospital presentation to 1 wk after discharge	Until hospital discharge to 8 wk
	3-min step test	26	65–67			38–42	Home	Immediately after discharge	6 wk
	3-min walk test	21	68–73.6		45.1–46.1		Inpatient	48 h after hospital presentation	Until hospital discharge
	2-minute step-in-place test	49	72.4–73.7		39–41		Inpatient	As soon as stable	Until hospital discharge
	CAT	11–94	69.2–78		34–39		Inpatient	1–2 days after hospital presentation	2 d to until hospital discharge

Category	Measure						Setting	Timing	Duration
Oxygen saturation	SpO$_2$	1–526	56.8–73.9		35–69.4	52–56	Inpatient, hospital outpatient department, and community	At hospital presentation to 8 d after hospital presentation	45 min–8 wk
Lung function	FEV$_1$	1–60	62.3–78		34–56.1	38–56	Inpatient, hospital outpatient department, and home	At hospital presentation to 3 wk after hospital discharge	45 min–18 mo
	FVC	11–59	62.3–78		34–39	38–56	Inpatient and home	At hospital presentation to immediately after hospital discharge	2 d–18 mo
	FEV$_1$/FVC	59	70.2			57.9–64.4	Inpatient	At hospital presentation	7 d
	PEF	38–45	61	NS			Inpatient	At hospital presentation	Until hospital discharge
	CRS	19	56.8		69.4		Community	Within 48 to 72 h after hospital presentation	3 wk
Body composition	Fat-free mass index	60	65–67		52		Hospital outpatient department	1 wk after hospital discharge	8 wk
	BMI	90	67.8–69.5		35.9–35.6	37.3–44.4	Inpatient	2 d after hospital presentation	Until hospital discharge
Physical activity	Accelerometer	29	67.8–64.1		39.1–41.7		Inpatient	3 d after hospital presentation	At least 3 sessions
Strength	MVIC	11–196	65–78.8		39.1–52	38–51.9	Inpatient, hospital outpatient department, and home	At hospital presentation to 1 wk after hospital discharge	7 d–8 wk
	TwQ	60	65–67		52		Hospital outpatient department	1 wk after hospital discharge	8 wk

	MIP	28	62.3–65.6		38		Inpatient	6–8 d after hospital presentation	11 d

6MWT = 6-min walk test; AE = acute exacerbation; BMI = body mass index; CRS = computerised respiratory sounds; ESWT = endurance shuttle walk test; FEV_1 = forced expiratory volume in 1 s; FEV_1pp = percentage predicted FEV_1; FVC = forced vital capacity; ISWT = incremental shuttle walk test; MIP = maximum inspiratory pressure; MVIC = maximal voluntary isometric contraction; NS = not stated; PEF = peak expiratory flow; SpO_2 = peripheral oxygen saturation; ST = stable; TwQ = quadriceps twitch responses.

Please note that for clarification purposes, references of the outcome measures were removed from the table and can be found in the original published article.

Phase 2: Properties of Measures

Study selection

The search for measurement properties identified 82 studies. After the removal of duplicates, 41 studies were screened. During the title and abstract screening, 18 studies were excluded. The full text of 23 studies was assessed and another 15 studies were excluded. Therefore, 8 original studies were selected. The search for relevant studies within the reference lists retrieved 24 additional studies. Therefore, a total of 32 studies were included in this review (Figure 1).
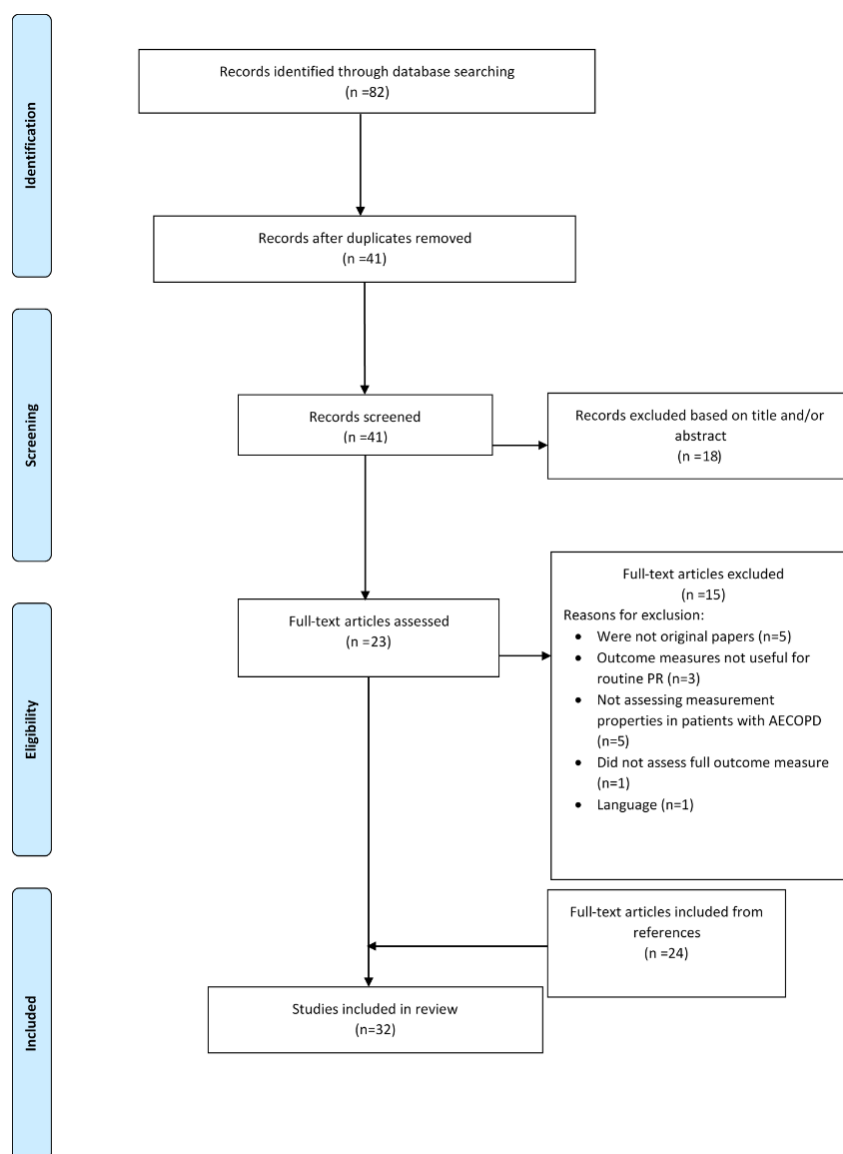
Figure 1. Flow diagram of the measurement properties studies included.

Measurement properties

The measurement properties of 22 PROMs used to assess 5 outcomes (i.e., dyspnoea [6 outcome measures], health-related quality of life [11 outcome measures], health status [2 outcome measures], activities of daily living [2 outcome measures], and general symptoms [1 outcome measure]) were reported by 26 of 32 studies. The measurement properties of 7 clinical outcome measures used to assess 4 outcomes (i.e., oxygen saturation [1 outcome measure], lung function [4 outcome measures], body composition [1 outcome measure], and physical activity [1 outcome measure]) were reported in 8 of 32 studies.

The methodological quality of each study and the quality of the measurement properties of each measure can be found in Tables 3 and 4. The agreement between the 2 independent reviewers using the COSMIN quality assessment was substantial ($\kappa=0.688$).

The characteristics of the included studies and synthesis of the results per outcome and outcome measure can be found in eAppendix 3 (available at: https://academic.oup.com/ptj; eTab. 1a and eTab. 1b).

Quality and properties of PROMs

Reliability was studied for 5 PROMs in 5 studies of fair to excellent methodological quality (i.e., SGRQ, Chronic Respiratory Diseases Questionnaire [CRQ], Clinical COPD Questionnaire [CCQ], and COPD Assessment Test [CAT]) (Antoniu, Puiu, Zaharia, & Azoicai, 2014; Jones et al., 2009; Katsoulas et al., 2010; Kocks et al., 2006; Tsai et al., 2008) and in 2 studies of poor methodological quality (i.e., CCQ and Exacerbations of Chronic Pulmonary Disease Tool–Patient-Reported Outcome [EXACT-PRO]) (Antoniu et al., 2014; Leidy et al., 2011). Studies were rated as poor mainly because an analysis of the unidimensionality of the scale was not preformed.

Measurement properties presented positive results in all reliability categories assessed (i.e., internal consistency and test-retest; measurement error has not been assessed) and for all outcome measures (Tab. 3).

Validity was studied for most PROMs, except for the mBorg, visual analog scale, Short-Form 6D, and Nottingham Health Profile, in 21 studies (Aaron et al., 2002; Antoniu et al., 2014; Bourbeau, Maltais, Rouleau, & Guimont, 2004; Doll, Duprat-Lomon, Ammerman, & Sagnier, 2003; Güryay et al., 2007; Hutchinson et al., 2010; Jones et al., 2011; Jones et al., 2009; Jones et al., 2012; Katsoulas et al., 2010; Kocks et al., 2006; Leidy, Murray, Jones, & Sethi, 2014; Leidy et al., 2011; Miravitlles et al., 2011; Monz et al., 2010; Paterson et al., 2000; Steer, Norman, Afolabi, Gibson, & Bourke, 2012; Trappenburg et al., 2010; Tsai et al., 2008; Tu, Zhang, & Fei, 2014; Yohannes, Baldwin, & Connolly, 2005). Overall, the methodological quality of the studies was rated from poor to fair, except for structural validity studied in the CRQ and the CAT, which were rated excellent (Jones et al., 2009; Tsai et al., 2008). For criterion validity, reasons for rating "poor" were related with the inadequacy of the gold standard used as comparator. Regarding to construct validity, weaknesses included lack of formulation of hypotheses and lack of description of the comparator instrument.

Criterion validity was indeterminate in 5 studies (i.e., modified Medical Research Council [MRC], MRC, extended MRC, CCQ, COPD severity score, EuroQol 5D [EQ-5D], Breathing Problems Questionnaire, London Chest Activities of Daily Living Scale [LCADL], and Manchester Respiratory Activities of Daily Living Questionnaire) (Güryay et al., 2007; Miravitlles et al., 2011; Steer et al., 2012; Trappenburg et al., 2010; Yohannes et al., 2005) and positive in 1 study (i.e., Global Initiative for Chronic Obstructive Lung Disease plus Symptom Severity Index [GOLD+SSI]) (Hutchinson et al., 2010). Structural validity presented positive results in 2 studies (i.e., CRQ and CAT) (Jones et al., 2009; Tsai et al., 2008). Construct validity, was indeterminate in 11 studies (i.e., Baseline Dyspnoea Index and Transition Dyspnoea Index [BDI/TDI], SGRQ, CRQ, CCQ, COPD severity score, EQ-5D, Short-Form 6D, Measure Your Medical Outcome Profile, and Medical Outcomes Study 6-Item General Health Survey, modified MRC, SGRQ, EXACT-PRO, and LCADL) (Aaron et al., 2002; Güryay et al., 2007; Jones et al., 2012; Katsoulas et al., 2010; Kocks et al., 2006; Leidy et al., 2014; Leidy et al., 2011; Miravitlles et al., 2011; Paterson et al., 2000;

Tu et al., 2014), negative in 2 studies (i.e., SGRQ and CRQ) (Doll et al., 2003; Tsai et al., 2008), and positive in 7 studies (i.e., SGRQ, CRQ, CCQ, CAT, and Cough and Sputum Assessment Questionnaire) (Antoniu et al., 2014; Bourbeau et al., 2004; Jones et al., 2011; Jones et al., 2009; Jones et al., 2012; Monz et al., 2010; Tu et al., 2014) (Tab. 3).

Responsiveness was studied for most PROMs, except for the modified MRC, MRC, extended MRC, Breathing Problems Questionnaire, GOLD+SSI, Manchester Respiratory Activities of Daily Living Questionnaire, and LCADL, in 19 studies of poor to fair methodological quality (Aaron et al., 2002; Antoniu et al., 2014; Bourbeau et al., 2004; Doll et al., 2003; Goossens, Nivens, Sachs, Monz, & Rutten-Van Mölken, 2011; Jones et al., 2012; Katsoulas et al., 2010; Kendrick, Baxi, & Smith, 2000; Kocks et al., 2006; Leidy et al., 2011; Lemasson et al., 2007; Mackay et al., 2012; Menn, Weber, & Holle, 2010; Miravitlles et al., 2011; Monz et al., 2010; Paterson et al., 2000; Trappenburg et al., 2010; Tsai et al., 2008; Tu et al., 2014). Common weaknesses of studies included lack of description of the comparator instrument and inadequacy of design and statistical methods used.

Responsiveness was indeterminate in 14 studies (i.e., SGRQ, CCQ, COPD severity score, EQ-5D, Short-Form 6D, Nottingham Health Profile, Measure Your Medical Outcome Profile, Medical Outcomes Study 6-Item General Health Survey, EXACT-PRO, Cough and Sputum Assessment Questionnaire, mBorg, visual analog scale, and CCQ) (Antoniu et al., 2014; Doll et al., 2003; Goossens et al., 2011; Jones et al., 2012; Katsoulas et al., 2010; Kendrick et al., 2000; Kocks et al., 2006; Leidy et al., 2011; Lemasson et al., 2007; Menn et al., 2010; Miravitlles et al., 2011; Monz et al., 2010; Paterson et al., 2000; Trappenburg et al., 2010), negative in 5 studies (i.e., SGRQ, CRQ, CAT, and EQ-5D) (Aaron et al., 2002; Bourbeau et al., 2004; Jones et al., 2012; Miravitlles et al., 2011; Tsai et al., 2008) and positive in 3 studies (i.e., BDI/TDI and CAT) (Aaron et al., 2002; Mackay et al., 2012; Tu et al., 2014) (Tab. 3).

Interpretability was found in 2 studies which presented values of the minimal clinically important difference (MCID) for the CRQ (MCID=1.01) (Tsai et al., 2008) and the CCQ (MCID=0.44) (Kocks et al., 2006).

Quality and properties of clinical measures

Reliability was not studied for any of the clinical outcome measures found (Tab. 4).

Validity was studied for all clinical outcome measures in 8 studies of fair to poor methodological quality (Aaron et al., 2002; Emerman & Cydulka, 1996; Güryay et al., 2007; Kelly, McAlpine, & Kyle, 2001; Pitta et al., 2006; Sanchez-Morillo, Leon-Jimenez, & Moreno, 2013; Tsimogianni et al., 2009; White, O'Brien, Hill, & Stockley, 2005). For criterion validity, reasons for rating "poor" were related with the inadequacy of the gold standard used as comparator, whereas for construct validity reasons were related to the lack of formulation of hypotheses and the lack of description of the comparator instrument.

Overall, measurement properties presented positive results for criterion validity assessed in 4 studies (i.e., peripheral oxygen saturation [SpO_2], forced vital capacity, and computerised respiratory sounds) (Güryay et al., 2007; Kelly et al., 2001; Sanchez-Morillo et al., 2013; Tsimogianni et al., 2009); however, in 1 study assessing the FEV_1, criterion validity was indeterminate (Güryay et al., 2007). Regarding to construct validity, indeterminate results were found in 2 studies (i.e., SpO_2, peak expiratory flow [PEF], FEV_1, and forced vital capacity) (Güryay et al., 2007; White et al., 2005) and positive results in 3 studies (i.e., SpO_2, PEF, and time spent in weight-bearing activities assessed with an accelerometer) (Emerman & Cydulka, 1996; Kelly et al., 2001; Pitta et al., 2006) (Tab. 4).

Responsiveness was studied for the PEF and FEV_1 in 2 studies (Aaron et al., 2002; Emerman & Cydulka, 1996) of fair and poor methodological quality, respectively. The study was rated as poor because it did not describe the measurement properties of the comparator instrument.

Responsiveness was rated positive for the PEF (Emerman & Cydulka, 1996) and indeterminate for the FEV_1 (Aaron et al., 2002) (Tab. 4).

Interpretability was not studied for any of the clinical outcome measures found (Tab. 4).

Table 3. Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) Evaluation, Quality of the Measurement Property, and Cost of Patient-Reported Outcomes.

Outcome	Outcome Measure	Study	Reliability		Validity			Responsiveness	Cost
			Internal Consistency	Test-Retest	Criterion Validity	Structural Validity	Construct Validity (Hypothesis Testing)		
Dyspnoea	mBorg	Kendrick et al. (2000)						Poor/?	Free
	VAS	Lemasson et al. (2007)						Poor/?	Free
	mMRC	Güryay et al. (2007)			Poor/ ?		Poor/?		Free
	MRC	Steer et al. (2012)			Poor/ ?				Free
	eMRC	Steer et al. (2012)			Poor/ ?				No information
	BDI/TDI	Aaron et al. (2002)					Poor/?	Fair/+	Not free for commercial use
HRQL	SGRQ	Doll et al. (2003)					Fair/−	Poor/?	Free
		Bourbeau et al. (2004)					Fair/+	Fair/−	
		Menn et al. (2010)						Poor/?	
		Katsoulas et al. (2010)		Fair/+			Good/?	Poor/?	
		Jones et al. (2012)					Poor/?	Poor/?	

		Tu et al. (2014)					Poor/?		
	CRQ	Bourbeau et al. (2004)					Fair/+	Fair/−	Not free
		Tsai et al. (2008)	Excellent/+			Excellent/ +	Poor/−	Fair/−	
		Aaron et al. (2002)					Poor/?	Fair/−	
	CCQ	Trappenburg et al. (2010)			Fair/?			Poor/?	Not free
		Antoniu et al. (2014)	Poor/+	Fair/+			Fair/+	Poor/?	
		Kocks et al. (2006)					Poor/?	Poor/?	
	CAT	Jones et al. (2009)	Excellent/+			Excellent/+	Fair/+		Not free for commercial use
		Jones et al. (2011)					Fair/+		
		Jones et al. (2012)					Fair/+	Poor/−	
		Mackay et al. (2012)						Fair/+	
		Tu et al. (2014)					Poor/+	Fair/+	
	COPDSS	Miravitlles et al. (2011)			Fair/?		Poor/?	Poor/?	Free
	EQ-5D	Menn et al. (2010)						Poor/?	Not free for clinical and commercial use
		Goossens et al. (2011)						Poor/?	
		Miravitlles et al. (2011)			Fair/?		Poor/?	Fair/−	

		Paterson et al. (2000)						Poor/?	Poor/?	
	SF-6D	Menn et al. (2010)							Poor/?	Not free for commercial use
	BPQ	Yohannes et al. (2005)			Poor/?					Not free for commercial use
	NHP	Doll et al. (2003)							Poor/?	Not free; copyright held by Galen
	MYMOP	Paterson et al. (2000)						Poor/?	Poor/?	Free
	MOS-6A	Paterson et al. (2000)						Poor/?	Poor/?	Free
Health status	EXACT-PRO	Leidy et al. (2014)						Poor/?		Not free for commercial use
		Leidy et al. (2011)	Poor/+					Poor/?	Poor/?	
	GOLD + SSI	Hutchinson et al. (2010)			Poor/+					Free
ADL	MRADL	Yohannes et al. (2005)			Poor/?					Not free for commercial use
	LCADL	Miravitlles et al. (2011)			Fair/?			Poor/?		Free
General symptoms	CASA-Q	Monz et al. (2010)						Poor/+	Poor/?	No information

ADL = activities of daily living; BDI/TDI = Baseline Dyspnoea Index and Transition Dyspnoea Index; BPQ = Breathing Problems Questionnaire; CASA-Q = Cough and Sputum Assessment Questionnaire; CAT = COPD [Chronic Obstructive Pulmonary Disease] Assessment Test; CCQ = Clinical COPD Questionnaire; COPDSS = COPD severity score; CRQ = Chronic Respiratory Disease Questionnaire; eMRC = extended Medical Research Council (MRC); EQ-5D = EuroQol 5D; EXACT-PRO = Exacerbations of Chronic Pulmonary Disease Tool–Patient-Reported Outcome; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRQL = Health-Related Quality of Life; LCADL = London Chest Activities of Daily Living Scale; mBorg = modified Borg Scale; mMRC = modified MRC; MOS-6A = Medical Outcomes Study 6-Item General Health Survey; MRADL = Manchester Respiratory Activities of Daily Living Questionnaire; MYMOP = Measure Your Medical Outcome Profile; NHP = Nottingham Health Profile; SF-6D = Short-Form 6D; SGRQ = St George Respiratory Questionnaire; SSI = Symptom Severity Index; VAS = visual analog scale; + = positive; − = negative; ? = indeterminate.

Table 4. Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) Evaluation, Quality of the Measurement Property, and Cost of Clinical Outcomes.

Outcome	Outcome Measure	Study	Reliability		Validity		Responsiveness	Cost
			Internal Consistency	Test-Retest	Criterion Validity	Construct Validity (Hypothesis Testing)		
Oxygen saturation	SpO$_2$ (%)	Güryay et al. (2007)			Fair/+	Poor/?		Not free
		Kelly et al. (2001)			Fair/+	Poor/+		
Lung function	PEF (pp)	Emerman and Cydulka (1996)				Poor/+	Fair/+	Not free
		Güryay et al. (2007)				Poor/?		
	FEV$_1$ (pp or L)	Güryay et al. (2007)			Poor/?	Poor/?		Not free
		Aaron et al. (2002)					Poor/?	
		White et al. (2005)				Poor/?		
	FVC (pp)	Güryay et al. (2007)				Poor/?		Not free
	CRS	Sanchez-Morillo et al. (2013)			Fair/+			Not free
Body composition	BMI (kg/m^2)	Tsimogianni et al. (2009)			Poor/+			Free
Physical activity	Time spent in weight-bearing activities (min)	Pitta et al. (2006)				Poor/+		Not free

BMI = body mass index; CRS = computerised respiratory sounds; FEV$_1$ = forced expiratory volume in 1 s; FVC = forced vital capacity; PEF = peak expiratory flow; pp = percentage of predicted normal value; SpO$_2$ = peripheral oxygen saturation; + = positive; − = negative; ? = indeterminate.

Discussion

To our knowledge, this is the first systematic review to provide a comprehensive overview of the measurement properties of the outcome measures most used in pulmonary rehabilitation programmes during AECOPD and that can be easily applied in a community setting. Twenty-three PROMs and 18 clinical outcome measures were identified in intervention studies. The most used measures were the St George Respiratory Questionnaire (n=15/37) and the 6-minute walk test (n=21/37). Several measures have been used only in isolated studies (i.e., New York Heart Association Functional Classification, Activities of Daily Living Dyspnoea Scale, diaries, Functional Assessment of Chronic Illness Therapy, feeling thermometer, mBorg fatigue, LCADL, 3-minute step test, 3-minute walk test, 2-minute step-in-place test, FEV_1/forced vital capacity, computerised respiratory sounds, fat-free mass index, body mass index, accelerometer, quadriceps twitch responses, and maximum inspiratory pressure). Measurement properties were only synthesised for 22 PROMs and 7 clinical outcome measures. The methodological quality of most studies was poor, and the results obtained for the measurement properties were indeterminate. The PROMs and clinical outcome measures exhibiting the most appropriate measurement properties were the CAT and SpO_2, respectively.

The most used PROMs were the mBorg and the SGRQ. Dyspnoea and health-related quality of life have been reported as the outcomes that better reflect the overall impact of the disease (Janson et al., 2013) and, therefore their monitoring during AECOPD, with appropriate outcome measures, is essential to guide health professionals on the most effective interventions. Nevertheless, the measurement properties of the mBorg have been little reported and, when reported, in studies of poor methodological quality. The BDI/TDI, although not commonly used, was the only outcome measure which rated fair and positive for responsiveness on dyspnoea. The SGRQ has shown appropriate test retest reliability but inconclusive validity and responsiveness. Although, the SGRQ has strong measurement properties in stable patients with COPD (Spruit et al., 2013; Weldam, Schuurmans, Liu, & Lammers, 2013) it reports to the past month, 3

months and 1 year. These inappropriate timeframes to assess improvements from an AECOPD, which usually takes 1 to 3 weeks to be meaningful to patients (Seemungal et al., 2000; Woodhead et al., 2011) might explain some of the divergent results found. Measurement properties of CAT have been assessed in a reasonable number of studies of fair methodological quality (Jones et al., 2011; Jones et al., 2009; Jones et al., 2012; Mackay et al., 2012; Tu et al., 2014) and positive results have been found. Therefore, the BDI/TDI and CAT may be promising PROMs to assess the effectiveness of community-based pulmonary rehabilitation in patients with AECOPD.

The most used clinical outcome measures were the FEV_1 and the 6-minute walk test. However, the measurement properties of the FEV_1 were found in studies of poor methodological quality and no studies were found reporting on the measurement properties of the 6-minute walk test in patients with AECOPD which impaired conclusions regarding its use. Similarly to exercise tolerance, no studies were found reporting on measurement properties of muscle strength. Currently, it is known that the inflammatory effects of AECOPD are not confined to the lungs but also impair peripheral muscle strength and exercise tolerance (Anzueto, 2010). Declines in these outcomes are independent predictors of hospitalisations and mortality (Maltais et al., 2014; Neder et al., 2016). Early rehabilitation may play a crucial role in preventing and reducing losses in exercise capacity, muscle strength and musculoskeletal dysfunction (Borges & Carvalho, 2014; Troosters et al., 2010), thus possibly reverting this cascade of events. Nevertheless, there is the urgent need to establish the measurement properties of clinical outcome measures for AECOPD to assess patients' dysfunctions, plan interventions, and verify their effectiveness.

This systematic review evidenced that the conflicting results of pulmonary rehabilitation programmes in patients with AECOPD (Borges & Carvalho, 2014; Greening et al., 2014; Puhan et al., 2016; Puhan et al., 2012) may not be related to the quality of treatment but with the lack of appropriateness of measurement proprieties of the outcome measures used. Additionally, whilst the methodology of this review target only measures that could be implemented in community

46

settings (i.e., simple and accessible measures), our results can also be applicable to other clinical settings where these measures are available. Nevertheless, since most AECOPD are recommended to be managed in the community and community-based pulmonary rehabilitation might be a promising intervention for minimising a patient's decline and prevent recurrence, robust studies on the validity, reliability and responsiveness, as well as on availability, cost and interpretability (i.e., by establishing the MCID), of outcome measures are urgently needed. These studies will contribute to clarify the role of community-based pulmonary rehabilitation in patients with AECOPD.

Study Limitations

This study has some limitations that need to be acknowledged. Several relevant studies for this systematic review (Aaron et al., 2002; Antoniu et al., 2014; Doll et al., 2003; Emerman & Cydulka, 1996; Goossens et al., 2011; Hutchinson et al., 2010; Jones et al., 2011; Jones et al., 2012; Kelly et al., 2001; Kendrick et al., 2000; Kocks et al., 2006; Leidy et al., 2014; Leidy et al., 2011; Lemasson et al., 2007; Mackay et al., 2012; Miravitlles et al., 2011; Pitta et al., 2006; Sanchez-Morillo et al., 2013; Steer et al., 2012; Trappenburg et al., 2010; Tsimogianni et al., 2009; White et al., 2005; Yohannes et al., 2005) were not found with the validated search strategy used and were only included after searching through the reference lists of the reviewed studies. Relevant studies may have fallen out of the search due the absence of keywords related to measurement properties in their title, abstract or keywords, which impaired the filter used to identify them. Adequate use of the Medical Subject Headings (MESH) terms is warranted to identify the purpose of the studies and improve the quality of the results found in future systematic reviews.

This systematic review has followed the COSMIN recommendations to assess the quality of the included studies. The COSMIN was originally developed for health-related PROMs, such as questionnaires (Terwee et al., 2012), and thus its validity, reliability and adequacy for assessing the methodological quality of clinical studies and outcome measures, may be questioned. Nonetheless, in the absence of a measure specifically designed to evaluate such studies and

outcome measures, the COSMIN is indicated as an adequate alternative tool (Bartels, de Groot, & Terwee, 2013; Dobson et al., 2012).

The selection of studies was performed by 1 reviewer which could have caused bias in the studies selection. This limitation has been mitigated by consulting a second reviewer when uncertainties were found and by defining strict inclusion and exclusion criteria prior to studies selection.

Finally, 3 of the studies included presented combined results of stable and exacerbated patients with COPD (Bourbeau et al., 2004; Doll et al., 2003; Leidy et al., 2011) which could have affected some of the conclusions established. Nevertheless, the results of these studies have been considered within the universe of all studies included, and thus we believe that any potential bias that could have been introduced was diluted. Future studies should focus on patients with AECOPD only, so that recommendations regarding its measurement properties can be established with confidence.

Conclusions

Although a large number of outcome measures easy to implement in a community-based setting have been used to assess pulmonary rehabilitation in patients with AECOPD, their measurement properties have been poorly studied. Given the wide availability of measures it does not seem necessary to develop new outcome measures to be used in community-based pulmonary rehabilitation of patients with AECOPD. Instead, studies following the COSMIN standards to evaluate the measurement properties (i.e., reliability, validity and responsiveness) of the existing outcome measures are recommended. Such studies would contribute to clarify the role of community-based pulmonary rehabilitation in patients with AECOPD and guide the development of core outcome sets.

References

Aaron, S., Vandemheen, K., Clinch, J., Ahuja, J., Brison, R., Dickinson, G., & Hebert, P. (2002). Measurement of short-term changes in dyspnea and disease-specific quality of life following an acute COPD exacerbation. *Chest, 121*(3), 688-696.

Aggarwal, R., Shaphe, A., George, C., & Vats, A. (2010). A comparison of flutter device and active cycle of breathing techniques in acute exacerbation of chronic obstructive pulmonary disease patients. *Indian Journal of Physiotherapy & Occupational Therapy, 4*(3), 60-64.

Antoniu, S., Puiu, A., Zaharia, B., & Azoicai, D. (2014). Health status during hospitalisations for chronic obstructive pulmonary disease exacerbations: The validity of the Clinical COPD Questionnaire. *Expert Review of Pharmacoeconomics and Outcomes Research, 14*(2), 283-287.

Anzueto, A. (2010). Impact of exacerbations on COPD. *European Respiratory Review, 19*(116), 113-118.

Babu, A., Noone, M., Haneef, M., & Samuel, P. (2010). The effects of 'on-call/out of hours' physical therapy in acute exacerbations of chronic obstructive pulmonary disease: A randomized controlled trial. *Clinical Rehabilitation, 24*(9), 802-809.

Bartels, B., de Groot, J., & Terwee, C. (2013). The six-minute walk test in chronic pediatric conditions: a systematic review of measurement properties. *Physical Therapy, 93*(4), 529-541.

Basoglu, O., Atasever, A., & Bacakoglu, F. (2005). The efficacy of incentive spirometry in patients with COPD. *Respirology, 10*(3), 349-353.

Behnke, M., Jorres, R., Kirsten, D., & Magnussen, H. (2003). Clinical benefits of a combined hospital and home-based exercise programme over 18 months in patients with severe COPD. *Monaldi Archives for Chest Disease, 59*(1), 44-51.

Behnke, M., Taube, C., Kirsten, D., Lehnigk, B., Jorres, R., & Magnussen, H. (2000). Home-based exercise is capable of preserving hospital-based

improvements in severe chronic obstructive pulmonary disease. *Respiratory Medicine, 94*(12), 1184-1191.

Björk, B-C., & Solomon, D. (2013). The publishing delay in scholarly peer-reviewed journals. *Journal of Informetrics, 7*(4), 914-923.

Borges, R., & Carvalho, C. (2014). Impact of Resistance Training in Chronic Obstructive Pulmonary Disease Patients During Periods of Acute Exacerbation. *Archives of Physical Medicine and Rehabilitation, 95*(9), 1638-1645.

Bourbeau, J., Maltais, F., Rouleau, M., & Guimont, C. (2004). French-Canadian version of the Chronic Respiratory and St George's Respiratory questionnaires: an assessment of their psychometric properties in patients with chronic obstructive pulmonary disease. *Canadian Respiratory Journal, 11*(7), 480-486.

Cambach, W., Chadwick-Straver, R., Wagenaar, R., van Keimpema, A., & Kemper, H. (1997). The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. *European Respiratory Journal, 10*(1), 104-113.

Carr, S., Hill, K., Brooks, D., & Goldstein, R. (2009). Pulmonary rehabilitation after acute exacerbation of chronic obstructive pulmonary disease in patients who previously completed a pulmonary rehabilitation program. *Journal of Cardiopulmonary Rehabilitation and Prevention, 29*(5), 318-324.

Cecins, N., Landers, H., & Jenkins, S. (2017). Community-based pulmonary rehabilitation in a non-healthcare facility is feasible and effective. *Chronic Respiratory Disease, 14*(1), 3-10.

Chaplin, E., Houchen, L., Greening, N., Harvey-Dunstan, T., Morgan, M., Steiner, M., & Singh, S. J. (2013). Neuromuscular stimulation of quadriceps in patients hospitalised during an exacerbation of COPD: a comparison of low (35 Hz) and high (50 Hz) frequencies. *Physiotherapy Research International, 18*(3), 148-156.

Clini, E., Crisafulli, E., Costi, S., Rossi, G., Lorenzi, C., Fabbri, L., & Arnbrosino, N. (2009). Effects of early inpatient rehabilitation after acute exacerbation of COPD. *Respiratory Medicine, 103*(10), 1526-1531.

Cross, J., Elender, F., Barton, G., Clark, A., Shepstone, L., Blyth, A., . . . Harvey, I. (2012). Evaluation of the effectiveness of manual chest physiotherapy techniques on quality of life at six months post exacerbation of COPD (MATREX): a randomised controlled equivalence trial. *BMC Pulmonary Medicine, 12*(1), 33-33.

De Vet, H., Terwee, C., Mokkink, L., & Knol, D. (2011). *Measurement in medicine: practical guide to biostatistics and epidemiology.* London: Cambridge University Press.

Deepak, T., Mohapatra, P., Janmeja, A., Sood, P., & Gupta, M. (2014). Outcome of pulmonary rehabilitation in patients after acute exacerbation of chronic obstructive pulmonary disease. *The Indian Journal Of Chest Diseases & Allied Sciences, 56*(1), 7-12.

Dobson, F., Hinman, R., Hall, M., Terwee, C., Roos, E., & Bennell, K. (2012). Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. *Osteoarthritis and Cartilage, 20*(12), 1548-1562.

Doll, H., Duprat-Lomon, I., Ammerman, E., & Sagnier, P. (2003). Validity of the St George's respiratory questionnaire at acute exacerbation of chronic bronchitis: Comparison with the Nottingham health profile. *Quality of Life Research, 12*(2), 117-132.

Eastwood, B., Jepsen, N., Coulter, K., Wong, C., & Zeng, I. (2016). Challenges of undertaking a clinical trial using bubble-PEP in an acute exacerbation of chronic obstructive pulmonary disease: A feasibility study. *New Zealand Journal of Physiotherapy, 44*(1), 8-16.

Eaton, T., Young, P., Fergusson, W., Moodie, L., Zeng, I., O'Kane, F., . . . Kolbe, J. (2009). Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. *Respirology, 14*(2), 230-238.

Emerman, C., & Cydulka, R. (1996). Use of peak expiratory flow rate in emergency department evaluation of acute exacerbation of chronic obstructive pulmonary disease. *Annals of Emergency Medicine, 27*(2), 159-163.

Giavedoni, S., Deans, A., McCaughey, P., Drost, E., MacNee, W., & Rabinovich, R. (2012). Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: A pilot study. *Respiratory Medicine, 106*(10), 1429-1434.

Goktalay, T., Akdemir, S., Alpaydin, A., Coskun, A., Celik, P., & Yorgancioglu, A. (2013). Does high-frequency chest wall oscillation therapy have any impact on the infective exacerbations of chronic obstructive pulmonary disease? A randomized controlled single-blind study. *Clinical Rehabilitation, 27*(8), 710-718.

Goossens, L., Nivens, M., Sachs, P., Monz, B., & Rutten-Van Mölken, M. (2011). Is the EQ-5D responsive to recovery from a moderate COPD exacerbation? *Respiratory Medicine, 105*(8), 1195-1202.

Greening, N., Williams, J., Hussain, S. N., Harvey-Dunstan, T., Bankart, M., Chaplin, E., . . . Steiner, M. (2014). An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *British Medical Journal, 349*, g4315.

Guarascio, A., Ray, S., Finch, C., & Self, T. (2013). The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *ClinicoEconomics and Outcomes Research, 5*, 235-245.

Güryay, M., Ceylan, E., Günay, T., Karaduman, S., Bengi, F., Parlak, I., . . . Cimrin, A. (2007). Can spirometry, pulse oximetry and dyspnea scoring reflect respiratory failure in patients with chronic obstructive pulmonary disease exacerbation? *Medical Principles and Practice, 16*(5), 378-383.

He, M., Yu, S., Wang, L., Lv, H., & Qiu, Z. (2015). Efficiency and safety of pulmonary rehabilitation in acute exacerbation of chronic obstructive pulmonary disease. *Medical Science Monitor: International Medical Journal Of Experimental And Clinical Research, 21*, 806-812.

Hill, K., Patman, S., & Brooks, D. (2010). Effect of airway clearance techniques in patients experiencing an acute exacerbation of chronic obstructive pulmonary disease: a systematic review. *Chronic Respiratory Disease, 7*(1), 9-17.

Holland, A. (2014). Physiotherapy management of acute exacerbations of chronic obstructive pulmonary disease. *Journal of Physiotherapy, 60*(4), 181-188.

Hutchinson, A., Thompson, M., Brand, C., Black, J., Anderson, G., & Irving, L. (2010). Community care assessment of exacerbations of chronic obstructive pulmonary disease. *Journal of Advanced Nursing, 66*(11), 2490-2499.

Janson, C., Marks, G., Buist, S., Gnatiuc, L., Gislason, T., McBurnie, M., . . . Burney, P. (2013). The impact of COPD on health status: findings from the BOLD study. *European Respiratory Journal, 42*(6), 1472-1483.

Jones, P., Brusselle, G., Dal Negro, R., Ferrer, M., Kardos, P., Levy, M. L., . . . Banik, N. (2011). Properties of the COPD assessment test in a cross-sectional European study. *European Respiratory Journal, 38*(1), 29-35.

Jones, P., Harding, G., Berry, P., Wiklund, I., Chen, W-H., & Kline Leidy, N. (2009). Development and first validation of the COPD Assessment Test. *European Respiratory Journal, 34*(3), 648-654.

Jones, P., Harding, G., Wiklund, I., Berry, P., Tabberer, M., Yu, R., & Leidy, N. (2012). Tests of the responsiveness of the COPD assessment test following acute exacerbation and pulmonary rehabilitation. *Chest, 142*(1), 134-140.

Katsoulas, T., Skordilis, E., Myrianthefs, P., Fildisis, G., Theodosopoulou, E., & Baltopoulos, G. (2010). Validity of St. George's Respiratory Questionnaire for Greek patients with chronic obstructive pulmonary disease. *Perceptual and Motor Skills, 110*(3 Pt 1), 772-788.

Kelly, A., McAlpine, R., & Kyle, E. (2001). How accurate are pulse oximeters in patients with acute exacerbations of chronic obstructive airways disease? *Respiratory Medicine, 95*(5), 336-340.

Kendrick, K., Baxi, S., & Smith, R. (2000). Usefulness of the modified 0-10 Borg scale in assessing the degree of dyspnea in patients with COPD and asthma. *Journal of Emergency Nursing, 26*(3), 216.

Kirsten, D., Taube, C., Lehnigk, B., Jorres, R., & Magnussen, H. (1998). Exercise training improves recovery in patients with COPD after an acute exacerbation. *Respiratory Medicine, 92*(10), 1191-1198.

Ko, F., Dai, D., Ngai, J., Tung, A., Ng, S., Lai, K., . . . Hui, D. (2011). Effect of early pulmonary rehabilitation on health care utilization and health status in patients hospitalized with acute exacerbations of COPD. *Respirology, 16*(4), 617-624.

Kocks, J., Tuinenga, M., Uil, S., van den Berg, J. , Ståhl, E., & van der Molen, T. (2006). Health status measurement in COPD: The minimal clinically important difference of the clinical COPD questionnaire. *Respiratory Research, 7*(62), 1-8.

Kodric, M., Garuti, G., Colomban, M., Russi, B., Porta, R., Lusuardi, M., & Confalonieri, M. (2009). The effectiveness of a bronchial drainage technique (ELTGOL) in COPD exacerbations. *Respirology, 14*(3), 424-428.

Lacasse, Y., Goldstein, R., Lasserson, T., & Martin, S. (2006). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(4), Art. No.: CD003793.

Landis, J. Richard, & Koch, Gary G. (1977). The Measurement of Observer Agreement for Categorical Data. *Biometrics, 33*(1), 159-174.

Leidy, N., Murray, L., Jones, P., & Sethi, S. (2014). Performance of the EXAcerbations of chronic pulmonary disease tool patient-reported outcome measure in three clinical trials of chronic obstructive pulmonary disease. *Annals of the American Thoracic Society, 11*(3), 316-325.

Leidy, N., Wilcox, T., Jones, P., Roberts, L., Powers, J., & Sethi, S. (2011). Standardizing measurement of chronic obstructive pulmonary disease exacerbations. Reliability and validity of a patient-reported diary. *American Journal of Respiratory and Critical Care Medicine, 183*(3), 323-329.

Lemasson, S., Nesme, P., Herblanc, A., Beuret, P., Louerat, C., Bourdin, G., . . . Guerin, C. (2007). Changes in inspiratory capacity during acute respiratory failure in COPD patients. *Revue des Maladies Respiratoires, 24*(3 Pt 1), 314-322.

Liao, L-Y, Chen, K-M, Chung, W-S, & Chien, J-Y. (2015). Efficacy of a respiratory rehabilitation exercise training package in hospitalized elderly patients with acute exacerbation of COPD: a randomized control trial. *International Journal of Chronic Obstructive Pulmonary Disease, 10*, 1703-1709.

Mackay, A., Donaldson, G., Patel, A., Jones, P., Hurst, J., & Wedzicha, J. (2012). Usefulness of the Chronic Obstructive Pulmonary Disease Assessment Test to evaluate severity of COPD exacerbations. *American Journal of Respiratory and Critical Care Medicine, 185*(11), 1218-1224.

Maltais, F., Decramer, M., Casaburi, R., Barreiro, E., Burelle, Y., Debigare, R., . . . Wagner, P. (2014). An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 189*(9), e15-62.

Man, W., Polkey, M., Donaldson, N., Gray, B., & Moxham, J. (2004). Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *British Medical Journal, 329*(7476), 1209.

Martín-Salvador, A., Colodro-Amores, G., Torres-Sánchez, I., Moreno-Ramírez, M., Cabrera-Martos, I., & Valenza, Marie C. (2016). Intervención fisioterápica durante la hospitalización en pacientes con exacerbación aguda de la enfermedad pulmonar obstructiva crónica y neumonía: un ensayo clínico aleatorizado. *Medicina Clínica, 146*(7), 301-304.

McCrory, D., Brown, C., Gelfand, S., & Bach, P. (2001). Management of acute exacerbations of COPD - A summary and appraisal of published evidence. *Chest, 119*(4), 1190-1209.

Meglic, U., Sorli, J., Kosnik, M., & Lainscak, M. (2011). Feasibility of transcutaneous electrical muscle stimulation in acute exacerbation of COPD. *Wiener klinische Wochenschrift, 123*(11-12), 384-387.

Menn, P., Weber, N., & Holle, R. (2010). Health-related quality of life in patients with severe COPD hospitalized for exacerbations - comparing EQ-5D, SF-12 and SGRQ. *Health and Quality of Life Outcomes, 8*(39), 1-9.

Miravitlles, M., Izquierdo, I., Herrejón, A., Torres, J., Baró, E., & Borja, J. (2011). COPD severity score as a predictor of failure in exacerbations of COPD. the ESFERA study. *Respiratory Medicine, 105*(5), 740-747.

Monz, B., Sachs, P., McDonald, J., Crawford, B., Nivens, M., & Tetzlaff, K. (2010). Responsiveness of the cough and sputum assessment questionnaire in exacerbations of COPD and chronic bronchitis. *Respiratory Medicine, 104*(4), 534-541.

Murphy, N., Bell, C., & Costello, R. (2005). Extending a home from hospital care programme for COPD exacerbations to include pulmonary rehabilitation. *Respiratory Medicine, 99*(10), 1297-1302.

Neder, J., Alharbi, A., Berton, D., Alencar, M., Arbex, F., Hirai, D., . . . O'Donnell, D. (2016). Exercise Ventilatory Inefficiency Adds to Lung Function in Predicting Mortality in COPD. *COPD, 13*(4), 416-424.

Neves, L., Reis, M., & Goncalves, T. (2016). Home or community-based pulmonary rehabilitation for individuals with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Cadernos de Saúde Pública, 32*(6).

Ngai, S., Jones, A., Hui-Chan, C., Ko, F., & Hui, D. (2013). An adjunct intervention for management of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). *Journal of Alternative and Complementary Medicine, 19*(2), 178-181.

Oliveira, A., & Marques, A. (2016). Exploratory mixed methods study of respiratory physiotherapy for patients with lower respiratory tract infections. *Physiotherapy, 102*(1), 111-118.

Oliveira, A., Pinho, C., & Marques, A. (2017). Effects of a respiratory physiotherapy session in patients with LRTI: a pre/post-test study. *The Clinical Respiratory Journal, 11*(6), 703-712.

Osadnik, C., McDonald, C., Jones, A., & Holland, A. (2012). Airway clearance techniques for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(3), Art. No.: CD008328.

Osadnik, C., McDonald, C., Miller, B., Hill, C., Tarrant, B., Steward, R., . . . Holland, A. (2014). The effect of positive expiratory pressure (PEP) therapy on symptoms, quality of life and incidence of re-exacerbation in patients with acute exacerbations of chronic obstructive pulmonary disease: A multicentre, randomised controlled trial. *Thorax, 69*(2), 137-143.

Papi, A., Luppi, F., Franco, F., & Fabbri, L. (2006). Pathophysiology of Exacerbations of Chronic Obstructive Pulmonary Disease. *Proceedings of the American Thoracic Society, 3*(3), 245-251.

Paterson, C., Langan, C., McKaig, G., Anderson, P., Maclaine, G., Rose, L., . . . Campbell, M. (2000). Assessing patient outcomes in acute exacerbations of chronic bronchitis: the measure your medical outcome profile (MYMOP), medical outcomes study 6-item general health survey (MOS-6A) and EuroQol (EQ-5D). *Quality of Life Research, 9*(5), 521-527.

Petersen, E. S., Esmann, V., Honcke, P., & Munkner, C. (1967). A controlled study of the effect of treatment on chronic bronchitis. An evaluation using pulmonary function tests. *Acta Medica Scandinavica, 182*(3), 293-305.

Pitta, F., Troosters, T., Probst, V., Spruit, M., Decramer, M., & Gosselink, R. (2006). Physical activity and hospitalization for exacerbation of COPD. *Chest, 129*(3), 536-544.

Puhan, M., Gimeno-Santos, E., Cates, C., & Troosters, T. (2016). Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews, 12*, Art. No.: CD005305.

Puhan, M., Spaar, A., Frey, M., Turk, A., Brandli, O., Ritscher, D., . . . Karrer, W. (2012). Early versus late pulmonary rehabilitation in chronic obstructive pulmonary disease patients with acute exacerbations: a randomized trial. *Respiration, 83*(6), 499-506.

Sanchez-Morillo, D., Leon-Jimenez, A., & Moreno, S. (2013). Computer-aided diagnosis of pneumonia in patients with chronic obstructive pulmonary disease. *Journal of the American Medical Informatics Association, 20*(e1), e111-117.

Seemungal, T., Donaldson, G., Bhowmik, A., Jeffries, D., & Wedzicha, J. (2000). Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 161*(5), 1608-1613.

Seymour, J., Moore, L., Jolley, C., Ward, K., Creasey, J., Steier, J., . . . Moxham, J. (2010). Outpatient pulmonary rehabilitation following acute exacerbations of COPD. *Thorax, 65*(5), 423-428.

Sonia, & Gupta, C. (2012). Effect of Acu-TENS on Pulmonary Functions in Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *Indian Journal of Physiotherapy & Occupational Therapy, 6*(4), 115-119.

Spruit, M., Singh, S., Garvey, C., ZuWallack, R., Nici, L., Rochester, C., . . . Wouters, E. (2013). An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine, 188*(8), e13-64.

Steer, J., Norman, E., Afolabi, O., Gibson, G., & Bourke, S. (2012). Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. *Thorax, 67*(2), 117-121.

Tang, C., Blackstock, F., Clarence, M., & Taylor, N. (2012). Early rehabilitation exercise program for inpatients during an acute exacerbation of chronic obstructive pulmonary disease: a randomized controlled trial. *Journal of Cardiopulmonary Rehabilitation and Prevention, 32*(3), 163-169.

Tang, C., Taylor, N., & Blackstock, F. (2010). Chest physiotherapy for patients admitted to hospital with an acute exacerbation of chronic obstructive pulmonary disease (COPD): A systematic review. *Physiotherapy, 96*(1), 1-13.

Terwee, C., Bot, S., de Boer, M., van der Windt, D., Knol, D., Dekker, J., . . . de Vet, H. (2007). Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of Clinical Epidemiology, 60*(1), 34-42.

Terwee, C., Jansma, E., Riphagen, I., & de Vet, H. (2009). Development of a methodological PubMed search filter for finding studies on measurement properties of measurement instruments. *Quality of Life Research, 18*(8), 1115-1123.

Terwee, C., Mokkink, L., Knol, D., Ostelo, R., Bouter, L., & de Vet, H. (2012). Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Quality of Life Research, 21*(4), 651-657.

The Global Initiative for Chronic Obstructive Lung Disease. (2017). Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease - 2017 Report: The Global Initiative for Chronic Obstructive Lung Disease, Inc.

Torres-Sanchez, I., Valenza, M., Saez-Roca, G., Cabrera-Martos, I., Lopez-Torres, I., & Rodriguez-Torres, J. (2016). Results of a Multimodal Program During Hospitalization in Obese COPD Exacerbated Patients. *COPD, 13*(1), 19-25.

Trappenburg, J., Touwen, I., de Weert-van Oene, G., Bourbeau, J., Monninkhof, E., Verheij, T., . . . Schrijvers, A. (2010). Detecting exacerbations using the Clinical COPD Questionnaire. *Health and Quality of Life Outcomes, 8*(102), 1-9.

Troosters, T., Probst, V., Crul, T., Pitta, F., Gayan-Ramirez, G., Decramer, M., & Gosselink, R. (2010). Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 181*(10), 1072-1077.

Tsai, C., Hodder, R., Page, J., Cydulka, R., Rowe, B., & Camargo, C. A. (2008). The short-form chronic respiratory disease questionnaire was a valid, reliable, and responsive quality-of-life instrument in acute exacerbations

of chronic obstructive pulmonary disease. *Journal of Clinical Epidemiology, 61*(5), 489-497.

Tsimogianni, A., Papiris, S., Stathopoulos, G., Manali, E., Roussos, C., & Kotanidou, A. (2009). Predictors of outcome after exacerbation of chronic obstructive pulmonary disease. *Journal of General Internal Medicine, 24*(9), 1043-1048.

Tu, Y. , Zhang, Y., & Fei, G. (2014). Utility of the CAT in the therapy assessment of COPD exacerbations in China. *BMC Pulmonary Medicine, 14*(42), 1-8.

Wedzicha, J., Miravitlles, M., Hurst, J., Calverley, P., Albert, R., Anzueto, A., . . . Krishnan, J. (2017). Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *European Respiratory Journal, 49*(3), 1600791.

Weldam, S., Schuurmans, M., Liu, R., & Lammers, J. (2013). Evaluation of Quality of Life instruments for use in COPD care and research: a systematic review. *International Journal of Nursing Studies, 50*(5), 688-707.

White, A., O'Brien, C., Hill, S., & Stockley, R. (2005). Exacerbations of COPD diagnosed in primary care: changes in spirometry and relationship to symptoms. *COPD, 2*(4), 419-425.

Woodhead, M., Blasi, F., Ewig, S., Garau, J., Huchon, G., Ieven, M., . . . Verheij, T. (2011). Guidelines for the management of adult lower respiratory tract infections--full version. *Clinical Microbiology and Infection, 17*(Suppl 6), E1-59.

Xie, X., Schaink, A., Wang, M., & Krahn, M. (2015). Pulmonary Rehabilitation for Postacute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): A Cost-effectiveness and Budget Impact Analysis *Ontario Health Technology Assessment Series* (pp. 1-47). Toronto: Queen's Printer for Ontario

Yohannes, A., Baldwin, R., & Connolly, M. (2005). Predictors of 1-year mortality in patients discharged from hospital following acute exacerbation of chronic obstructive pulmonary disease. *Age and Ageing, 34*(5), 491-496.

Yohannes, A., & Connolly, M. (2003). Early mobilization with walking aids following hospital admission with acute exacerbation of chronic obstructive pulmonary disease. *Clinical Rehabilitation, 17*(5), 465-471.

Chapter III

Empirical studies

_____

Study I

_____

Reliability, validity, and minimal detectable change of computerised respiratory sounds in patients with Chronic Obstructive Pulmonary Disease

Oliveira A, Lage S, Rodrigues J, Marques A

Abstract

Introduction: Computerised respiratory Sounds (CRS) are closely related to the movement of air within the tracheobronchial tree and are promising outcome measures in patients with chronic obstructive pulmonary disease (COPD). However, CRS measurement properties have been poorly tested.

Objective: The aim of this study was to assess the reliability, validity and the minimal detectable changes (MDC) of CRS in patients with stable COPD.

Methods: Fifty patients ($36\male$, 67.26 ± 9.31y, FEV_1 $49.52\pm19.67\%$predicted) were enrolled. CRS were recorded simultaneously at seven anatomic locations (trachea; right and left anterior, lateral and posterior chest). The number of crackles, wheeze occupation rate, median frequency (F50) and maximum intensity (Imax) were processed using validated algorithms. Within-day and between-days reliability, criterion and construct validity, validity to predict exacerbations and MDC were established.

Results: CRS presented moderate-to-excellent within-day reliability ($ICC_{1,3}\geq0.51$; $p<0.05$) and moderate-to-good between-days reliability ($ICC_{1,2}\geq0.47$; $p<0.05$) for most locations. Negligible-to-moderate correlations with $FEV_1\%$predicted were found ($-0.53<r_s<-0.28$; $p<0.05$), and the inspiratory number of crackles were the best discriminator between mild-to-moderate and severe-to-very severe airflow limitations (area under the curve >0.78). CRS correlated poorly with patient-reported outcomes ($r_s<0.48$; $p<0.05$) and did not predict exacerbations. Inspiratory number of crackles at posterior right chest, inspiratory F50 at trachea and anterior left chest and expiratory Imax at anterior right chest were simultaneously reliable and valid, and their MDC were 2.41, 55.27, 29.55 and 3.98, respectively.

Conclusion: CRS are reliable and valid. Their use, integrated with other clinical and patient-reported measures, may fill the gap of assessing small airways and contribute toward a patient's comprehensive evaluation.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterised by persistent respiratory symptoms and airflow limitation due to smaller airway and/or alveolar abnormalities (The Global Initiative for Chronic Obstructive Lung Disease, 2017). Although diagnosis and monitoring of airflow limitation is usually performed by spirometry (gold standard test of lung function) (The Global Initiative for Chronic Obstructive Lung Disease, 2017), its usefulness to assess interventions has been questioned, as it mainly assesses large airways (McNulty & Usmani, 2014), changes in response to treatments are small (Calverley et al., 2003; Zwick et al., 2009), and correlates poorly with patient-reported outcomes (Jones, 2001). Thus, international Respiratory Societies have been stressing the need to validate instruments that can express peripheral respiratory function, assess patient's response to interventions and correlate with patient-reported outcomes (Celli et al., 2015). Computerised respiratory sounds are a simple, objective and noninvasive outcome measure that are directly related to the movement of air within the tracheobronchial tree (Gavriely, Nissan, Cugell, & Rubin, 1994). Therefore, changes in airway and/or alveolar mechanisms may be primarily detected by changes in the frequency/intensity of normal respiratory sounds and by the presence of adventitious respiratory sounds (i.e., crackles and wheezes) (Gavriely et al., 1994). This theoretical potential of computerised respiratory sounds to be used as an outcome measure has been motivating research of their characteristics and measurement properties (Jácome & Marques, 2015a; Jácome, Oliveira, & Marques, 2017; Oliveira, Pinho, & Marques, 2017). A recent study in stable patients with COPD has shown that respiratory sounds have adequate within-day reliability (Jácome & Marques, 2015a). However, other measurement properties need to be studied before computerised respiratory sounds utilisation can be recommended for clinical practice (Terwee et al., 2007). Between-days reliability and validity are crucial measurement properties of an outcome measure which, according to the authors' best knowledge, have never been explored in computerised respiratory sounds, hindering the interpretation of its actual usefulness to assess lung function

(validity) and its repeatability during prolonged stable phases (reliability). This study aimed to evaluate the between-days reliability, criterion, construct and predictive validity of computerised respiratory sounds in patients with COPD. The authors hypothesised that computerised respiratory sounds would present (a) significant and moderate between-days reliability; (b) significant, negative and low-to-moderate correlations with lung function; (c) significant, negative and moderate correlations with patient-reported outcome measures and (d) significant ability to predict acute exacerbations of COPD up to 1 year.

Materials and methods

Study design

A cross-sectional study was conducted. Reliability and validity were explored, described and interpreted following the COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN) guidelines (Terwee et al., 2007; Terwee et al., 2012).

Sample size

The sample size was determined according to the COSMIN guidelines, which have established that a study with good methodological quality should enroll a minimum of 50cparticipants (Terwee et al., 2012).

Participants

Outpatients with stable COPD were recruited from a central hospital between January 2016 and 2017. Inclusion criteria were diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (The Global Initiative for Chronic Obstructive Lung Disease, 2017) and clinical stability for one month prior to the study (i.e., no hospital admissions, exacerbations as defined by GOLD, or changes in respiratory system medication). Patients were excluded if they had severe co-existing respiratory, neurological, cardiac, musculoskeletal, or psychiatric impairments. Approvals for this study were obtained from the ethics committee of the Central Hospital (13NOV'1514:40065682) and National Data Protection Committee (8828/2016).

Eligible patients were identified by clinicians and then contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. When patients agreed to participate, an appointment with the researchers was scheduled and written informed consent was obtained.

Data collection

Participants were asked to attend to two testing sessions with a 5–7 days interval. In the first session, patients completed a questionnaire with sociodemographic (age and gender) and health-related (smoking status, exacerbations in the previous year, symptoms and impact of the disease) information. Height and weight were recorded to calculate the body mass index (BMI). Smoking status was evaluated with a two-question survey on current and previous smoking habits. Cough and wheezing were assessed through a standardised numeric rating scale (NRS) in which the patient reported the severity of the symptoms in the previous 24 hours. The NRS is reliable (Intraclass correlation coefficient, ICC=0.54 to 0.86) and valid to assess symptoms in patients with respiratory diseases (Boulet et al., 2015; Morris et al., 2007). Dyspnoea was collected using the modified Medical Research Council (mMRC) dyspnoea scale (Doherty et al., 2006). The patients read the 5-point mMRC scale and pointed the grade (0–4) that most closely matched his or her breathlessness. Higher scores represent more breathlessness. The mMRC has shown to be a reliable (ICC=0.82) (Mahler et al., 2009) and valid measure of disability related with dyspnoea (Bestall et al., 1999). Impact of the disease was collected with the COPD Assessment Test (CAT). The CAT is a reliable (Cronbach α=0.88) and valid self-administered eight-question questionnaire, which allows the assessment of the impact of COPD on health status within only a few minutes (Jones et al., 2009). Higher scores represent higher impact of COPD. Then, three respiratory sounds recordings were performed with air-coupled electret microphones (C 417 PP; AKG Acoustics GmbH, Vienna, Austria) (Vannuccini et al., 2000) following the computerised respiratory sound analysis (CORSA) guidelines for short-term acquisitions (Rossi et al., 2000). Finally, lung function was assessed with a portable spirometer (MicroLab 3535; CareFusion, Kent, UK)

70

according to the guidelines (Miller et al., 2005). In the second session, only respiratory sounds were recorded. Effort was made to keep all factors associated with the testing sessions consistent, specifically the time of day, location of the sessions, chest locations of the microphones and order of testing. Additionally, participants were telephoned every 3 months, up to 1 year of their initial assessment, to gather information about the occurrence of an exacerbation (The Global Initiative for Chronic Obstructive Lung Disease, 2017).

Respiratory sound recordings

Recordings were performed simultaneously at seven anatomic locations (trachea and right and left anterior upper, lateral middle and posterior lower chest) (Rossi et al., 2000). The recording system included eight air-coupled electret microphones, a multi-channel audio interface (AudioBox 1818 VSL; PreSonus, Baton Rouge, LA) and a laptop computer running LungSounds@UA interface (Pinho, Oliveira, Oliveira, Dinis, & Marques, 2014). Seven microphones, mounted in couplers made Teflon (Kraman, Wodicka, Oh, & Pasterkamp, 1995), were attached on the participant's skin with double-faced adhesive tapes (Double Stick Discs; 3M Littmann, Cheshire, UK), and one microphone was placed closed to the patient to record the background noise. The analog sound signals acquired were amplified and converted to digital by the audio interface with a 24-bit resolution and a sampling rate of 44.1 kHz. Each data acquisition session lasted for 20 seconds (Vyshedskiy & Murphy, 2012), and the recorded data were later converted to.wav format.

Signal processing

Respiratory sound files were processed by automatic algorithms implemented in Matlab R2009a (MathWorks, Natick, Massachusetts). Data were obtained for number of crackles, occupation rate of wheezes (%Wh), median frequency (F50) and maximum intensity (Imax) per respiratory phase (i.e., inspiration and expiration) and per chest location.

Number of crackles per respiratory phase was calculated using the following equation:

$$number\ of\ crackles = \frac{\text{sum of crackles per respiratory phase}}{\text{total number of respiratory phases}} \quad (1)$$

%Wh was calculated through the following equations:

$$rate\ of\ each\ wheeze = \frac{\text{duration of wheeze in the respiratory phase}}{\text{total duration of the respiratory phase}} \times 100 \quad (2)$$

$$\%Wh = \sum (\text{rate of each wheeze in the respiratory phase}) \quad (3)$$

F50 and Imax were calculated following the methodology proposed by (Pasterkamp, Powell, & Sanchez, 1996) after excluding adventitious respiratory sounds in each file. F50 and Imax were analysed within a frequency band of 300–600 Hz, as this has been indicated as the most representative frequency band for patients with respiratory diseases (Hossain & Moussavi, 2004; Sulzer, Schüttler, Penzel, & Wichert, 1997). All analyses were checked by two respiratory experts and the average respiratory sound spectra and background noise were plotted to ensure the quality of sound recordings. Background noise was closely superimposed to respiratory sound intensity at lateral chest; hence, these locations were excluded from further analyses. The average spectra of normal respiratory sounds at trachea, anterior, lateral and posterior chest can be found in the Supporting Information and a detailed description of the signal processing is provided elsewhere (Oliveira, Sen, Kahya, Afreixo, & Marques, 2017).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corporation, Armonk, New York) and plots were created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, California). The level of significance was set at 0.05. Descriptive statistics were used to describe the sample. Characteristics were compared between patients at stages I-II and III-IV of airflow limitation (The Global Initiative for Chronic Obstructive Lung Disease, 2017), using independent t-tests for normally distributed data (age, BMI and lung function), Mann-Whitney U-tests for ordinal data (mMRC, CAT and NRS) and Chi-squared tests for categorical data (gender, smoking status and number of exacerbations/year).

Reliability

Within-day reliability and between-days reliability were determined. Relative and absolute reliability were calculated with the ICC and the Bland and Altman method, respectively (Rankin & Stokes, 1998). Within-day reliability was computed using the ICC equation1, k), where k=3 corresponds to the three recordings performed in session 1. The Bland and Altman method assesses the agreement between two sets of measures (Bland & Altman, 1986); thus, random numbers were generated in MATLAB to delete one recording. Between-days reliability was computed using the ICC equation (Equation 1, k), where k=2 corresponds to the two recordings used (one from session 1 and one from session 2). Bland and Altman plots were also created to analyse the distribution of results from session 1 and 2. ICC was interpreted as excellent (>0.75), moderate-to-good (0.4-0.75) or poor (<0.4) (Fleiss, 1986).

Validity

Criterion validity was assessed by analysing the degree to which respiratory sounds correlated with lung function (i.e., percent predicted forced expiratory volume in 1 second, FEV_1%predicted) using Spearman's rank correlation coefficient. The strength of the correlations was interpreted as negligible (i.e., 0-0.30), low (0.31-0.50), moderate (0.51-0.70), high (0.71-0.90) or very high (0.91-1) (Mukaka, 2012). Receiver operating characteristic (ROC) analysis was used to assess the ability of respiratory sounds to differentiate between patients' airflow limitation severity. The ROC analysis only allows to plot the performance of a binary classification, thus, patients classified in the GOLD criteria as I and II were labelled as mild-to-moderate airflow limitation and patients classified as III and IV were labelled as severe-to very severe airflow limitation. The cut-off for each respiratory sound parameter was chosen as the point where the sensitivity and specificity were simultaneously maximised. Area under the curves (AUC) and the 95% confidence interval were determined. AUC was interpreted as: AUC=0.5 no discrimination; 0.7≤AUC<0.8 acceptable discrimination; 0.8≤AUC<0.9 excellent discrimination and AUC≥0.9 outstanding discrimination (Hosmer Jr, Lemeshow, & Sturdivant, 2013). Construct validity

was assessed by examining the relationship between adventitious respiratory sounds, NRS, mMRC and CAT using Spearman's rank correlation coefficient. Predictive validity up to 12 months exacerbations were explored with ROC analysis and the influence of independent predictors (i.e., number of crackles, %Wh, F50 and Imax) on the time until the first exacerbation was analysed by univariate and multivariate Cox regression analyses.

Minimal detectable changes (MDC)

MDC were only computed for respiratory sound parameters and locations that have simultaneously shown adequate between-days reliability (significant ICC>0.75) and validity (significant correlations with FEV_1%predicted). To determine the MDC, first, the standard error of measurement (SEM) was calculated using the following equation:

$$SEM = SD \sqrt{(1 - ICC_{1,2})} \text{ (4)}$$

where SD is the standard deviation of the scores obtained from all participants and ICC is the between-days reliability coefficient. The MDC at the 95% level of confidence (MDC95) was calculated as follows:

$$MDC_{95} = SEM \times 1.96 \times \sqrt{2} \text{ (5)}$$

The MDC was also expressed as a percentage (MDC%), defined as

$$MDC_{\%} = (MDC_{95}/mean) \times 100 \text{ (6)}$$

where "mean" is the mean of the scores obtained in the two testing sessions. A MDC% below 30% was considered acceptable (Portney & Watkins, 2000).

Results

Participants

Fifty-eight patients were contacted and invited to participate in the study. However, seven refused to participate, as they did not perceive the study as relevant (n=5) or had family constrains to their participation (n=2), and one did

74

not complete the assessment. Therefore, 50 participants (36 males) were enrolled in the study. Participants' characteristics are summarised in Table 1.

Table 1. Sample characterisation.

Characteristics		Total (n=50)	GOLD stages I-II (n=21)	GOLD stages III-IV (n=29)	p-value
Age, years		67.26±9.31	67.29±11.22	67.24±7.87	0.987
Gender (male), n(%)		36 (72)	13 (62)	23 (79)	0.213
BMI, kg/m^2		27.26±8.22	29.93±11.26	25.32±4.28	0.049*
Smoking status, n(%)					0.056
	Current	7 (14)	5 (24)	2 (7)	
	Former	26 (52)	7 (33)	19 (66)	
	Never	17 (34)	9 (43)	8 (28)	
Packs/year, M[IQR]		50 [32-77]	48 [24-54]	50 [33-90]	0.294
Exacerbations/year, n(%)					0.638
	0	18 (36)	6 (29)	12 (41)	
	1	9 (18)	4 (19)	5 (18)	
	≥2	23 (46)	11 (52)	12 (41)	
FEV$_1$, L		1.24±0.53	1.65±0.53	0.95±0.28	<0.001*
FEV$_1$, %predicted		49.52±19.67	69.10±10.65	35.34±10.04	<0.001*
FEV$_1$/FVC, %		49.76±13.24	58.71±8.65	43.28±12.24	<0.001*
GOLD stages, n(%)					
	I	3 (6)			
	II	18 (36)			
	III	21 (42)			
	IV	8 (16)			
CAT, M[IQR]		13 [8-21]	12 [9-18]	14 [7-23]	0.582
mMRC, M[IQR]		2 [1-2]	1 [1-2]	2 [1-3]	0.004*
NRS, M[IQR]					
	Cough	1 [0-3]	2 [0-5]	1 [0-3]	0.233
	Wheezing	2 [0-4]	2 [0-3]	3 [0-5]	0.236

Abbreviations: BMI, body mass index; CAT, COPD Assessment Test; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, interquartile range; M, median; mMRC, Modified British Medical Research Council questionnaire; SD, standard deviation; NRS, numeric rating scale. Values are presented as mean±standard deviation, unless otherwise stated. *P<.05.

Reliability

Adventitious respiratory sounds presented excellent within-day reliability ($ICC_{1,3}$>0.75); except at trachea in both respiratory phases (0.57<$ICC_{1,3}$<0.74) and moderate-to-good reliability at anterior chest during expiration (0.65<$ICC_{1,3}$<0.73) for the number of crackles and at anterior right chest during both phases (0.51<$ICC_{1,3}$<0.68) for %Wh. F50 and Imax also presented excellent reliability, except at anterior right chest during inspiration (0.51<$ICC_{1,3}$<0.73).

Absolute reliability showed no systematic bias for any location and/or respiratory phase according to the Bland and Altman plots. Further information of within-day reliability is in the Supporting Information.

Table 2 presents the relative between-days reliability. During inspiration, crackles and wheezes showed moderate-to-good or excellent reliability ($0.48 \leq ICC_{1,2} \leq 0.96$; $P<.05$) at anterior and posterior chest. F50 and Imax showed moderate-to-good or excellent reliability ($ICC_{1,2}>0.47$ and $ICC_{1,2} \geq 0.60$, respectively; $P<.05$), except at posterior left chest ($ICC_{1,2}<0.41$; $P>.05$). During expiration, %Wh and normal respiratory sounds were reliable at trachea and at the anterior chest ($ICC_{1,2}>0.54$; $P<.05$) and the number of crackles was only reliable at trachea ($ICC_{1,2}=0.79$; $P<.05$).

Table 2. Between-days reliability ($ICC_{1,2}$) for normal and adventitious respiratory sounds.

	Inspiration				Expiration			
	No. crackles	%Wh	F50	Imax	No. crackles	%Wh	F50	Imax
Trachea	0.38 [-0.12-0.69]	0.62* [0.31; 0.79]	0.79* [0.62-0.83]	0.62* [0.32-0.79]	0.79* [0.62-0.88]	0.69* [0.44-0.83]	0.71* [0.47-0.84]	0.84* [0.72-0.91]
Anterior right	0.63* [0.33-0.796]	0.92* [0.86-0.96]	0.51* [0.12-0.73]	0.60* [0.27-0.78]	0.44 [-0.02-0.69]	0.54* [0.16-0.74]	0.54* [0.16-0.75]	0.78* [0.60-0.88]
Anterior left	0.88* [0.78-0.94]	0.96* [0.92-0.96]	0.86* [0.73-0.93]	0.73* [0.48-0.86]	0.36 [-0.22-0.66]	0.70* [0.43-0.85]	0.75* [0.52-0.87]	0.60* [0.24-0.79]
Posterior right	0.79* [0.62-0.89]	0.57* [0.21-0.76]	0.47* [0.03-0.71]	0.65* [0.35-0.81]	0.42 [-0.05-0.68]	-0.01 [-0.85-0.45]	0.39 [-0.11-0.66]	0.43 [-0.03-0.69]
Posterior left	0.74* [0.52-0.86]	0.48* [0.04-0.72]	0.41 [-0.10-0.68]	0.15 [-0.58-0.54]	0.25 [-0.39-0.59]	0.07 [-0.73-0.50]	0.31 [-0.29-0.63]	0.07 [-0.72-0.50]

Abbreviations: %Wh, wheeze occupation rate; F50, median frequency; Imax, maximum intensity. Values are presented as $ICC_{1,2}$ (95% confidence interval). *$P<.05$.

Good absolute between-days reliability with no systematic bias was found in the Bland and Altman plots for number of crackles and normal respiratory sounds. However, large limits of agreement were found at trachea for all respiratory sound parameters and for %Wh in all locations, especially during

expiration. Figures 1 and 2 show the Bland-Altman plots obtained at posterior right and left chest, respectively. The remaining plots are found in the Supporting Information.
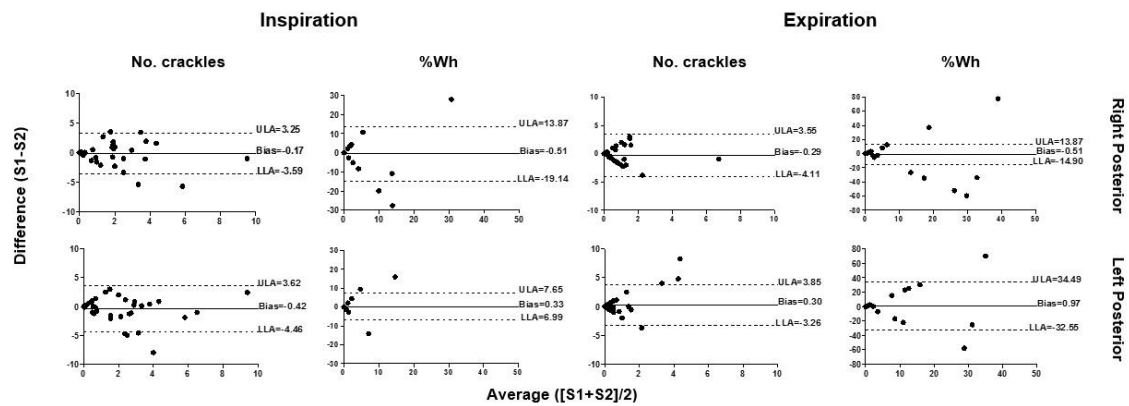
Figure 1. Bland and Altman plots of number of crackles and wheeze occupation rate (%Wh) collected at session 1 (S1) and session 2 (S2) at posterior right and left chest. Solid lines represent the zero value, and dashed lines show the associated bias and 95% upper limit of agreement (ULA) and lower limit of agreement (LLA).

Figure 2. Bland and Altman plots of median frequency (F50) and maximum intensity (Imax) collected at session 1 (S1) and session 2 (S2) at posterior right and left chest. Solid lines represent the zero value, and dashed lines show the associated bias and 95% upper limit of agreement (ULA) and lower limit of agreement (LLA).
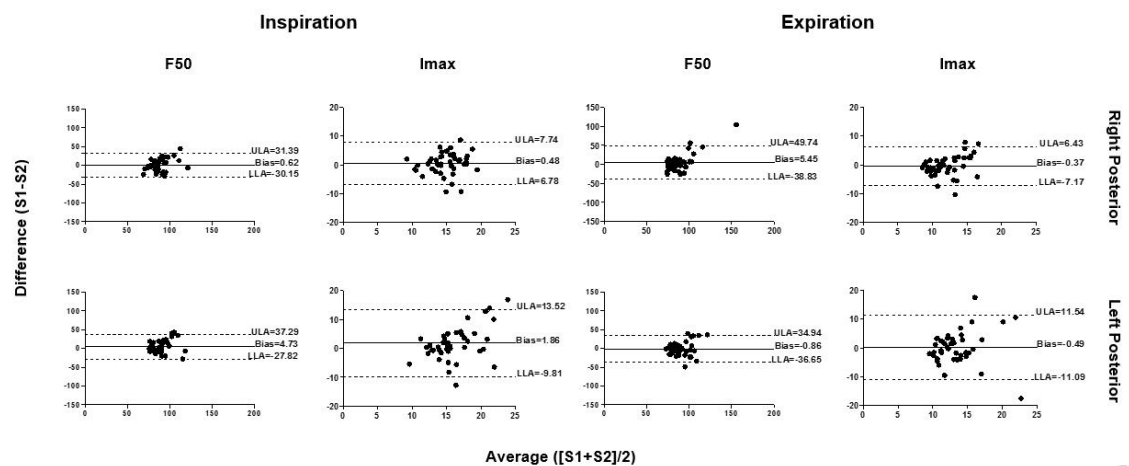
Validity

Concerning criterion validity, significant negligible-to-moderate negative correlations (–0.53<rs<–0.28; P<.05) between FEV_1%predicted and adventitious respiratory sounds were found, especially for the number of crackles during inspiration. Significant correlations were also found for normal respiratory sounds, being negative for inspiratory F50 and positive for Imax, especially during inspiration. Table 3 presents the correlations between FEV_1%predicted and computerised respiratory sounds.

Table 3. Correlations between lung function (FEV_1%predicted) and computerised respiratory sounds.

	Inspiration				Expiration				
	No. crackles	%wh	F50	Imax	No. crackles	%wh	F50	Imax	
Trachea	r_s=-0.07	r_s=-0.09	r_s=-0.35*	r_s=0.28*	r_s=-0.20	r_s=-0.37*	r_s=-0.18	r_s=0.26	
Anterior right	r_s=-0.11	r_s=-0.09	r_s=-0.18	r_s=0.32*	r_s=-0.16	r_s=-0.20	r_s=0.04	r_s=0.32*	FEV_1 %predicted
Anterior left	r_s=-0.42*	r_s=-0.13	r_s=-0.37*	r_s=0.36*	r_s=-0.53*	r_s=-0.18	r_s=0.04	r_s=0.03	
Posterior right	r_s=-0.44*	r_s=-0.23	r_s=0.06	r_s=0.23	r_s=-0.11	r_s=-0.21	r_s=0.02	r_s=0.28	
Posterior Left	r_s=-0.42*	r_s=-0.22	r_s=0.02	r_s=0.07	r_s=-0.16	r_s=-0.12	r_s=0.14	r_s=-0.08	

Abbreviations: %Wh, wheeze occupation rate; F50, median frequency; Imax, maximum intensity. Values are presented as Spearman's correlations. *P<.05.

AUCs of all variables analysed ranged from 0.27 to 0.81, indicating 'no discrimination' to 'acceptable discrimination'. Higher AUCs were found for inspiratory number of crackles recorded at posterior right (AUC=0.78; 95% CI=0.51-1.00; P<.001) and left (AUC=0.81; 95% CI=0.68-0.93; P<.001) chest (Figure 3). To differentiate between participants with mild-to-moderate from participants with severe-to-very severe airflow limitation, cut-off points of 0.1 (sensitivity=81%; specificity=71%) and of 0.5 (sensitivity= 74%; specificity= 80%) for the mean number of crackles at posterior right and left chest, respectively, were identified. Results from the ROC analysis of all computerised respiratory sounds are shown in the Supporting Information.
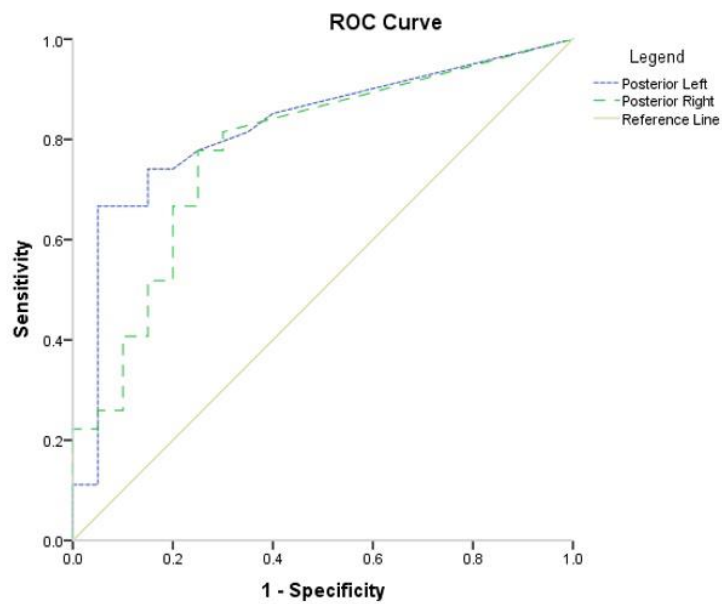
Figure 3. Receiver operator characteristics (ROC) of the inspiratory number of crackles at posterior right and left chest to differentiate between participants with mild-to-moderate airflow limitation and participants with severe-to-very severe airflow limitation.

Concerning construct validity, significant low positive (r_s<0.48; P<.05) correlations were found between patient-reported outcome measures and computerised respiratory sounds. Values for all correlations are shown in the Supporting Information. Concerning predictive validity, both adventitious and normal respiratory sounds showed no ability to predict exacerbations up to 1 year, with AUCs ranging from 0.00 to 0.58 (P>.05). None of the computerised respiratory sound parameters were predictors of the time until the first exacerbation (P>.05; hazard ratios between 0.95 and 1.04).

MDC

The respiratory sounds parameters presenting adequate reliability and validity were inspiratory number of crackles at posterior right chest, inspiratory F50 at trachea and anterior left chest and expiratory Imax at anterior right chest. The MDC95 was 2.41 (SEM=0.87; MDC%=175.38%), 55.27 (SEM=19.94; MDC%=41.22%), 29.55 (SEM=10.66; MDC%=31.86%) and 3.98 (SEM=1.43; MDC%=35.47%) for number of crackles, F50 at trachea, F50 at anterior left chest and Imax, respectively.

Discussion

To the authors' best knowledge, this is the first study describing computerised respiratory sounds reliability and validity according to the COSMIM guidelines. The main findings indicate that respiratory sounds (a) present moderate-to-excellent within-day reliability and moderate-to-good between-days reliability; (b) are valid to express lung function, especially inspiratory number of crackles at posterior chest; (c) correlate poorly with patient-reported outcome measures; (d) do not predict COPD exacerbations and (e) present high values of MDC.

Moderate-to-excellent within-day reliability was found for all respiratory sound parameters, which is in line with data previously reported ($ICC_{1,3}$ from 0.66 to 0.89) (Jácome & Marques, 2015a). Regarding to between-days reliability, slightly lower values were found. This was expected, as it is known that better reliability is achieved when repeated tests are performed within short periods of time (Shin, Ro du, Lee, Oh, & Kim, 2012). The number of inspiratory crackles, recorded at posterior chest, and inspiratory and expiratory %Wh, recorded at anterior chest, were the most reliable parameters. It is known that COPD is characterised by changes in airflow mechanics targeting mainly the smaller airways (The Global Initiative for Chronic Obstructive Lung Disease, 2017); thus, inspiratory crackles at posterior regions have been indicated as the most common and persistent finding in these patients (Jácome & Marques, 2015a, 2015b). Wheezes are also a usual characteristic of patients with bronchial obstruction (Meslier, Charbonneau, & Racineux, 1995). In the present study, inspiratory wheezes were slightly more reliable than expiratory wheezes, which may be explained by their genesis. Patients with COPD usually experience expiratory low frequency wheezes (also known as rhonchi) in upper airways that are generally produced by increased sputum and are easily removed by cough (Bohadana, Izbicki, & Kraman, 2014; Jácome & Marques, 2015b). In contrast, inspiratory wheezes are more related with severe airway obstruction (Meslier et al., 1995),

which characterises most of our sample, and thus are more difficult to change with respiratory manoeuvres.

Regarding construct validity, significant and positive, although low, correlations were found between respiratory sounds and patient-reported outcome measures. Similar results have been found for FEV_1 ($0.14<r<0.41$) (Jones, 2001) and for respiratory sounds ($0.33<r< 0.57$) (Jácome & Marques, 2017) in previous studies and further confirms that clinical outcome measures significantly differ from the individuals' experience of the disease effects on health status and hence, should not be used isolated (Westwood et al., 2011).

Respiratory sounds presented no ability to predict exacerbations up to 1 year after the baseline assessment. Although changes in the tracheobronchial tree are closely related with changes in respiratory acoustics (Pasterkamp, Kraman, & Wodicka, 1997), such associations are likely to be unravelled in time periods close to exacerbations, when the beginning of the inflammatory and/or infectious process has occurred. Additionally, although COPD is mainly characterised by changes in smaller airways, COPD exacerbations are frequently triggered by upper respiratory tract infections (Wedzicha & Donaldson, 2003); thus, it is reasonable that predictions of these events are better detected by changes in larger airways. Indeed, recent studies have shown that computerised respiratory sounds, recorded at trachea, have potential to predict exacerbations in the short term (i.e., 5 days ahead of medical attention); however, such predictions have been determined based on complex analysis (principal component analysis) that cannot be easily understood and applicable by clinicians in clinical practice (Fernandez-Granero, Sanchez-Morillo, & Leon-Jimenez, 2015). Our results have shown that F50 and Imax recorded at upper anatomical locations are valid and reliable parameters and can be more easily determined or even perceived by clinicians during auscultation. Thus, we recommend future studies on COPD telemonitoring to explore the efficacy of these normal respiratory parameters to early detect exacerbations.

High MDC values were found for all respiratory sound parameters which might be related with patients' high inter-subject variability, as reported in previous studies (Jácome & Marques, 2015a). These results highlight the importance of supporting health care professionals' clinical decisions in the interpretation of respiratory sound changes at an individual level and in combination with other patient-reported outcome measures. Nevertheless, this was the first study to calculate MDC for respiratory sounds and provides a valuable cut-off point to represent minimum detectable change in repeated measures beyond the threshold of error.

Limitations

This study has some potential limitations that need to be discussed. Flows and/or volumes were not controlled during respiratory sounds recordings and it is known that respiratory sound acoustics depends on volume and rate of respiratory manoeuvres (Pasterkamp et al., 1997). However, this can be arguable for the purposes of this study as it has been previously demonstrated that even without airflow control, respiratory sounds present adequate reliability (ICC>0.70) and are almost as reliable as during recordings at controlled flows (Jácome & Marques, 2015a). Moreover, this study was designed to be as close to clinical practice as possible and, currently, equipment for airflow monitoring is expensive, little portable and requires trained professionals for its interpretation, which hinders its use in such settings. This study followed the COSMIN methodological recommendations to test the suitability of an outcome measure to be implemented in the clinical practice. The COSMIN was originally developed for health-related, patient-reported outcome measures, such as questionnaires (Terwee et al., 2007). Therefore, the application of the COSMIN as a tool for guiding methodology of studies testing clinical outcome measures can be questioned. Nonetheless, in the absence of guidelines specifically designed to conduct such studies, the COSMIN is indicated as an adequate alternative tool (Bartels, de Groot, & Terwee, 2013).

Conclusions

The number of crackles recorded at posterior locations and the normal respiratory sounds recorded at trachea and anterior regions are reliable and valid parameters to assess and monitor patients with stable COPD. Nonetheless, results from criterion and construct validity showed that computerised respiratory sounds should not be used isolated, but rather integrated with other clinical and patient reported outcome measures, as they may fill the gap of assessing small airways and contribute toward a patient's comprehensive evaluation.

References

Bartels, B., de Groot, J., & Terwee, C. (2013). The six-minute walk test in chronic pediatric conditions: a systematic review of measurement properties. *Physical Therapy, 93*(4), 529-541.

Bestall, J., Paul, E., Garrod, R., Garnham, R., Jones, P., & Wedzicha, J. (1999). Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax, 54*(7), 581-586.

Bland, J Martin, & Altman, DouglasG. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet, 327*(8476), 307-310.

Bohadana, A., Izbicki, G., & Kraman, S. (2014). Fundamentals of lung auscultation. *New England Journal of Medicine, 370*(8), 744-751.

Boulet, L., Coeytaux, R., McCrory, D., French, C., Chang, A., Birring, S., . . . Irwin, R. (2015). Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report. *Chest, 147*(3), 804-814.

Calverley, P., Boonsawat, W., Cseke, Z., Zhong, N., Peterson, S., & Olsson, H. (2003). Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *European Respiratory Journal, 22*(6), 912-919.

Celli, B., Decramer, M., Wedzicha, J., Wilson, K., Agusti, A., Criner, G., . . . ZuWallack, R. (2015). An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. *European Respiratory Journal, 45*(4), 879-905.

Doherty, D., Belfer, M., Brunton, S., Fromer, L., Morris, C., & Snader, T. (2006). Chronic obstructive pulmonary disease: consensus recommendations for early diagnosis and treatment. *Journal of Family Practice, 55*(11), S1-S1.

Fernandez-Granero, M., Sanchez-Morillo, D., & Leon-Jimenez, A. (2015). Computerised Analysis of Telemonitored Respiratory Sounds for Predicting Acute Exacerbations of COPD. *Sensors, 15*(10), 26978-26996.

Fleiss, J. (1986). Reliability of measurement. In J. Fleiss (Ed.), *Design and analysis of clinical experiments.* (pp. 1-32). New York: John Wiley & Sons.

Gavriely, N., Nissan, M., Cugell, D. W., & Rubin, A. H. (1994). Respiratory health screening using pulmonary function tests and lung sound analysis. *European Respiratory Journal, 7*(1), 35-42.

Hosmer Jr, D., Lemeshow, S., & Sturdivant, R. (2013). *Applied logistic regression* (Vol. 398). Hoboken, NJ: John Wiley & Sons.

Hossain, I., & Moussavi, Z. (2004). *Finding the lung sound-flow relationship in normal and asthmatic subjects.* Paper presented at the 26th Annual International Conference of the IEEE, San Francisco, USA.

Jácome, C., & Marques, A. (2015a). Computerized Respiratory Sounds Are a Reliable Marker in Subjects With COPD. *Respiratory Care, 60*(9), 1264-1275.

Jácome, C., & Marques, A. (2015b). Computerized respiratory sounds in patients with COPD: a systematic review. *COPD, 12*(1), 104-112.

Jácome, C., & Marques, A. (2017). Computerized Respiratory Sounds: Novel Outcomes for Pulmonary Rehabilitation in COPD. *Respiratory Care, 62*(2), 199-208.

Jácome, C., Oliveira, A., & Marques, A. (2017). Computerized respiratory sounds: a comparison between patients with stable and exacerbated COPD. *The Clinical Respiratory Journal, 11*(5), 612-620.

Jones, P. (2001). Health status measurement in chronic obstructive pulmonary disease. *Thorax, 56*(11), 880-887.

Jones, P., Harding, G., Berry, P., Wiklund, I., Chen, W-H., & Kline Leidy, N. (2009). Development and first validation of the COPD Assessment Test. *European Respiratory Journal, 34*(3), 648-654.

Kraman, S., Wodicka, G., Oh, Y., & Pasterkamp, H. (1995). Measurement of respiratory acoustic signals: effect of microphone air cavity width, shape, and venting. *Chest, 108*(4), 1004-1008.

Mahler, D., Ward, J., Waterman, L., McCusker, C., ZuWallack, R., & Baird, J. (2009). Patient-reported dyspnea in COPD reliability and association with stage of disease. *Chest, 136*(6), 1473-1479.

McNulty, W., & Usmani, O. (2014). Techniques of assessing small airways dysfunction. *European Clinical Respiratory Journal, 1*(1), 25898.

Meslier, N., Charbonneau, G., & Racineux, J. (1995). Wheezes. *European Respiratory Journal, 8*(11), 1942-1948.

Miller, M., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., . . . Gustafsson, P. (2005). Standardisation of spirometry. *European Respiratory Journal, 26*(2), 319-338.

Morris, N., Sabapathy, S., Adams, L., Kingsley, R., Schneider, D., & Stulbarg, M. (2007). Verbal numerical scales are as reliable and sensitive as visual analog scales for rating dyspnea in young and older subjects. *Respiratory Physiology & Neurobiology, 157*(2-3), 360-365.

Mukaka, M. (2012). A guide to appropriate use of correlation coefficient in medical research. *Malawi Medical Journal, 24*(3), 69-71.

Oliveira, A., Pinho, C., & Marques, A. (2017). Effects of a respiratory physiotherapy session in patients with LRTI: a pre/post-test study. *The Clinical Respiratory Journal, 11*(6), 703-712.

Oliveira, A., Sen, I., Kahya, Y., Afreixo, V., & Marques, A. (2017). Computerised respiratory sounds can differentiate smokers and non-smokers. *Journal of Clinical Monitoring and Computing, 31*(3), 571-580.

Pasterkamp, H., Kraman, S., & Wodicka, G. (1997). Respiratory sounds. Advances beyond the stethoscope. *American Journal of Respiratory and Critical Care Medicine, 156*(3 Pt 1), 974-987.

Pasterkamp, H., Powell, R., & Sanchez, I. (1996). Lung sound spectra at standardized air flow in normal infants, children, and adults. *American Journal of Respiratory and Critical Care Medicine, 154*(2), 424-430.

Pinho, C., Oliveira, A., Oliveira, D., Dinis, J., & Marques, A. (2014). LungSounds@ UA interface and multimedia database. *International Journal of E-Health and Medical Communications, 5*(1), 81-95.

Portney, L., & Watkins, M. (2000). *Foundations of clinical research: applications to practice* (2 ed.). Upper Saddle River, NJ: Prentice Hall

Rankin, G., & Stokes, M. (1998). Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. *Clinical Rehabilitation, 12*(3), 187-199.

Rossi, M., Sovijarvi, A., Piirila, P., Vannuccini, L., Dalmasso, F., & Vanderschoot, J. (2000). Environmental and subject conditions and breathing manoeuvres for respiratory sound recordings. *European Respiratory Review, 10*(77), 611-615.

Shin, S., Ro du, H., Lee, O., Oh, J., & Kim, S. (2012). Within-day reliability of shoulder range of motion measurement with a smartphone. *Manual Therapy, 17*(4), 298-304.

Sulzer, J., Schüttler, F., Penzel, T., & Wichert, P. (1997, October 15–17). *A simple method for detecting bronchial breathing sound.* Paper presented at the 22nd International Conference on Lung Sounds, Tokyo, Japan.

Terwee, C., Bot, S., de Boer, M., van der Windt, D., Knol, D., Dekker, J., . . . de Vet, H. (2007). Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of Clinical Epidemiology, 60*(1), 34-42.

Terwee, C., Mokkink, L., Knol, D., Ostelo, R., Bouter, L., & de Vet, H. (2012). Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Quality of Life Research, 21*(4), 651-657.

The Global Initiative for Chronic Obstructive Lung Disease. (2017). Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease - 2017 Report: The Global Initiative for Chronic Obstructive Lung Disease, Inc.

Vannuccini, L., Earis, J., Helisto, P., Cheetham, B., Rossi, M., Sovijarvi, A., & Vanderschoot, J. (2000). Capturing and preprocessing of respiratory sounds. *European Respiratory Review, 10*(77), 616-620.

Vyshedskiy, A., & Murphy, R. (2012). Crackle pitch rises progressively during inspiration in pneumonia, CHF, and IPF patients. *Pulmonary Medicine, 2012*, Article ID 240160.

Wedzicha, J., & Donaldson, G. (2003). Exacerbations of chronic obstructive pulmonary disease. *Respiratory Care, 48*(12), 1204-1213.

Westwood, M., Bourbeau, J., Jones, P., Cerulli, A., Capkun-Niggli, G., & Worthy, G. (2011). Relationship between FEV1 change and patient-reported outcomes in randomised trials of inhaled bronchodilators for stable COPD: a systematic review. *Respiratory Research, 12*(40), 1-9.

Zwick, R., Burghuber, O., Dovjak, N., Hartl, S., Kossler, W., Lichtenschopf, A., . . . Zwick, H. (2009). The effect of one year outpatient pulmonary rehabilitation on patients with COPD. *Wiener klinische Wochenschrift, 121*(5-6), 189-195.

Study II

_____

Minimal important and detectable differences of respiratory measures in outpatients with AECOPD

Oliveira A, Machado A, Marques A

Abstract

Interpreting clinical changes during acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is challenging due to the absence of established minimal detectable (MDD) and important (MID) differences for most respiratory measures. This study established MDD and MID for respiratory measures in outpatients with AECOPD following pharmacological treatment.

COPD assessment test (CAT), modified Borg scale (MBS), modified British Medical Research Council questionnaire (mMRC), peripheral oxygen saturation (SpO_2), computerised respiratory sounds and forced expiratory volume in one second (FEV_1) were collected within 24-48h of an AECOPD and after 45 days of pharmacological treatment. MID and MDD were calculated using anchor- (ROC and linear regression analysis) and distribution-based methods (effect size, SEM, 0.5*SD and MDC95) and pooled using Meta XL.

Forty-four outpatients with AECOPD (31♂; 68.2±9.1yrs; FEV_1 51.1±20.3%predicted) participated. Significant correlations with CAT were found for the MBS (r=0.34), mMRC (r=0.39) and FEV_1 (r=0.33), resulting in MIDs of 0.8, 0.5-0.6 and 0.03L, respectively. MDD of 0.5-1.4 (MBS), 0.4-1.2 (mMRC), 0.10-0.28L (FEV_1), 3.6-10.1% (FEV_1%predicted), 0.9-2.4% (SpO_2), 0.7-1.9 (number of inspiratory crackles), 1.1-4.5 (number of expiratory crackles), 7.1-25.8% (inspiratory wheeze rate) and 11.8-63.0% (expiratory wheeze rate) were found.

Pooled data of MID/MDD showed that improvements of 0.9 for the MBS, 0.6 for the mMRC, 0.15L for the FEV_1, 7.6% for the FEV_1%predicted, 1.5% for the SpO_2, 1.1 for the inspiratory and 2.4 for the number of expiratory number of crackles, 14.1% for the inspiratory and 32.5% for the expiratory wheeze rate are meaningful following an AECOPD managed with pharmacological treatment on an outpatient basis.

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are frequent events during the course of COPD (Boer et al., 2018). Recovery from AECOPD can take up to 91 days, and it is known that some patients may never fully recover to their baseline status (Seemungal et al., 1998). Additionally, costs associated with the management of AECOPD are estimated in $7.100 per patient, per exacerbation (Guarascio, Ray, Finch, & Self, 2013). These facts place AECOPD as the main responsible for patients' clinical deterioration and increased healthcare costs in COPD (Anzueto, 2010).

The health and economic burden of AECOPD demand timely and appropriate management of these events (Viniol & Vogelmeier, 2018), and a significant amount of research is currently being conducted with this purpose (Viniol & Vogelmeier, 2018; Wedzicha et al., 2017). Nevertheless, the interpretation of improvements seen during the recovery from AECOPD remains difficult, due to the absence of minimal important differences (MID) for most respiratory measures used in the assessment and monitoring of these patients (Oliveira & Marques, 2018).

MID, defined as a meaningful important change for patients, which would lead to consider a change in the patients' management (Brożek, Guyatt, & Schünemann, 2006), is currently the standard to interpret results obtained, guide changes in patient's treatments and to calculate sample sizes in clinical research. According to the authors best knowledge, MIDs for patients with AECOPD have been established mainly in inpatients (Kon et al., 2014; Tsai et al., 2008) and for patient-reported measures, such as the Clinical COPD Questionnaire (Oliveira & Marques, 2018), the Chronic Respiratory Disease Questionnaire (Oliveira & Marques, 2018) and the COPD Assessment Test (CAT) (Kon et al., 2014). This limits the management of patients treated on an outpatient basis, which correspond to more than 80% of AECOPD (The Global Initiative for Chronic Obstructive Lung Disease, 2018), and the interpretation of changes in other important and widely used clinical respiratory measures, such as peripheral

oxygen saturation (SpO_2), auscultation and lung function (Fernandez-Villar et al., 2018; Oliveira & Marques, 2018). Additionally, the interpretability of specific measures of dyspnoea, the most representative and valued symptom in patients presenting an AECOPD (Parker, Voduc, Aaron, Webb, & O'Donnell, 2005; Seemungal et al., 1998), is yet to be established. Incorrect interpretations of patients' improvements in these outcomes may lead to the development of suboptimal therapies and ultimately increase the rate of patients' deterioration.

Thus, this study aimed to estimate the MID in outpatients with AECOPD for the following respiratory measures: modified Borg scale (MBS), modified British Medical Research Council (mMRC) questionnaire, SpO_2, computerised respiratory sounds, namely crackles and wheezes, and forced expiratory volume in one second (FEV_1). Additionally, the minimal detectable difference (MDD), i.e., the minimal change in a specific measure that fall outside the measurement error (de Vet et al., 2006), was also calculated for each outcome measure.

Methods

Study design and participants

An observational study, part of a longitudinal study conducted in outpatients with AECOPD recruited from the urgent care of a Central hospital (Oliveira, Rodrigues, & Marques, 2018), was conducted. Inclusion criteria were diagnosis of an AECOPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Exclusion criteria were hospitalisation (defined as the need to be admitted as an inpatient at the respiratory or intensive care unit for further assessment/treatment after consultation with the urgency physician), patients requiring emergency intubation, and/or mechanical ventilation; patients with compromised neurological status or hemodynamic instability or presence of severe co-existing respiratory, neurological (e.g., Parkinson disease), cardiac (e.g., uncontrolled symptomatic heart failure), musculoskeletal (e.g., kyphoscoliosis), or signs of psychiatric impairments. Eligible patients were

identified by physicians and contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. An appointment with the researchers was scheduled within 48 hours of the hospital visit with those interested to participate.

Approval for this study was obtained from the ethics committee of the Centro Hospitalar do Baixo Vouga (13NOV'1514:40065682) and from the National Data Protection Committee (8828/2016). Written informed consent, following the guidelines of the Declaration of Helsinki, was obtained from patients before any data collection.

Data collection

Patients were asked to attend to 4 assessment sessions: within 48 hours of the urgent care visit (T1 – exacerbation onset) and approximately 8 days (T2 – during exacerbation), 15 days (T3 – following exacerbation) (Seemungal, Donaldson, Bhowmik, Jeffries, & Wedzicha, 2000) and 45 days after the hospital visit (T4 – at stability post exacerbation). Data collection occurred at the urgent care, in the facilities of the Respiratory Research and Rehabilitation Laboratory (Lab3R) of the School of Health Sciences, University of Aveiro (Portugal) or at patients' home.

According to the time interval used in previous studies to establish minimal important differences for clinical measures in AECOPD (i.e., 14 days to 3 months) (Jones, Harding, et al., 2012; Kocks et al., 2006; Kon et al., 2014; Tsai et al., 2008), and to ensure patients' stability after the AECOPD (defined according to patient's reports of symptoms stability - i.e., no changes beyond their day-to-day variability, no visits to health care units and no changes in their medication in the month preceding the evaluation) (Soler-Cataluna, Alcazar-Navarrete, & Miravitlles, 2014), only data from T1 and T4 were explored.

Sociodemographic (age, sex), anthropometric (height, weight and body mass index - BMI) and general clinical data (smoking habits, number of

exacerbations in the past year, medication and activities related dyspnoea) were first collected.

In each data collection moment, impact of the disease, dyspnoea at rest and during activities, SpO_2, computerised respiratory sounds and lung function were collected by a trained physiotherapist following the described standardised order.

Impact of the disease was measured with the CAT, a disease-specific questionnaire consisting of eight items (i.e., cough, sputum, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep, and energy) scored from 0 to 5 (Jones et al., 2009). Each item individual score is added to provide a total CAT score that can range from 0 to 40 (Jones et al., 2009). Higher scores indicate more impact of the disease on patients' life. CAT was chosen as the anchor to determine the MID of the respiratory measures since it reflects a global rating of impact in health, is responsive to change, and has a MID established for patients with AECOPD (Kon et al., 2014).

Dyspnoea at rest was assessed with the MBS (Sulzer, Schüttler, Penzel, & Wichert, 1997), and activity limitation due to dyspnoea was assessed using the mMRC questionnaire (Doherty et al., 2006). The MBS is a categorical scale with a score from 0 to 10, where 0 corresponds to the sensation of normal breathing and 10 corresponds to the patients' maximum possible sensation of dyspnoea (Crisafulli & Clini, 2010). The mMRC questionnaire is a 5-point scale where level 0 represents the lowest level of dyspnoea impairment perceived and level 4 the greatest dyspnoea impairment (Crisafulli & Clini, 2010). Both scales have been shown to be valid and reliable in patients with COPD (Crisafulli & Clini, 2010; Meek & Lareau, 2003).

Peripheral oxygen saturation was collected at rest with a pulse oximeter (Pulsox 300i, Konica Minolta, Tokyo, Japan). This measure has been widely used to assess effectiveness of interventions in patients with AECOPD and has shown

fair validity against arterial oxygen saturation (bias in the Bland and Altman of - 0.78; 95% confidence interval – CI of 8.2 to 6.7) in this population (Oliveira & Marques, 2018).

Computerised respiratory sounds, specifically the inspiratory and expiratory mean number of crackles and wheeze occupation rate, acquired at the posterior chest, were analysed. Respiratory sounds were acquired with air-coupled electret microphones (C 417PP, AKG Acoustics GmbH, Vienna, Austria) and a multi-channel audio interface (AudioBox 1818 VSL, PreSonus, Florida, USA) and were analysed with previous validated algorithms (Huq & Moussavi, 2010; Pinho, Oliveira, Jácome, Rodrigues, & Marques, 2016; Taplidou & Hadjileontiadis, 2007). Number of crackles and wheeze occupation rate acquired in posterior locations have been shown to be valid against lung function (-$0.11 < r_s < -0.44$) (Oliveira, Lage, Rodrigues, & Marques, 2018), reliable ($0.25 < ICC_{1,2} < 0.86$) (Jácome & Marques, 2015; Oliveira, Lage, et al., 2018) and sensitive to changes in patients with stable and exacerbated COPD (Jácome, Oliveira, & Marques, 2017; Oliveira, Rodrigues, et al., 2018). Further details on respiratory sound acquisition and analysis have been provided elsewhere (Oliveira, Sen, Kahya, Afreixo, & Marques, 2017).

Lung function was assessed with a portable spirometer (MicroLab 3535, CareFusion, Kent, UK) (Miller et al., 2005) according to international guidelines (American Thoracic Society, & European Respiratory Society, 2002). FEV_1 in litres and as percentage of predicted (FEV_1 percentage predicted) were extracted for each patient. These parameters have been shown to be feasible, valid and reliable (ICC=0.89) to assess in patients with AECOPD (Fernandez-Villar et al., 2018).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA) or Meta XL 5.3 (EpiGear International, Queensland, Australia). Plots were created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA) or Meta XL 5.3. The level of

significance was set at 0.05. Descriptive statistics were used to describe the sample, and participants' characteristics were expressed as relative frequencies, mean (standard deviation) or median (interquartile range) as appropriate. Outlier's analysis was performed by plotting the studied variables (i.e. MBS, mMRC, SpO_2, computerised respiratory sounds, FEV_1 and FEV_1 percentage predicted) against the CAT (i.e., the anchor used to compute the MID) on a graph and visually inspecting the graph for wayward (extreme) points (Aggarwal & Ranganathan, 2016). The outliers found were removed for both MID and MDD analysis. Significance of changes between T1 and T4 was calculated with paired t-tests or Wilcoxon signed-rank tests depending on normality.

Minimal important difference

MIDs were calculated through questionnaire referencing methods using CAT as an anchor. Then, changes in CAT were correlated with changes in MBS, mMRC, SpO_2, inspiratory and expiratory mean number of crackles and wheeze occupation rate, FEV_1 and FEV_1 percentage predicted, using Pearson correlation coefficient, to determine suitability for its use as an anchor. Significant correlations equal or superior to 0.3 were considered suitable and used in further analysis to establish the MID (Revicki, Hays, Cella, & Sloan, 2008). To discriminate patients who improved from those who did not improve their health status, the established MID in the CAT total score for patients with AECOPD (two points improvement) was used (Jones, Harding, et al., 2012; Kon et al., 2014). MIDs were calculated using receiver operating characteristic (ROC) curves and linear regression analysis. For each ROC curve, the area under the curve (AUC) and 95% confidence intervals were obtained and the MID for each respiratory measure was chosen as the point where the sensitivity (SN) and specificity (SP) were simultaneously maximised (i.e., the data point closest to the upper left corner of the ROC curve) (Table 1). For linear regression analysis, the equations developed which reached statistical significance were used to estimate change in respiratory scores corresponding to the MID improvement for the CAT (Table 1).

Minimal detectable difference

Distribution-based methods used to calculate MDD were (1) effect sizes (34), interpreted as small ($d_z>0.2$), medium ($d_z>0.5$) or large ($d_z\geq0.8$) (Portney & Watkins, 2000); (2) 0.5 times the standard deviation (SD) of the baseline session (33); (3) standard error of measurement (SEM) (Hosmer Jr, Lemeshow, & Sturdivant, 2013) and (4) minimal detectable change (MDC) at the 95% level of confidence (Shin, Ro du, Lee, Oh, & Kim, 2012) (Table 1). The intraclass correlation coefficient ($ICC_{1,2}$) used for the SEM calculation was established based on the between-days reliability previously published by Sant'Anna et al. (2017) for SpO_2 ($ICC_{3,1}=0.89$) and MBS ($ICC_{3,1}=0.95$), Mahler et al. (2009) for mMRC (ICC=0.82) and FEV_1 (ICC=0.96), and by Oliveira, Lage, et al. (2018) for number of crackles (inspiratory crackles $ICC_{1,2}=0.79$; expiratory crackles $ICC_{1,2}=0.42$) and wheeze occupation rate (inspiratory wheezes $ICC_{1,2}=0.57$; expiratory wheezes $ICC_{1,2}=0.07$). The pooling of data was performed based on what has been previously described by Alma et al. (2006, 2008). MIDs and MDD estimated with each of the anchor- and distribution-based methods for the MBS, mMRC, SpO_2, inspiratory and expiratory mean number of crackles and wheeze occupation rate, FEV_1, and FEV_1 percentage predicted were pooled using Meta XL 5.3. The input data were the estimated MID/MDD with each method and respective confidence interval, when appropriated, being the output the same as the input. Given that anchor- are preferred over distribution-based methods for the establishment of clinically significance (Angst, Aeschlimann, & Angst, 2017; Revicki et al., 2008), a quality effects model (Doi & Thalib, 2008) was used to incorporate the weight of each method in the pooled estimate, where anchor methods weighted more than distribution methods (Alma et al., 2018).

Table 1. Anchor and distribution-based methods to estimate the minimal important and detectable differences.

Method	Approach	Statistics
Anchor-based method	ROC curve	-
	Linear regression analysis	-
Distribution-based method	ES	$(mean_{T4} - mean_{T1})/\sqrt{(SD_{T1}^2 + SD_{T4}^2)/2}$
	0.5 times SD	$0.5 \times SD_{T1}$
	SEM	$SD_{T1}\sqrt{(1 - ICC_{1,2})}$
	MDC$_{95}$	$MDC_{95} = SEM \times 1.96 \times \sqrt{2}$

ES, effect size; MDC95, minimal detectable change at the 95% level of confidence; ROC, receiver operator characteristics; SD, standard deviation; SEM, standard error of measurement.

Results

Participants

Seventy-eight non-hospitalised patients with AECOPD were referred for possible inclusion in the study. Of these, 34 were excluded because, at T1, presented lung function tests and clinical history incompatible with a diagnosis of COPD (n=22), did not meet the definition for AECOPD (n=1), presented lung neoplasia (n= 2), severe heart failure (n=1), were unable to comply with testing (n=3), or decline to participate in the study (n=5). Forty-four non-hospitalised patients with AECOPD (31 males; 68.2±9.1 years; 51.1±20.3 FEV$_1$ percentage predicted) were invited and agreed to participate in the study. Nineteen patients were excluded from the respiratory sound analysis because the respiratory sound data collection was not completed (n=6) and their respiratory sounds (collected at the urgent care) had a significant amount of background noise hindering the use of the algorithms described in the Data collection section (n=13). Participants' characteristics are summarised in Table 2.

Table 2. Sample characterisation.

Characteristics	Patients with AECOPD (n=44)	Patients included for RS analysis (n=25)
Age, years,	68.2±9.1	70.0±9.8
Sex (male), n(%)	31 (70.5)	16 (47.1)
BMI, kg/m^2	25.9±4.8	26.7±4.9
Smoking status, n(%)		
Current	8 (18.2)	4 (16.0)
Former	22 (50.0)	11 (44.0)
Never	14 (31.8)	10 (40.0)
Packs/year	45.0 [22.0-67.3]	30.0 [15.0-70.0]
Exacerbations/year, n(%)		
0	8 (18.2)	5 (20.0)
1	11 (25.0)	5 (20.0)
≥2	25 (56.8)	15 (60.0)
FEV$_1$, L	1.22±0.51	1.25±0.54
FEV$_1$, %predicted	51.1±20.3	54.2±20.6
FEV$_1$/FVC, %	50.5±13.6	51.7±13.8
GOLD stages, n(%)		
A	6 (13.6)	4 (6.8)
B	5 (11.4)	3 (5.1)
C	5 (11.4)	5 (8.5)
D	26 (59.1)	13 (22.0)
Medication, n(%)		
Antibiotics	28 (65.1)	17 (70.8)
Bronchodilators		
SABA	9 (20.9)	3 (12.5)
SAMA	6 (14.0)	3 (12.5)
SABA/SAMA combination	6 (14.0)	6 (25.0)
LABA	5 (11.6)	3 (12.5)
LAMA	22 (51.2)	13 (54.2)
LABA/LAMA combination	5 (11.6)	2 (8.3)
ICS	7 (16.3)	5 (20.8)
ICS/LABA combination	27 (62.8)	16 (66.7)
Xanthines	16 (37.2)	8 (33.3)
LTRA	4 (9.3)	3 (12.5)
Expectorants	20 (46.5)	12 (50)
Oral Corticosteroids	9 (20.9)	5 (20.8)
mMRC	1.0 [0.5-2.0]	1.0 [0.5-2.0]

Values are presented as mean±standard deviation or median [interquartile range], unless otherwise stated. BMI, body mass index; FEV$_1$, forced expiratory volume in one second (at stability); FVC, forced vital capacity (at stability); GOLD, global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; mMRC, modified British Medical Research Council questionnaire; SD, standard deviation; SABA, short-acting beta agonists; SAMA, short-acting muscarinic-antagonist.

Minimal important difference

Following the AECOPD, 31 patients improved beyond the MID of the CAT (mean difference of -10.7±5.3), 6 patients did not improve beyond the MID (mean difference of 6.2±3.2) and 7 failed to complete the post-AECOPD assessment. Outlier's examination leads to the removal of three participants. No differences were found between included participants and outliers for their baseline characteristics ($p > 0.05$). Distribution of scores in SpO_2, MBS, mMRC, respiratory sounds, FEV_1 and FEV_1 percentage predicted for all participants and according to differences in CAT are presented in Table 3.

Table 3. Mean scores at the onset of AECOPD (T1), after 45 days of AECOPD (T4) and mean change for the respiratory measurement by the COPD Assessment Score.

		Exacerbation onset	Stability post exacerbation	Mean difference	p-value
ΔSpO$_2$		92.6±2.6	94.0±2.7	1.3±2.5	0.004
	≥2 CAT	92.7±2.6	94.0±2.8	1.5±2.7	
	<2 CAT	92.2±2.6	94.0±2.4	2.0±2.1	
ΔMBS		2.3±2.2	1.0±1.9	-1.3±2.1	0.001
	≥2 CAT	2.2±2.2	0.7±1.2	-1.5±2.1	
	<2 CAT	2.8±2.6	2.4±3.9	-0.4±1.8	
ΔmMRC		2.6±1.0	1.4±1.0	-0.9±1.1	<0.001
	≥2 CAT	2.3±1.1	1.3±0.9	-1.1±0.9	
	<2 CAT	1.8±0.8	2.4±2.0	0.4±0.6	
ΔInspiratory CR		1.4±1.6	0.7±1.0	-0.7±1.1	0.013
	≥2 CAT	1.4±1.7	0.6±0.8	-0.6±1.1	
	<2 CAT	1.4±1.7	1.5±1.8	-1.0±1.1	
ΔExpiratory CR		1.3±2.0	0.3±6.5	-0.1±2.2	0.026
	≥2 CAT	1.1±1.7	0.3±0.7	-0.8±1.8	
	<2 CAT	3.5±4.9	0.4±0.7	-3.5±4.9	
ΔInspiratory %Wh		8.1±13.7	2.0±5.8	-6.3±16.3	0.096
	≥2 CAT	7.6±14.3	2.3±6.2	-5.6±16.9	
	<2 CAT	13.7±1.9	0.0±0.0	-13.7±1.9	
ΔExpiratory %Wh		16.2±8.4	8.4±17.0	-5.6±30.7	0.307
	≥2 CAT	17.6±23.6	6.9±15.9	-9.8±29.9	
	<2 CAT	2.1±3.0	18.7±24.1	25.5±23.1	
FEV$_1$		1.09±0.51	1.23±0.50	0.12±0.33	0.037
	≥2 CAT	1.11±0.53	1.30±0.50	0.16±0.34	
	<2 CAT	0.98±0.43	0.86±0.28	-0.07±0.26	

	FEV$_1$% predicted	46.2±18.2	52.8±20.0	5.6±14.3	0.049
≥2 CAT	48.2±18.8	56.5±19.2	6.9±14.9	
<2 CAT	36.3±10.7	32.4±10.2	-1.2±8.0	

Values are presented as mean± standard deviation. %Wh, wheeze occupation rate; CAT, COPD assessment test; CR, crackle; FEV1 (L), forced expiratory volume in one second; MBS, modified Borg scale; mMRC, Modified British Medical Research Council questionnaire; SpO2 (%), peripheral oxygen saturation.

Correlations with changes in CAT equal or superior to 0.3 were found for changes in MBS (r=0.34; p=0.05), mMRC (r=0.39; p=0.025) and FEV$_1$ (r=-0.33; p=0.048) (Figure 1). No significant correlations were observed with changes in SpO$_2$ (r=-0.02; p=0.894), FEV$_1$ percentage predicted (r=-0.29; p=0.102), inspiratory (r=-0.21; p=0.356) and expiratory (r=-0.22; p=0.324) number of crackles, and inspiratory (r=0.24; p=0.291) and expiratory (r=0.36; p=0.102) wheeze occupation rate. Therefore, MID could only be calculated for MBS, mMRC and FEV$_1$.

Figure 1. Correlations between changes in the CAT and changes in the (A) modified Borg scale, (b) modified British Medical Research Council questionnaire (mMRC) and (C) forced expiratory volume in one second (FEV$_1$).

Using ROC statistics, the AUCs generated for the mMRC showed (AUC=0.92; 95%CI=0.82–1.00; p=0.003) adequate discrimination between those improving above and below the MID for CAT (Figure 2). No significant results were observed for the discrimination ability of the MBS (AUC=0.63; 95%CI=0.37–0.89; p=0.366) and for the FEV_1 (AUC=0.67; 95%CI=0.43–0.90; p=0.243). Using ROC, a MID of -0.5 (SN=79%; SP=100%) was obtained for mMRC. Since significance was not reached for the MBS and FEV_1, MID were not established.
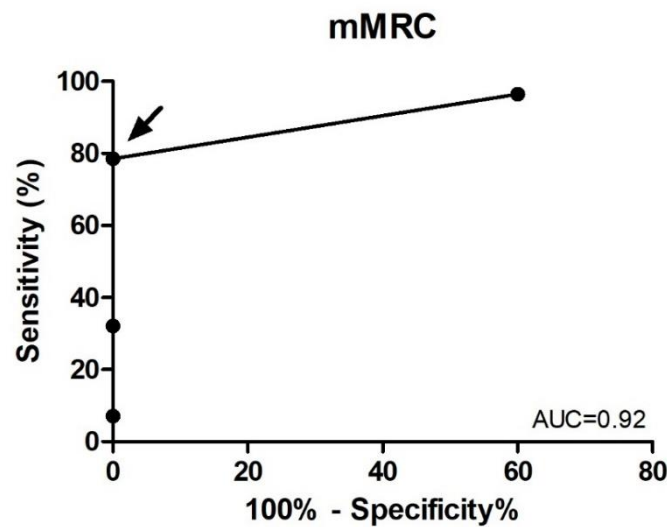
Figure 2. ROCs to discriminate between patients improving above and below the MID in CAT (i.e. two points) for the modified British Medical Research Council questionnaire (mMRC).

Using linear regression, the estimated minimum important improvement for the MBS, mMRC and FEV_1 was -0.8 (95% CI -1.65 to 0.00; p=0.05), -0.6 (95% CI -1.00 to -0.22; p=0.025) and 0.03L (95% CI -0.11 to 0.17; p=0.049), respectively (Figure 3).
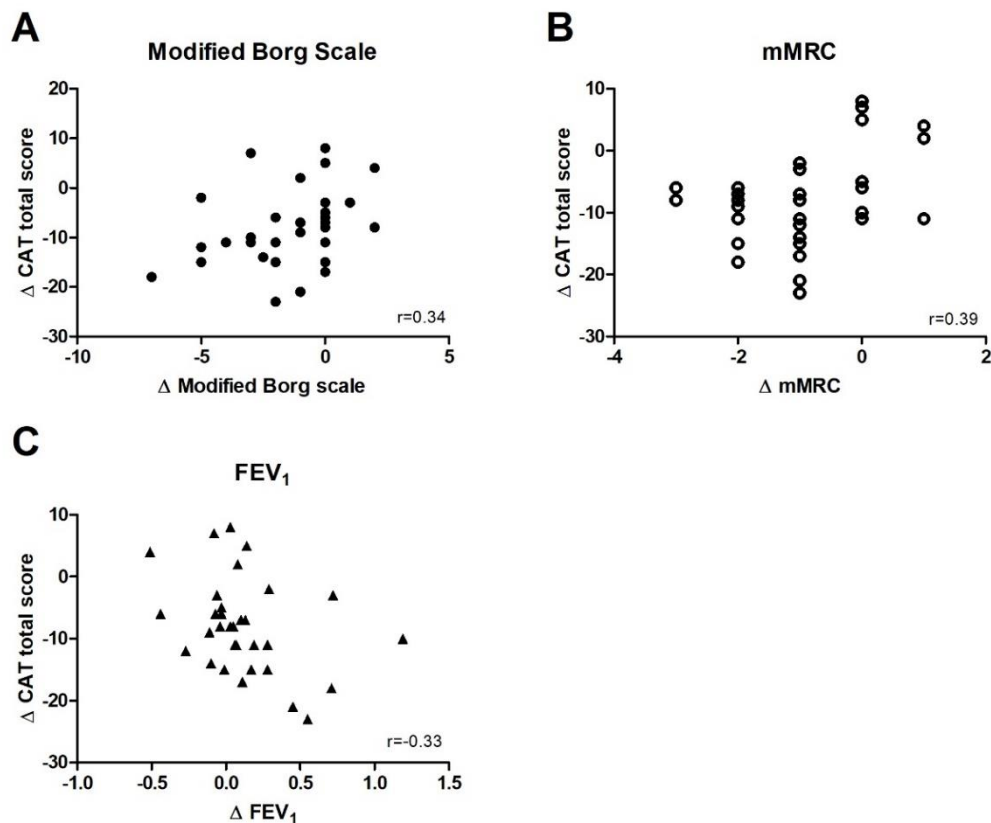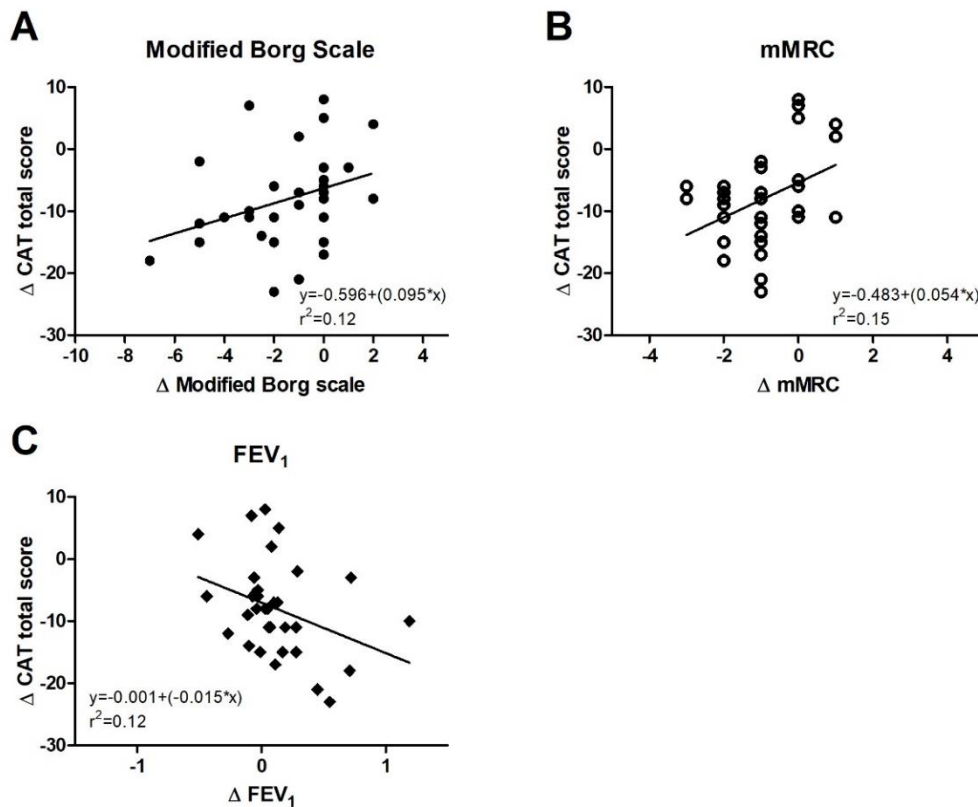
Figure 3. Linear regression between the CAT and the (A) modified Borg scale, (b) modified British Medical Research Council questionnaire (mMRC) and (C) FEV_1.

Minimal detectable difference

Small effect sizes were found for the MBS ($d_z=0.37$), FEV_1 ($d_z=0.28$), FEV_1 percentage predicted ($d_z=0.34$), inspiratory number of crackles ($d_z=0.48$) and expiratory wheeze rate ($d_z=0.39$), medium effect sizes were found for the inspiratory wheeze rate ($d_z=0.58$), expiratory number of crackles ($d_z=0.65$) and SpO_2 ($d_z=0.52$) and large effect sizes were found for the mMRC ($d_z=0.80$) (Table 4). Values of the 0.5*SD, SEM and MDC95 can be found in the summary of Table 4.

Pooled MID and MDD

Pooled MID and MDD for the MBS, mMRC, FEV_1, FEV_1 percentage predicted, SpO_2, inspiratory number of crackles, expiratory number of crackles, inspiratory wheeze rate and expiratory wheeze rate were of 0.9, 0.6, 0.15L, 7.6%,

1.5%, 1.1, 2.4, 14.1% and 32.5%, respectively. Individual and pooled values can be found in Table 4 and plots of pooled MID and MDD for MBS, mMRC, FEV_1 can be found in Figure 4.

Table 4. Anchor-based and distribution-based estimates of the minimal important and detectable differences of the respiratory measures.

Measures	Anchor-based methods		Distribution-based method				Pooled value
	ROC curve	Linear regression analysis	ES	0.5*SD	SEM	MDC95	
MBS	-	0.8	0.37	1.1	0.5	1.4	0.9
mMRC	0.5	0.6	0.80	0.5	0.4	1.2	0.6
FEV_1		0.03	0.28	0.3	0.1	0.3	0.15
FEV_1% predicted	-	-	0.34	9.1	3.6	10.1	7.6
SpO_2	-	-	0.52	1.3	0.9	2.4	1.5
Insp. CR	-	-	0.48	0.8	0.7	1.9	1.1
Exp CR	-	-	0.65	1.1	1.6	4.5	2.4
Insp. %Wh	-	-	0.58	7.1	9.3	25.8	14.1
Exp. %Wh	-	-	0.39	11.8	22.7	63.0	32.5

%Wh, wheeze occupation rate; CR, crackle; ES, effect size; FEV_1, forced expiratory volume in one second; MBS, modified Borg scale; MDC95, minimal detectable change at the 95% level of confidence; mMRC, Modified British Medical Research Council questionnaire; ROC, receiver operating characteristic; SD, standard deviation; SEM, standard error of measurement; SpO_2, peripheral oxygen saturation. Results are presented as absolute values.
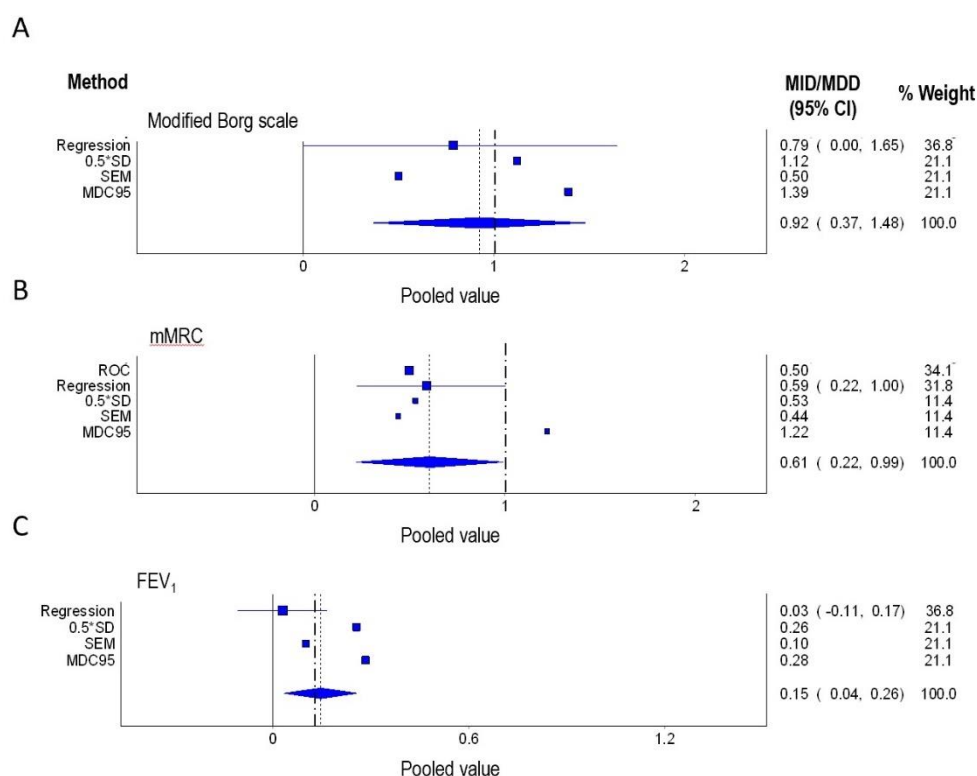
Figure 4. Summary plots of the pooled values of the MID and MDD for the (A) modified Borg scale; (B) modified British Medical Research Council (mMRC) questionnaire and (C) forced expiratory volume in one second (FEV_1). The horizontal plots represent the minimal clinically important difference estimates derived in this study, classified per method. Where appropriate the estimates include the 95% confidence interval. The bold dotted vertical line resembles the MID estimate as obtained from the literature for stable patients with COPD.

Discussion

This study showed a pooled MID and MDD of 0.9 for the MBS, 0.6 for the mMRC, 0.15L for the FEV_1, 7.6% for the FEV_1 percentage predicted, 1.5% for the SpO_2, 1.1 for inspiratory and 2.4 for the expiratory number of crackles, 14.1% for the inspiratory and 32.5% for the expiratory wheeze occupation rate.

The pooled MID and MDD for dyspnoea scales were similar to those reported in pharmacological trials (approximately 1 point in the MBS) (Jones et al., 2014; Ries, 2005) and slightly lower than those reported for pulmonary rehabilitation and surgical intervention (approximately two points in the MBS and

one point in the mMRC) (Crisafulli & Clini, 2010) in stable patients with COPD. Large benefits of these last two interventions are quickly perceived and reported by patients, since they either target specifically dyspnoea (i.e., pulmonary rehabilitation) or are invasive and affect directly the mechanics of breathing (i.e., surgery), contrary to the effects of pharmacological treatments, which mainly target inflammation and/or infection (Ries, 2005). Attention to patients' baseline dyspnoea and to the ability to change of the outcome measure is also needed when interpreting these data. MBS is not strictly linear, and having a sample with higher scores of dyspnoea (previous studies ranged from 1.8 to 8.5) than those reported in our study, will lead to larger changes, as at the higher end of the scale there are larger numerical intervals between word anchors for symptom severity (Ries, 2005). The mMRC presented large effect sizes following the recovery period of the AECOPD than in previous studies with stable patients, showing to be more sensitive to changes with interventions during AECOPD than in stable stages of the disease (Crisafulli & Clini, 2010; Jones et al., 2014).

Although the values of the MID and MDD are similar between disease stages, which facilitates their used interchangeably during stable and exacerbation periods, health professionals should be aware that the time needed to achieve these MID/MDD was shorter in patients with AECOPD (approximately 45 days), than the three months of treatments commonly used in stable patients (Crisafulli & Clini, 2010; Jones et al., 2009; Ries, 2005).

Therefore, the nature of the interventions, patients' baseline dyspnoea, the sensitivity to change of the measure used and the time until treatment effects are main aspects to consider when interpreting MID and MDD for dyspnoea scales. These novel results not only attribute meaning to patients' improvements during AECOPD but will also aid health professionals to establish specific timings to follow-up dyspnoea symptoms in these patients.

Similar to dyspnoea scales, the MID achieved for the FEV_1 matched those reported in the literature for stable patients (0.10–0.18 litres) (Donohue, 2005). Nevertheless, few studies have determined MID for the FEV_1, mainly due to the

lack of correlation between lung function and patient-reported outcomes (Donohue et al., 2018; Jones, Miravitlles, van der Molen, & Kulich, 2012) and because lung function is commonly not a goal in the management of COPD (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Conversely, lung function is still the primary endpoint most frequently used by regulatory authorities to interpret drug efficacy in COPD trials (Cazzola et al., 2008) and spirometry has been found to be reliable and valid during AECOPD (Fernandez-Villar et al., 2018). Thus, our findings may be used in future clinical trials to establish therapies effectiveness during AECOPD, further contributing to the current health and research priority of finding the most appropriate management for AECOPD (Wedzicha et al., 2017).

Due to the lack of correlation with the anchor chosen, only MDD could be established for the FEV_1 percentage predicted, SpO_2 and respiratory sounds. These outcome measures have been extensively used to assess the effects of interventions in patients with AECOPD, however little is known about their measurement properties and interpretability (Oliveira & Marques, 2018). There is only one recommendation from the European Respiratory Society to consider an increment of 9% in FEV_1 percentage predicted for bronchodilator responsiveness in stable patients, which is identical to our results (Quanjer et al., 1993).

A medium effect size was found for SpO_2, after the intervention, meaning that SpO_2 may be little sensitive to changes in outpatients with AECOPD. Although a MID could not be obtained, according to the oxyhaemoglobin dissociation curve, it would not be expected that a difference of 1.5% would be clinically significant for patients already presenting baseline SpO_2 higher than 92%. Nevertheless, such difference might be meaningful in more hypoxemic patients, as it will make a difference in their ability to perform activities of daily living (Saglam et al., 2015). Future studies including patients with different levels of baseline SpO_2 are needed to further explore this hypothesis and establish recommendations for clinical practice.

Minimal detectable differences found for computerised respiratory sounds were lower than those previously published in stable patients (i.e., MDD of 2.4 for inspiratory crackles) (Oliveira, Lage, et al., 2018), but significantly higher than the differences found before and after a pulmonary rehabilitation programme in stable patients (i.e., mean difference of 0.8 for expiratory crackles and median difference of less than 10% in inspiratory and expiratory %Wh) (Jácome & Marques, 2017) and during the course of an AECOPD (mean difference of less than 1 crackle and less than 10% in inspiratory and expiratory number of crackles and %Wh, respectively) (Oliveira, Rodrigues, et al., 2018). These results imply that although statistically significant, the changes being observed in the literature may be within the error of the measure. Nevertheless, these interpretations need caution, as it is known that respiratory sounds present high intersubject variability (Jácome & Marques, 2015), which have probably influenced the MDD obtained using distribution methods.

Limitations and future work

This study has some limitations that need to be acknowledged. Treatment of exacerbations was not standardised, but optimised according to the physician best judgement, using pharmacology as the standard treatment. Although the effects of therapies were not of interest in this study, it must be acknowledged that different combination of treatments might influence patient's recovery. Additionally, MID could not be established for FEV_1 percentage predicted, SpO_2 and computerised respiratory sounds, which may reduce their usefulness to interpret clinical changes. These outcome measures have great potential to be used at bedside of patients with AECOPD, as they are simple non-invasive and widely available. Thus, it is important that future studies build knowledge from our results and find relevant anchors to establish MID for FEV_1 percentage predicted, SpO_2 and computerised respiratory sounds. Also, patient's stable state prior to the exacerbation was not assessed, and thus it cannot be firmly stated that all patients have returned to their baseline symptoms as reported by themselves. However, as only outpatients, which present less severe exacerbations (The Global Initiative for Chronic Obstructive Lung Disease, 2018), were included, and

no reports of relapses and changes in treatment occurred, we strongly believe that patients were in a stable state of their disease during the last data collection moment and that the established MID/MDD can be used with confidence. Although the most recommended anchor and distribution methods have been used to establish the MID and MDD, other important anchor methods (Alma et al., 2016; Angst et al., 2017), such as patient and health professional referencing, using global rate of change scales and criterion-referencing, through correlation with key health-related events in COPD were not implemented. Thus, further examination of the interpretability of these respiratory measures is recommended, including using additional anchor methods but also establishing MID for different relevant interventions and patients with different levels of severity of their AECOPD. Finally, the sample included in this study is part of a primary research aiming at exploring the time course of AECOPD in outpatients (Oliveira, Afreixo, & Marques, 2018; Oliveira, Rodrigues, et al., 2018), thus a sample size calculation was not computed specifically to address the establishment of MID and MDD. This limitation may have caused our study to be underpowered for this aim. Nevertheless, according to the authors' best knowledge, this is the first study to contribute to establish MID and MDD of several respiratory outcome measures used in the monitoring of patients with AECOPD, and thus it has potential to be used, not only in clinical practice, to aid clinical interpretations of responses to interventions, but also as a booster for future research in the area, by providing data to compute appropriate sample sizes.

Conclusion

Pooled data of MID and MDD showed that improvements of 0.9 for the MBS, 0.6 for the mMRC, 0.15L for the FEV_1, 7.6% for the FEV_1 percentage predicted, 1.5% for the SpO_2, 1.1 for the inspiratory and 2.4 for the expiratory number of crackles, 14.1% for the inspiratory and 32.5% for the expiratory wheeze occupation rate are meaningful following an AECOPD managed with pharmacological treatment on an outpatient basis. These estimates might be

useful in clinical practice to aid clinical interpretations of responses to interventions and to monitor recovery of outpatients with AECOPD.

References

Aggarwal, R., & Ranganathan, P. (2016). Common pitfalls in statistical analysis: The use of correlation techniques. *Perspectives in Clinical Research, 7*(4), 187-190.

Alma, H., de Jong, C., Jelusic, D., Wittmann, M., Schuler, M., Flokstra-de Blok, B., . . . van der Molen, T. (2016). Health status instruments for patients with COPD in pulmonary rehabilitation: defining a minimal clinically important difference. *NPJ Primary Care Respiratory Medicine, 26*, 16041.

Alma, H., de Jong, C., Tsiligianni, I., Sanderman, R., Kocks, J., & van der Molen, T. (2018). Clinically relevant differences in COPD health status: systematic review and triangulation. *European Respiratory Journal, 52*(3), 1800412.

American Thoracic Society, & European Respiratory Society. (2002). ATS/ERS Statement on respiratory muscle testing. *American Journal of Respiratory and Critical Care Medicine, 166*(4), 518-624.

Angst, F., Aeschlimann, A., & Angst, J. (2017). The minimal clinically important difference raised the significance of outcome effects above the statistical level, with methodological implications for future studies. *Journal of Clinical Epidemiology, 82*, 128-136.

Anzueto, A. (2010). Impact of exacerbations on COPD. *European Respiratory Review, 19*(116), 113-118.

Boer, L., Bischoff, E., Borgijink, X., Vercoulen, J., Akkermans, R., Kerstjens, H., . . . Schermer, T. (2018). 'Exacerbation-free time'to assess the impact of exacerbations in patients with chronic obstructive pulmonary disease (COPD): a prospective observational study. *NPJ Primary Care Respiratory Medicine, 28*(1), 12.

Brożek, J., Guyatt, G., & Schünemann, H. (2006). How a well-grounded minimal important difference can enhance transparency of labelling claims and

improve interpretation of a patient reported outcome measure. *Health and Quality of Life Outcomes, 4*(69), 1-7.

Cazzola, M., MacNee, W., Martinez, F., Rabe, K., Franciosi, L., Barnes, P., . . . Wouters, E. (2008). Outcomes for COPD pharmacological trials: from lung function to biomarkers. *European Respiratory Journal, 31*(2), 416-469.

Crisafulli, E., & Clini, E. (2010). Measures of dyspnea in pulmonary rehabilitation. *Multidisciplinary Respiratory Medicine, 5*(3), 202-210.

de Vet, H., Terwee, C., Ostelo, R., Beckerman, H., Knol, D., & Bouter, L. (2006). Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. *Health and Quality of Life Outcomes, 4*(54), 1-5.

Doherty, D., Belfer, M., Brunton, S., Fromer, L., Morris, C., & Snader, T. (2006). Chronic obstructive pulmonary disease: consensus recommendations for early diagnosis and treatment. *Journal of Family Practice, 55*(11), S1-S1.

Doi, S., & Thalib, L. (2008). A quality-effects model for meta-analysis. *Epidemiology, 19*(1), 94-100.

Donohue, J. (2005). Minimal clinically important differences in COPD lung function. *COPD, 2*(1), 111-124.

Donohue, J., Jones, P., Bartels, C., Marvel, J., D'Andrea, P., Banerji, D., . . . Fogel, R. (2018). Correlations between FEV1 and patient-reported outcomes: A pooled analysis of 23 clinical trials in patients with chronic obstructive pulmonary disease. *Pulmonary Pharmacology & Therapeutics, 49*, 11-19.

Fernandez-Villar, A., Represas-Represas, C., Mouronte-Roibas, C., Ramos-Hernandez, C., Priegue-Carrera, A., Fernandez-Garcia, S., & Lopez-Campos, J. (2018). Reliability and usefulness of spirometry performed during admission for COPD exacerbation. *PLoS One, 13*(3), e0194983.

Guarascio, A., Ray, S., Finch, C., & Self, T. (2013). The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *ClinicoEconomics and Outcomes Research, 5*, 235-245.

Hosmer Jr, D., Lemeshow, S., & Sturdivant, R. (2013). *Applied logistic regression* (Vol. 398). Hoboken, NJ: John Wiley & Sons.

112

Huq, S., & Moussavi, Z. (2010, Aug 31 - Sep 4). *Automatic breath phase detection using only tracheal sounds.* Paper presented at the Annual International Conference of the IEEE, Buenos Aires, Argentina.

Jácome, C., & Marques, A. (2015). Computerized Respiratory Sounds Are a Reliable Marker in Subjects With COPD. *Respiratory Care, 60*(9), 1264-1275.

Jácome, C., & Marques, A. (2017). Computerized Respiratory Sounds: Novel Outcomes for Pulmonary Rehabilitation in COPD. *Respiratory Care, 62*(2), 199-208.

Jácome, C., Oliveira, A., & Marques, A. (2017). Computerized respiratory sounds: a comparison between patients with stable and exacerbated COPD. *The Clinical Respiratory Journal, 11*(5), 612-620.

Jones, P., Beeh, K., Chapman, K., Decramer, M., Mahler, D., & Wedzicha, J. (2014). Minimal clinically important differences in pharmacological trials. *American Journal of Respiratory and Critical Care Medicine, 189*(3), 250-255.

Jones, P., Harding, G., Berry, P., Wiklund, I., Chen, W-H., & Kline Leidy, N. (2009). Development and first validation of the COPD Assessment Test. *European Respiratory Journal, 34*(3), 648-654.

Jones, P., Harding, G., Wiklund, I., Berry, P., Tabberer, M., Yu, R., & Leidy, N. (2012). Tests of the responsiveness of the COPD assessment test following acute exacerbation and pulmonary rehabilitation. *Chest, 142*(1), 134-140.

Jones, P., Miravitlles, M., van der Molen, T., & Kulich, K. (2012). Beyond FEV(1) in COPD: a review of patient-reported outcomes and their measurement. *International Journal of Chronic Obstructive Pulmonary Disease, 7*, 697-709.

Kocks, J., Tuinenga, M., Uil, S., van den Berg, J. , Ståhl, E., & van der Molen, T. (2006). Health status measurement in COPD: The minimal clinically important difference of the clinical COPD questionnaire. *Respiratory Research, 7*(62), 1-8.

Kon, S., Canavan, J., Jones, S., Nolan, C., Clark, A., Dickson, M., . . . Man, W. (2014). Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. *Lancet Respiratory Medicine, 2*(3), 195-203.

Mahler, D., Ward, J., Waterman, L., McCusker, C., ZuWallack, R., & Baird, J. (2009). Patient-reported dyspnea in COPD reliability and association with stage of disease. *Chest, 136*(6), 1473-1479.

Meek, P., & Lareau, S. (2003). Critical outcomes in pulmonary rehabilitation: assessment and evaluation of dyspnea and fatigue. *Journal of Rehabilitation Research and Development, 40*(5 Suppl 2), 13-24.

Miller, M., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., . . . Gustafsson, P. (2005). Standardisation of spirometry. *European Respiratory Journal, 26*(2), 319-338.

Oliveira, A., Afreixo, V., & Marques, A. (2018). Enhancing our understanding of the time course of AECOPD managed on an outpatient basis. *International Journal of Chronic Obstructive Pulmonary Disease, 13*, 3759—3766.

Oliveira, A., Lage, S., Rodrigues, J., & Marques, A. (2018). Reliability, validity and minimal detectable change of computerized respiratory sounds in patients with chronic obstructive pulmonary disease. *The Clinical Respiratory Journal, 12*(5), 1838-1848.

Oliveira, A., & Marques, A. (2018). Outcome Measures Used in Pulmonary Rehabilitation in Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review. *Physical Therapy, 98*(3), 191-204.

Oliveira, A., Rodrigues, J., & Marques, A. (2018). Enhancing our understanding of computerised adventitious respiratory sounds in different COPD phases and healthy people. *Respiratory Medicine, 138*, 57-63.

Oliveira, A., Sen, I., Kahya, Y., Afreixo, V., & Marques, A. (2017). Computerised respiratory sounds can differentiate smokers and non-smokers. *Journal of Clinical Monitoring and Computing, 31*(3), 571-580.

Parker, C., Voduc, N., Aaron, S., Webb, K., & O'Donnell, D. (2005). Physiological changes during symptom recovery from moderate exacerbations of COPD. *European Respiratory Journal, 26*(3), 420-428.

Pinho, C., Oliveira, A., Jácome, C., Rodrigues, J., & Marques, A. (2016). Integrated approach for automatic crackle detection based on fractal dimension and box filtering. *International Journal of Reliable and Quality E-Healthcare, 5*(4), 34-50.

Portney, L., & Watkins, M. (2000). *Foundations of clinical research: applications to practice* (2 ed.). Upper Saddle River, NJ: Prentice Hall

Quanjer, P. H., Tammeling, G. J., Cotes, J. E., Pedersen, O. F., Peslin, R., & Yernault, J. C. (1993). Lung volumes and forced ventilatory flows. *European Respiratory Journal, 6*(Suppl 16), 5-40.

Revicki, D., Hays, R., Cella, D., & Sloan, J. (2008). Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *Journal of Clinical Epidemiology, 61*(2), 102-109.

Ries, A. (2005). Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. *COPD, 2*(1), 105-110.

Saglam, M., Vardar-Yagli, N., Savci, S., Inal-Ince, D., Calik-Kutukcu, E., Arikan, H., & Coplu, L. (2015). Functional capacity, physical activity, and quality of life in hypoxemic patients with chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease, 10*, 423-428.

Sant'Anna, T., Donaria, L., Furlanetto, K., Morakami, F., Rodrigues, A., Grosskreutz, T., . . . Pitta, F. (2017). Development, Validity and Reliability of the Londrina Activities of Daily Living Protocol for Subjects With COPD. *Respiratory Care, 62*(3), 288-297.

Seemungal, T., Donaldson, G., Bhowmik, A., Jeffries, D., & Wedzicha, J. (2000). Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 161*(5), 1608-1613.

Seemungal, T., Donaldson, G., Paul, E., Bestall, J., Jeffries, D., & Wedzicha, J. (1998). Effect of exacerbation on quality of life in patients with chronic

obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 157*(5 Pt 1), 1418-1422.

Shin, S., Ro du, H., Lee, O., Oh, J., & Kim, S. (2012). Within-day reliability of shoulder range of motion measurement with a smartphone. *Manual Therapy, 17*(4), 298-304.

Soler-Cataluna, J., Alcazar-Navarrete, B., & Miravitlles, M. (2014). The concept of control of COPD in clinical practice. *International Journal of Chronic Obstructive Pulmonary Disease, 9*, 1397-1405.

Sulzer, J., Schüttler, F., Penzel, T., & Wichert, P. (1997, October 15–17). *A simple method for detecting bronchial breathing sound.* Paper presented at the 22nd International Conference on Lung Sounds, Tokyo, Japan.

Taplidou, S., & Hadjileontiadis, L. (2007). Wheeze detection based on time-frequency analysis of breath sounds. *Computers in Biology and Medicine, 37*(8), 1073-1083.

The Global Initiative for Chronic Obstructive Lung Disease. (2018). Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease - 2018 Report: The Global Initiative for Chronic Obstructive Lung Disease, Inc.

Tsai, C., Hodder, R., Page, J., Cydulka, R., Rowe, B., & Camargo, C. A. (2008). The short-form chronic respiratory disease questionnaire was a valid, reliable, and responsive quality-of-life instrument in acute exacerbations of chronic obstructive pulmonary disease. *Journal of Clinical Epidemiology, 61*(5), 489-497.

Viniol, C., & Vogelmeier, C. (2018). Exacerbations of COPD. *European Respiratory Review, 27*(147), 170103.

Wedzicha, J., Miravitlles, M., Hurst, J., Calverley, P., Albert, R., Anzueto, A., . . . Krishnan, J. (2017). Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *European Respiratory Journal, 49*(3), 1600791.

Study III

_____

Enhancing our understanding of computerised adventitious respiratory sounds in different COPD phases and healthy people.

Oliveira A, Rodrigues J, Marques A

Respir Med 2018; 138:57-63

Abstract

Background: Timely diagnosis of acute exacerbations of COPD (AECOPD) is challenging as it depends on patients' reports. AECOPD are characterised by increased airway obstruction, mucus and air trapping, which results in changes in lung acoustics. Thus, adventitious respiratory sounds (ARS) may be useful to detect/monitor AECOPD.

Objective: To evaluate computerised ARS changes during AECOPD.

Methods: 25 non-hospitalised patients with AECOPD (16♂, 70 [62.5–77.0] yrs, FEV_1 59 [31.5–73.0] %predicted) and 34 healthy volunteers (17♂, 63.5 [57.7–72.3] yrs, FEV_1 103.0 [88.8–125.3] %predicted) were enrolled. ARS at anterior and posterior right and left chest were recorded at hospital presentation (T1), 15 days (T2) and 45 days (T3) after hospital presentation from patients with AECOPD and only once from healthy participants. A subsample of 9 patients (7♂; 66 [60.0–76.0] yrs; FEV_1 62 [26.5–74.0] %predicted) was also included to study ARS pre-AECOPD (T0). Number of crackles and wheeze occupation rate (%Wh) were processed using validated algorithms.

Results: During AECOPD, patients presented more inspiratory crackles at T1 than T3 (p=0.013) and more inspiratory %Wh at T1 than T2 (p=0.006), at posterior chest. Patients with stable COPD presented more inspiratory crackles (p=0.012), at posterior chest, and more expiratory %Wh, both at anterior (p<0.001) and posterior (p=0.001) chest, than healthy participants. No differences were observed for the remaining ARS parameters or subsamples (p>0.05).

Conclusions: Inspiratory crackles seem to persist until 15 days post exacerbation whilst inspiratory %Wh decreased after this period. ARS seem to be sensitive to monitor AECOPD. This information may allow advances in monitoring the recovery time of patients with AECOPD across all clinical and non-clinical settings.

119

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disease frequently punctuated by acute exacerbations (AECOPD) (Wedzicha & Wilkinson, 2006), i.e., "acute worsening of respiratory symptoms that result in additional therapy" (The Global Initiative for Chronic Obstructive Lung Disease, 2018). These events account for half of the total respiratory admissions for COPD (Gibson, Loddenkemper, Lundback, & Sibille, 2013) and are closely related with increases in healthcare costs (AECOPD related costs vary approximately from $88 to $7.757 per exacerbation worldwide) (Toy, Gallagher, Stanley, Swensen, & Duh, 2010). Furthermore, AECOPD are responsible for accelerating lung function decline, decrease quality of life and increase mortality (Anzueto, 2010).

The early identification and timely management of AECOPD has been shown to reduce hospital admissions and recovery time, while improving quality of life (Wilkinson, Donaldson, Hurst, Seemungal, & Wedzicha, 2004). Nevertheless, most exacerbations are still not timely treated as the diagnosis/monitoring relies exclusively on patients' reports of symptoms worsening (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Such reports require patients' collaboration and judgment, which are frequently affected by their pronounced dyspnoea and anxiety associated with these events (Bailey, 2004; Parker, Voduc, Aaron, Webb, & O'Donnell, 2005).

Physiologically, AECOPD are characterised by an increase in airway inflammation and obstruction, abnormal bronchial mucus production and marked air trapping (The Global Initiative for Chronic Obstructive Lung Disease, 2018), which results in changes in lung acoustics. As respiratory sounds are directly related to the movement of air within the tracheobronchial tree (Gavriely, Nissan, Cugell, & Rubin, 1994), the changes in respiratory mechanics related with AECOPD may be primarily detected by changes in respiratory sounds, namely adventitious respiratory sounds (ARS, crackles and wheezes). Recent studies have shown respiratory sounds ability to differentiate between groups of patients

with stable and exacerbated COPD (Jácome, Oliveira, & Marques, 2017) and to characterise AECOPD into two phenotypes, based on computerised analysis (Sanchez Morillo, Astorga Moreno, Fernandez Granero, & Leon Jimenez, 2013).

Nevertheless, there is little information available on the time course of respiratory sounds changes during recovery from AECOPD, within the same group of patients. This information may advance the monitoring of patients with COPD across all clinical and non-clinical settings, as respiratory sounds are non-invasive, population-specific and nearly universally available by simple means (Bohadana, Izbicki, & Kraman, 2014). Additionally, improved knowledge on ARS behaviour preceding, during and after an exacerbation may aid to standardise and optimise the length of treatment, and to plan appropriate follow-up and clinical studies involving AECOPD.

This study aimed to evaluate ARS changes during the course of AECOPD. A secondary aim was to explore prospectively the influence of exacerbations in ARS in a subsample of patients with stable COPD followed by an AECOPD.

Materials and methods

Study design and participants

A longitudinal observational study was conducted in non-hospitalised patients with AECOPD recruited from the urgent care of a Central hospital between January 2016 and February 2017. Inclusion criteria were diagnosis of AECOPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (The Global Initiative for Chronic Obstructive Lung Disease, 2018). A subsample of stable patients with COPD was recruited from routine pulmonology appointments of a Central hospital and asked to contact the researchers if an episode of exacerbation requiring hospital visit occurred. Patients were included if they were diagnosed with COPD according to the GOLD criteria and were clinically stable for 1 month prior to the study (no hospital admissions, exacerbations or changes in medication for the respiratory system) (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Exclusion

criteria for both samples were hospitalisation or presence of severe co-existing respiratory, neurological, cardiac, musculoskeletal (e.g., kyphoscoliosis), or signs of psychiatric impairments. Eligible patients were identified by clinicians and contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. When subjects agreed to participate, an appointment with the researchers was scheduled.

A group of healthy non-smokers, matched for gender, age and body mass index (BMI), were also recruited to serve as control, as currently there are no established reference values for ARS (Oliveira & Marques, 2014). Healthy nonsmokers were recruited from the university campus and surrounding community and excluded if they presented one or more of the following conditions: acute (within the past month) or chronic respiratory disease, cardiac disease, musculoskeletal or signs of psychiatric impairments.

Approval for this study was obtained from the ethics committee of the Central Hospital (13NOV'1514:40065682) and of the University of Aveiro (8/2015) and from the National Data Protection Committee (8828/2016). Written informed consent was obtained before data collection.

Sample size

A sample size estimation with 95% power at 5% significance determined that a significant difference in the inspiratory mean number of crackles obtained through repeated measures from patients with COPD at exacerbated (2.97±1.98) and stable (1.20±0.80) phases of their disease would be detected with a minimum of 23 participants (Jácome et al., 2017). A high statistical power was chosen due to the great amount of inter and intra subject variability presented by ARS (Jácome & Marques, 2015a; Oliveira, Lage, Rodrigues, & Marques, 2018), which could potentially cause type II errors if the study was underpowered (Biau, Kernéis, & Porcher, 2008). In health-related longitudinal studies, dropout rates are of approximately 20–45% (Bildt et al., 2001; Soyseth, Johnsen, & Kongerud, 2008) thus, 36 participants with AECOPD were aimed to be recruited. Sample

size estimation was performed using the G*Power 3.1 software (University Düsseldorf, Germany).

Data collection

Participants with AECOPD recruited from the urgent care were asked to attend to 3 assessment sessions: at the exacerbation onset (T1 – 24–48 h of the hospital visit), 15 days (T2 – following exacerbation) (Aaron et al., 2012; Seemungal, Donaldson, Bhowmik, Jeffries, & Wedzicha, 2000) and 45 days after the hospital visit (T3 – at stability post exacerbation). The subsample of patients recruited from routine pulmonology appointments were asked to attend to 4 assessment sessions: 24–48 h after the pulmonology routine appointment (T0 – at stability pre exacerbation), at the exacerbation onset (T1 – 24–48 h of the hospital visit), 15 days (T2 – following exacerbation) (Aaron et al., 2012; Seemungal et al., 2000) and 45 days after the hospital visit (T3 – at stability post exacerbation). Data from healthy non-smokers was only collected once (T0) (Fig. 1). Data collection occurred at the urgent care, in the facilities of the University of Aveiro or at patients' home.
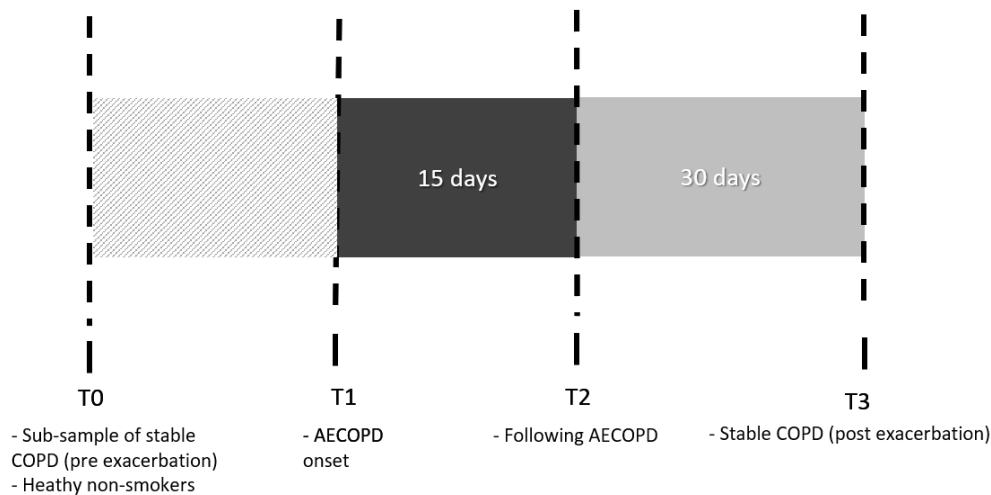

Figure 1. Time points of data collection.

Sociodemographic (age, gender), anthropometric (height, weight and BMI) and general clinical data (smoking habits, number of exacerbations in the past year, medication and dyspnoea) were first collected. Dyspnoea was assessed

with the modified British Medical Research Council questionnaire (Doherty et al., 2006). The questionnaire comprises five grades in a scale from 0 to 4, with higher grades indicating greater perceived dyspnoea. Then, computerised respiratory sounds (recorded as described below) and lung function, assessed with a portable spirometer (MicroLab 3535, CareFusion, Kent, UK) according to standardised guidelines were collected (Miller et al., 2005). Respiratory sounds were collected in all data collection moments and spirometry was also performed at T3, during the stable phase, post exacerbation.

All assessments were performed by a physiotherapist following the described standardised order.

Respiratory sound recordings

Respiratory sound recordings followed computerised respiratory sound analysis guidelines for short-term acquisitions (Rossi et al., 2000) (i.e., participants were in a seated-upright position, wearing a nose clip and were asked to breathe deeper than normal through the mouth). Recordings were performed simultaneously at 7 anatomic locations (trachea and right and left anterior, lateral, and posterior chest). The system for respiratory sound recordings included eight air-coupled electret microphones with 20–20000Hz frequency bandwidth (C 417 PP, AKG Acoustics GmbH, Vienna, Austria) (Vannuccini et al., 2000), a multi-channel audio interface (AudioBox 1818 VSL, PreSonus, Florida, USA), and a laptop computer running LungSounds@UA software (Pinho, Oliveira, Oliveira, Dinis, & Marques, 2014). Seven microphones, mounted in capsules made of Teflon (Kraman, Wodicka, Oh, & Pasterkamp, 1995; Wodicka, Kraman, Zenk, & Pasterkamp, 1994), were attached on the participant's skin with double-faced adhesive tapes (Double Stick Discs, 3M Littmann, Cheshire, UK). The eighth microphone was placed close to the patient to record background noise. The analog sound signals acquired were amplified and converted to digital by the audio interface with a 24-bit resolution and a sampling rate of 44.1 kHz. Each data acquisition session lasted for 20-s

(Vyshedskiy & Murphy, 2012) and the recorded data were later converted to WAV format.

Signal processing

All sound files were analysed using automatic algorithms implemented in Matlab R2009a (MathWorks, Natick, Massachusetts).

Breathing cycles were semi-automatically detected using the algorithm developed by Huq and Moussavi (95.5% sensitivity and 95.6% specificity) (Huq & Moussavi, 2010). Crackles were detected using a validated algorithm based on the combination of fractal dimension and box filtering techniques (Pinho, Oliveira, Jácome, Rodrigues, & Marques, 2016). Wheezes were detected using an algorithm based on timefrequency analysis (Taplidou & Hadjileontiadis, 2007). The mean number of crackles (total, fine and coarse) and wheeze occupation rate (%Wh – total, monophonic and polyphonic), per breathing phase (inspiration and expiration) and per chest location was extracted. Normal respiratory sounds were also analysed but were only slightly louder than the superimposed background sound so these data were excluded from further analyses (please see supplementary material 1). The average spectra of normal respiratory sounds at trachea, anterior and posterior chest can be found in the supplementary material 1 and a detailed description of the signal processing is provided elsewhere (Oliveira, Sen, Kahya, Afreixo, & Marques, 2017). Lateral locations were also excluded from the analysis, as previous literature has shown that this anatomical location presents a great number of artefacts and is poorly reliable (Oliveira et al., 2018). All analyses were checked by two respiratory experts to ensure the quality of the sound recordings.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corporation, Armonk, NY, USA) and plots created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at 0.05.

Descriptive statistics were used to describe the sample. Characteristics were compared between healthy non-smokers and patients with COPD at stable phases (T3) using independent t-tests for normally distributed data (i.e., BMI), Mann-Whitney U-tests for nonnormally distributed data (i.e., age, lung function, packs-year) and ordinal data (i.e., mMRC), and Chi-square tests for categorical data (i.e., gender, smoking status and exacerbations/year).

Computerised ARS data were explored for each of the five analysed locations; however, no significant differences were found between right and left chest of the same region (i.e., anterior, lateral or posterior), thus, to simplify the interpretability of the findings, data from right and left were pooled for each chest region (Oliveira, Sen, et al., 2017). Then, the number of participants with crackles and wheezes in each chest region was calculated and the Cochran test with Bonferroni corrections was used to compare number of participants presenting crackles and wheezes among T1, T2 and T3. Fisher's exact test was used to investigate differences between healthy non-smokers and patients with COPD at stable phases (T3) on the number of participants presenting crackles and wheezes. Comparisons of number of crackles and %Wh among T1, T2 and T3 in patients with COPD were performed with the Friedman test, and multiple comparisons with the Wilcoxon sign-rank test. Multiple comparisons were corrected for number of comparisons using Bonferroni corrections. Comparisons between healthy non-smokers and patients with COPD at stable phases regarding mean number of crackles and %Wh was performed with Mann–Whitney U test. When statistically significant differences were found for the number of crackles or %Wh, a comparison of the type of crackles or wheezes was also performed.

An additional analysis, similar to the described previously for patients recruited at the onset of the AECOPD, was conducted with the subsample of patients presenting data collected prior to the exacerbation.

Results

Participants

Seventy-four non-hospitalised patients with AECOPD were referred for possible inclusion in the study. Of these, 34 patients refereed with AECOPD were excluded because at T1 they had pulmonary function test not compatible with a diagnosis of COPD (n=22), did not meet the definition for AECOPD (n=1), presented lung neoplasia (n=2), severe heart failure (n=1), were unable to comply with data collection (n=3), or declined to participate in the study (n=5). Fifteen patients were further excluded from the analysis because failed to complete all time points of data collection (i.e., T1, T2 and T3) (n=6) and their respiratory sounds (collected at the urgent care) had a significant amount of background noise hindering the use of the algorithms described in the Signal processing section (n=9). Thirty-four healthy nonsmokers were also contacted and invited to participate. Thus, twenty-five participants with AECOPD (16 males; 70 [62.5–77.0] years old; FEV_1 59 [31.5–73.0] % predicted) and thirty-four healthy non-smokers (17 male; 63.5 [57.7–72.3] years old; FEV_1 103.0 [88.8–125.3] % predicted) were enrolled in the study. Participants' characteristics are summarised in Table 1.

Table 1. Sample characterisation.

Characteristics		Patients with AECOPD (n=25)	Healthy non-smokers (n=34)	p-value
Age, years		70 [62.5-77.0]	63.5 [57.7-72.3]	0.061
Gender (male), n(%)		16 (47.1)	17 (68.0)	0.090
BMI, kg/m^2, mean±SD		26.7±4.9	27.4±4.7	0.568
Smoking status, n(%)				0.002*
	Current	4 (16.0)	-	
	Former	11 (44.0)	6 (17.6)	
	Never	10 (40.0)	28 (82.4)	
Packs/year		30.0 [15.0-70.0]	6.5 [1.8-18.8]	0.010*
Exacerbations/year, n(%)				<0.001*
	0	5 (20)	34 (100)	
	1	5 (20)	-	
	≥2	15 (60)	-	
FEV_1, L		1.2 [0.8-1.7]	2.6 [2.1-3.0]	<0.001*

FEV$_1$, %predicted		59 [31.5-73.0]	103.0 [88.8-125.3]	<0.001*
FEV$_1$/FVC, %		52 [40.0-62.0]	83 [79.5-88.3]	<0.001*
GOLD stages, n(%)				
	A	4 (6.8)	-	
	B	3 (5.1)	-	
	C	5 (8.5)	-	
	D	13 (22.0)	-	
Medication use, n(%)		Stability	AECOPD (extra)	
Antibiotics		1 (4)	15 (60)	-
Bronchodilators				-
Beta-adrenergic agonists		7 (28)	0 (0)	0
Cholinergic antagonists		15 (60)	3 (12)	0
Anti-inflammatory		4 (16)	1 (4)	0
Xanthines		8 (32)	0	0
Associations of bronchodilators with cholinergic antagonists		17 (68)	5 (20)	0
Expectorants		4 (16)	6 (24)	0
mMRC		1 [0.5-2.0]	0.0 [0.0-1.0]	<0.001*

*p<0.05. Values are presented as median [interquartile range], unless otherwise stated. Legend: BMI, body mass index; FEV$_1$, forced expiratory volume in one second (at stability); FVC, forced vital capacity (at stability); GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified British Medical Research Council questionnaire; SD, standard deviation.

A subsample of 9 participants with stable COPD a priori was also included and followed up until an AECOPD occurred and during its recovery. This sub-group of participants (7 males; 66 [60.0–76.0] years old; FEV$_1$ 62 [26.5–74.0] % predicted) was slightly overweight (27.9±4.46 kg/m^2), presented a median number of packs/year of 21.2 [10.0–30.0] and were mainly former smokers (n=5; 55.6%; current smokers: n=2; 22.2%; never smokers: n=2; 22.2%). Most participants were classified as being in a stage D of the GOLD classification (n=5; 55.6%; GOLD B: n=2; 22.2%; GOLD C: n=2; 22.2%), presented more than 2 AECOPD in the past year (n=6; 66.7%; 1 AECOPD: n=2; 22.2%; 0 AECOPD: n=1; 11.1%) and were treated for their AECOPD with antibiotics (n=5; 56%), cholinergic antagonist bronchodilators (n=2; 22%), anti-inflammatory bronchodilators (n=1; 11%) and expectorants (n=3; 33%). Patients presented a median mMRC of 2 [1–3]. Median time to exacerbation was 23 [18–146] days.

Computerised respiratory sounds

Crackles

Significant differences were found in the total number of inspiratory (p=0.008) and coarse (p=0.003) crackles within patients with AECOPD at T1, T2

and T3 at the posterior chest. Patients presented significantly more inspiratory (p=0.013) and coarse (p=0.013) crackles at T1 than at T3. Fig. 2 presents the number of crackles at each chest region in healthy participants and patients with AECOPD. A detailed characterisation of crackles can be found in the supplementary material 2.
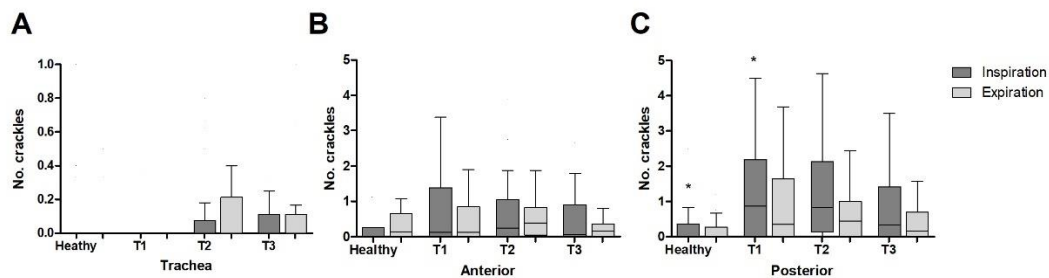

Figure 2. Number of inspiratory and expiratory crackles in healthy participants and participants with COPD (T1, T2, T3) at A) trachea, B) anterior and C) posterior chest regions. * significantly different from T3.

Patients with stable COPD presented significantly more inspiratory crackles (p=0.012), both fine (p=0.003) and coarse (p=0.013) crackles, at the posterior chest than healthy participants. No significant differences were found regarding the remaining variables, locations or respiratory phases (p>0.05).

Wheezes

Significant differences were found in the inspiratory %Wh (p=0.019) and inspiratory monophonic %Wh (p=0.012), within patients with AECOPD at T1, T2 and T3 at posterior chest. Namely, patients presented significantly more inspiratory %Wh (p=0.006) and monophonic %Wh (p=0.045) at T1 than at T2. A higher number of patients presenting inspiratory wheezes and monophonic wheezes were found at T1 than at T2 at trachea (p=0.037) and anterior chest region (p=0.014). The number of patients with expiratory monophonic wheezes was also higher at T1 than at T3 at the anterior chest (p=0.029). No significant differences were found regarding the remaining variables, locations and respiratory phases (p>0.05). Fig. 3 presents the %Wh at each chest region in

healthy participants and patients with AECOPD. A detailed characterisation of wheezes can be found in the supplementary material 3.
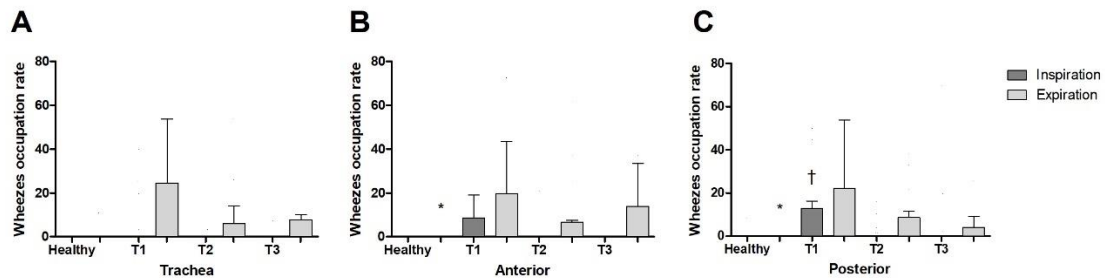

Figure 3. Inspiratory and expiratory wheeze occupation rate in healthy participants and participants with COPD (T1, T2, T3) at A) trachea, B) anterior and C) posterior chest regions. * significantly different from T3. † significantly different from T2.

Patients with stable COPD presented significantly more expiratory and monophonic %Wh, both at anterior (total %Wh: $p<0.001$; monophonic %Wh: $p=0.007$) and posterior (total %Wh: $p=0.001$; monophonic %Wh: $p<0.001$) chest regions than healthy participants. No differences were found regarding the number of healthy participants and stable patients with wheezes ($p>0.05$).

Sub-analysis

No differences were found among the four-time points of data collection for inspiratory and expiratory crackles and wheezes at all anatomical locations ($p>0.05$), in the subsample of patients with stable COPD a priori. A detailed characterisation of the respiratory sounds of this subsample can be found in the supporting information 4 and 5.

Discussion

The main findings of this study were that inspiratory crackles and wheezes change significantly during the course of AECOPD and patients with stable COPD presented significantly more inspiratory crackles and expiratory wheezes than healthy peers.

130

Differences in ARS found during the course of AECOPD and between stable patients with COPD and healthy peers were mainly observed at posterior and more peripheral chest locations, both for crackles and wheezes. In previous studies, the posterior region has been indicated as the most reliable and valid chest location for auscultation in patients with COPD (Jácome & Marques, 2015a; Oliveira et al., 2018). These findings, added to physiological and epidemiological data showing that COPD is primarily targeted by smaller airway and/or alveolar abnormalities (The Global Initiative for Chronic Obstructive Lung Disease, 2018) and that approximately 70–80% of AECOPD are due to infections, especially of the small airways (Sethi & Murphy, 2008), might lead us to confidently identify the posterior chest region as the preferred location of auscultation to monitor patients with COPD.

Coarse crackles and monophonic wheezes during inspiration were the respiratory sounds parameters presenting significant degrees of change. Previous research, conducted in independent samples of stable and exacerbated patients with COPD, has shown equivalent results for the number of coarse crackles (Jácome et al., 2017), despite acknowledging that respiratory tract infections, the main cause of AECOPD, are mainly characterised by fine crackles. Such results have been attributed to the frequency response of stethoscopes used which might be cutting high frequencies of interest, and consequently affecting fine crackles detection (Murphy et al., 2004). Thus, a deeper understanding of this matter is yet needed. Respiratory tract infections define a wide range of infectious diseases, including pneumonia, acute bronchitis, AECOPD and acute infective exacerbations of asthma (Greene et al., 2011). Pneumonia is the respiratory infection most studied for ARS (Alcon, Fabregas, & Torres, 2005). It should be emphasised that AECOPD and pneumonia differ greatly in their pathophysiology (Alcon et al., 2005; The Global Initiative for Chronic Obstructive Lung Disease, 2018). AECOPD are characterised by an increase in airway inflammation and obstruction, abnormal bronchial mucus and marked air trapping (The Global Initiative for Chronic Obstructive Lung Disease, 2018), whilst pneumonia usually presents lung consolidation and a filling of the

alveolar air spaces with exudate, inflammatory cells, and fibrin (Alcon et al., 2005). Accordingly, AECOPD are more prompt to develop hypersecretions than pneumonia and thus, generate more coarse crackles, which "indicates intermittent airway opening related to secretions", than fine crackles that are "unrelated to secretions" (Bohadana et al., 2014).

Contrary to what has been reported in previous literature (Jácome et al., 2017), only inspiratory wheezes presented significant changes during the course of AECOPD. Compared to crackles, wheezes usually present higher inter subject variability (Jácome & Marques, 2015a) and, in patients with more severe airway obstruction, expiratory wheezes have been indicated as a poorly reliable parameter, as they are strongly influenced by air-flow and respiratory manoeuvres (Oliveira et al., 2018). Because previous research has been conducted using independent samples of patients with stable and AECOPD, variability might be increased, explaining the differences found. Also, previous studies have included mainly mild to moderate patients with COPD (Jácome et al., 2017; Oliveira, Pinho, & Marques, 2017), whilst our sample included mostly severe patients, where inspiratory wheezes might be more representative. Considering the changes in ARS during the course of AECOPD, %Wh, specifically monophonic, significantly decreased after 15 days of treatment (i.e., approximate time needed to resolve an AECOPD (Seemungal et al., 2000)), whilst crackles, specifically coarse crackles, only decreased significantly after 45 days post-exacerbation. Previous studies conducted during an AECOPD have shown an improvement in air-flow limitation (assessed by FEV_1 and peak expiratory flow - PEF) approximately 15-days post exacerbation (Parker et al., 2005; Seemungal et al., 2000). Knowing that %Wh is highly associated with the degree of bronchial obstruction (Bentur et al., 2004; Fiz et al., 2002), this was an expected result and enhances the role of wheezes auscultation to monitor AECOPD. Crackles are more related to changes (i.e., inflammation and/or infection) in more peripheral airways which usually take longer to resolve (Piirila & Sovijarvi, 1995; Woodhead et al., 2011).

No differences were observed in the subsample of patients with stable COPD studied a priori and during AECOPD across any time points. Thus, it was not possible to demonstrate if ARS recovered to baseline characteristics after an exacerbation, or if AECOPD have a cumulative effect in ARS similar to other outcomes, such as muscle strength and lung function (Anzueto, 2010). It is known that ARS present high inter and intra subject variability (Jácome & Marques, 2015a) and thus, the sample size included in this sub-analysis might have been insufficient to detect significant changes. Nevertheless, if ARS are to be used clinically, knowing their evolution before and after exacerbations is essential to better interpret and manage treatment. This sub-analysis was therefore a needed first step towards ARS use in the monitoring of AECOPD and can be used as a pilot study to compute sample sizes in future studies (data are in supporting information 4 and 5).

Patients with COPD presented significantly more inspiratory crackles and expiratory wheezes than healthy peers. It is known that COPD is mainly characterised by inspiratory and coarse crackles and expiratory wheezes (Jácome & Marques, 2015b), when compared with other chronic diseases, such as fibrosis, asthma, pneumonia, bronchiectasis and heart failure. Thus, this was an expected result. However, few studies have compared ARS in healthy people and patients with COPD, even though the presence of ARS has been recognised in healthy people (Oliveira & Marques, 2014). Although differences in ARS were found between patients with COPD and healthy people, the number of people with ARS in both groups was not significantly different. Therefore, our results further enhance the recommendation of not using the presence of ARS as an indicator of pathology (Oliveira et al., 2018), but instead investigate ARS characteristics (i.e., number, type, position in the respiratory cycle) and place it together with other clinical findings.

Comparing to previous studies, a small number of crackles and low %Wh were found in patients with COPD (median no. of crackles per respiratory phase between 0.3 in stable patients to 0.6 in AECOPD; median %Wh of approximately

0) and healthy people (median no. of crackles and %Wh of approximately 0). Studies have been indicating a mean number of crackles between 0.8 and 5 per respiratory phase and a mean %Wh of 0.79% to approximately 10% in patients with COPD (Jácome & Marques, 2015b, 2017; Jácome et al., 2017) and approximately 1.5 crackles and 35% %Wh in healthy people (Oliveira, Sen, et al., 2017). Reasons for these differences might be explained by the different protocols used to collect and analyse ARS. In this study, ARS were collected using AKG air-coupled electret microphones (response rate 20–20000Hz) mounted in capsules made of Teflon to minimise noise and increase sound transmission (Kraman et al., 1995; Wodicka et al., 1994). Additionally, all participants, independently of having ARS or not, were included in the analysis to potentiate the comprehensiveness and generalisation of our findings. Previous studies have used sensors with different frequency responses (e.g., 40–15000Hz (Oliveira, Sen, et al., 2017); 50–1800Hz; 4–20000Hz; 65–20000Hz (Jácome & Marques, 2015b)), diverse set ups of data collection (e.g., electret microphones imbedded in a soft foam mat and electret condenser microphones connected to the diaphragm or main tube of conventional stethoscopes (Jácome & Marques, 2015b, 2017; Jácome et al., 2017)) and analysis (have only included in their analysis people presenting ARS (Oliveira, Sen, et al., 2017)). Such variety of procedures may produce recordings of different quality and range of sound spectrum, influencing the results achieved and thus impairing comparisons among studies.

Limitations

This study has some limitations that need to be acknowledged. Firstly, treatment of exacerbations during this study was not standardised, but rather prescribed according to the physician best judgment and clinical indication. Although for the purpose of this study the effects of therapies used were not of interest, it has to be acknowledged that different combination of drugs might have influenced the recovery times and outcomes of individual patients. Secondly, flows and/or volumes were not controlled during ARS recordings, which might have affected the results, since ARS characteristics depend on the rate and

volume of the respiratory manoeuvres (Pasterkamp, Kraman, & Wodicka, 1997). However, patients with AECOPD often present severe dyspnoea and anxiety (Bailey, 2004; Parker et al., 2005) which causes the use of a mouthpiece or facemask (necessary to assess flows and/or volumes) to be highly uncomfortable or even not tolerated. Furthermore, the primary purpose of this study was to assess computerised ARS utility in a community-based clinical setting, where control of airflow is often not practical. Thirdly, the complex set up used to record ARS may be perceived as a limitation to the use of computerised respiratory sounds in the clinical practice. Future research should focus in developing technologies for acquiring high quality data at bedside with minimal setup. Finally, although statistically significant differences were found for inspiratory number of crackles and %Wh at posterior regions, the absolute differences among data collection times were small and possibly not detected by health professionals with standard auscultation. Thus, it is imperative that future studies explore the minimal clinical important difference of ARS to enhance the clinical meaning of this measure and potentiate the development and implementation of friendly used computerised auscultation systems that can be translated into clinical practice.

Conclusion

Inspiratory crackles and wheezes changed significantly during the course of AECOPD, and patients with stable COPD presented significantly more inspiratory crackles and expiratory wheezes than healthy peers. Inspiratory crackles seem to persist until 15 days after the exacerbations (i.e., approximate time needed to resolve AECOPD) whilst inspiratory %Wh significantly decreased after this period. Crackles and wheezes seem to be sensitive to monitor the course of AECOPD. This information may allow further advances in the monitoring of patients with COPD across all clinical and non-clinical settings, as respiratory sounds are non-invasive, population-specific and nearly universally available by simple means. Further studies with larger samples and including data collected before the AECOPD are needed to confirm these findings.

References

Aaron, S., Donaldson, G., Whitmore, G., Hurst, J., Ramsay, T., & Wedzicha, J. (2012). Time course and pattern of COPD exacerbation onset. *Thorax, 67*(3), 238-243.

Alcon, A., Fabregas, N., & Torres, A. (2005). Pathophysiology of pneumonia. *Clinics in Chest Medicine, 26*(1), 39-46.

Anzueto, A. (2010). Impact of exacerbations on COPD. *European Respiratory Review, 19*(116), 113-118.

Bailey, P. (2004). The dyspnea-anxiety-dyspnea cycle--COPD patients' stories of breathlessness: "It's scary /when you can't breathe". *Qualitative Health Research, 14*(6), 760-778.

Bentur, L., Beck, R., Berkowitz, D., Hasanin, J., Berger, I., Elias, N., & Gavriely, N. (2004). Adenosine bronchial provocation with computerized wheeze detection in young infants with prolonged cough: correlation with long-term follow-up. *Chest, 126*(4), 1060-1065.

Biau, D., Kernéis, S., & Porcher, R. (2008). Statistics in Brief: The Importance of Sample Size in the Planning and Interpretation of Medical Research. *Clinical Orthopaedics and Related Research, 466*(9), 2282-2288.

Bildt, C., Alfredsson, L., Punnett, L., Theobald, H., Torgen, M., & Wikman, A. (2001). Effects of drop out in a longitudinal study of musculoskeletal disorders. *Occupational and Environmental Medicine, 58*(3), 194-199.

Bohadana, A., Izbicki, G., & Kraman, S. (2014). Fundamentals of lung auscultation. *New England Journal of Medicine, 370*(8), 744-751.

Doherty, D., Belfer, M., Brunton, S., Fromer, L., Morris, C., & Snader, T. (2006). Chronic obstructive pulmonary disease: consensus recommendations for early diagnosis and treatment. *Journal of Family Practice, 55*(11), S1-S1.

Fiz, J., Jane, R., Homs, A., Izquierdo, J., Garcia, M., & Morera, J. (2002). Detection of wheezing during maximal forced exhalation in patients with obstructed airways. *Chest, 122*(1), 186-191.

Gavriely, N., Nissan, M., Cugell, D. W., & Rubin, A. H. (1994). Respiratory health screening using pulmonary function tests and lung sound analysis. *European Respiratory Journal, 7*(1), 35-42.

Gibson, G., Loddenkemper, R., Lundback, B., & Sibille, Y. (2013). Respiratory health and disease in Europe: the new European Lung White Book. *European Respiratory Journal, 42*(3), 559-563.

Greene, G., Hood, K., Little, P., Verheij, T., Goossens, H., Coenen, S., & Butler, C. (2011). Towards clinical definitions of lower respiratory tract infection (LRTI) for research and primary care practice in Europe: an international consensus study. *Primary Care Respiratory Journal, 20*(3), 299-306.

Huq, S., & Moussavi, Z. (2010, Aug 31 - Sep 4). *Automatic breath phase detection using only tracheal sounds.* Paper presented at the Annual International Conference of the IEEE, Buenos Aires, Argentina.

Jácome, C., & Marques, A. (2015a). Computerized Respiratory Sounds Are a Reliable Marker in Subjects With COPD. *Respiratory Care, 60*(9), 1264-1275.

Jácome, C., & Marques, A. (2015b). Computerized respiratory sounds in patients with COPD: a systematic review. *COPD, 12*(1), 104-112.

Jácome, C., & Marques, A. (2017). Computerized Respiratory Sounds: Novel Outcomes for Pulmonary Rehabilitation in COPD. *Respiratory Care, 62*(2), 199-208.

Jácome, C., Oliveira, A., & Marques, A. (2017). Computerized respiratory sounds: a comparison between patients with stable and exacerbated COPD. *The Clinical Respiratory Journal, 11*(5), 612-620.

Kraman, S., Wodicka, G., Oh, Y., & Pasterkamp, H. (1995). Measurement of respiratory acoustic signals: effect of microphone air cavity width, shape, and venting. *Chest, 108*(4), 1004-1008.

Miller, M., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., . . . Gustafsson, P. (2005). Standardisation of spirometry. *European Respiratory Journal, 26*(2), 319-338.

Murphy, R., Vyshedskiy, A., Power-Charnitsky, V., Bana, D., Marinelli, P., Wong-Tse, A., & Paciej, R. (2004). Automated lung sound analysis in patients with pneumonia. *Respiratory Care, 49*(12), 1490-1497.

Oliveira, A., Lage, S., Rodrigues, J., & Marques, A. (2018). Reliability, validity and minimal detectable change of computerized respiratory sounds in patients with chronic obstructive pulmonary disease. *The Clinical Respiratory Journal, 12*(5), 1838-1848.

Oliveira, A., & Marques, A. (2014). Respiratory sounds in healthy people: a systematic review. *European Respiratory Journal, 108*(4), 550-570.

Oliveira, A., Pinho, C., & Marques, A. (2017). Effects of a respiratory physiotherapy session in patients with LRTI: a pre/post-test study. *The Clinical Respiratory Journal, 11*(6), 703-712.

Oliveira, A., Sen, I., Kahya, Y., Afreixo, V., & Marques, A. (2017). Computerised respiratory sounds can differentiate smokers and non-smokers. *Journal of Clinical Monitoring and Computing, 31*(3), 571-580.

Parker, C., Voduc, N., Aaron, S., Webb, K., & O'Donnell, D. (2005). Physiological changes during symptom recovery from moderate exacerbations of COPD. *European Respiratory Journal, 26*(3), 420-428.

Pasterkamp, H., Kraman, S., & Wodicka, G. (1997). Respiratory sounds. Advances beyond the stethoscope. *American Journal of Respiratory and Critical Care Medicine, 156*(3 Pt 1), 974-987.

Piirila, P., & Sovijarvi, A. (1995). Crackles: recording, analysis and clinical significance. *European Respiratory Journal, 8*(12), 2139-2148.

Pinho, C., Oliveira, A., Jácome, C., Rodrigues, J., & Marques, A. (2016). Integrated approach for automatic crackle detection based on fractal dimension and box filtering. *International Journal of Reliable and Quality E-Healthcare, 5*(4), 34-50.

Pinho, C., Oliveira, A., Oliveira, D., Dinis, J., & Marques, A. (2014). LungSounds@ UA interface and multimedia database. *International Journal of E-Health and Medical Communications, 5*(1), 81-95.

Rossi, M., Sovijarvi, A., Piirila, P., Vannuccini, L., Dalmasso, F., & Vanderschoot, J. (2000). Environmental and subject conditions and breathing

manoeuvres for respiratory sound recordings. *European Respiratory Review, 10*(77), 611-615.

Sanchez Morillo, D., Astorga Moreno, S., Fernandez Granero, M., & Leon Jimenez, A. (2013). Computerized analysis of respiratory sounds during COPD exacerbations. *Computers in Biology and Medicine, 43*(7), 914-921.

Seemungal, T., Donaldson, G., Bhowmik, A., Jeffries, D., & Wedzicha, J. (2000). Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 161*(5), 1608-1613.

Sethi, S., & Murphy, T. (2008). Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *New England Journal of Medicine, 359*(22), 2355-2365.

Soyseth, V., Johnsen, H., & Kongerud, J. (2008). Prediction of dropout from respiratory symptoms and airflow limitation in a longitudinal respiratory study. *Scandinavian Journal of Work, Environment & Health, 34*(3), 224-229.

Taplidou, S., & Hadjileontiadis, L. (2007). Wheeze detection based on time-frequency analysis of breath sounds. *Computers in Biology and Medicine, 37*(8), 1073-1083.

The Global Initiative for Chronic Obstructive Lung Disease. (2018). Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease - 2018 Report: The Global Initiative for Chronic Obstructive Lung Disease, Inc.

Toy, E., Gallagher, K., Stanley, E., Swensen, A., & Duh, M. (2010). The economic impact of exacerbations of chronic obstructive pulmonary disease and exacerbation definition: a review. *COPD, 7*(3), 214-228.

Vannuccini, L., Earis, J., Helisto, P., Cheetham, B., Rossi, M., Sovijarvi, A., & Vanderschoot, J. (2000). Capturing and preprocessing of respiratory sounds. *European Respiratory Review, 10*(77), 616-620.

Vyshedskiy, A., & Murphy, R. (2012). Crackle pitch rises progressively during inspiration in pneumonia, CHF, and IPF patients. *Pulmonary Medicine, 2012*, Article ID 240160.

Wedzicha, J., & Wilkinson, T. (2006). Impact of chronic obstructive pulmonary disease exacerbations on patients and payers. *Proceedings of the American Thoracic Society, 3*(3), 218-221.

Wilkinson, T., Donaldson, G., Hurst, J., Seemungal, T., & Wedzicha, J. (2004). Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 169*(12), 1298-1303.

Wodicka, G., Kraman, S., Zenk, G., & Pasterkamp, H. (1994). Measurement of respiratory acoustic signals. Effect of microphone air cavity depth. *Chest, 106*(4), 1140-1144.

Woodhead, M., Blasi, F., Ewig, S., Garau, J., Huchon, G., Ieven, M., . . . Verheij, T. (2011). Guidelines for the management of adult lower respiratory tract infections--full version. *Clinical Microbiology and Infection, 17*(Suppl 6), E1-59.

Study IV

_____

Understanding symptoms variability in outpatients with AECOPD

Oliveira A, Marques A

Letter to the editor

Symptoms are the cornerstone for diagnosing acute exacerbations of chronic obstructive pulmonary disease (AECOPD), however little information is available on their variability during these events and on their relationships with objective clinical measures. This study explored changes in patients' symptoms and their relationships with objective clinical measures during AECOPD.

Methods

A longitudinal observational study was conducted with thirty-six outpatients with AECOPD (24 males; 68.4±9.9 years; forced expiratory volume in one second (FEV_1) 50.7±20.4 %predicted) recruited from the urgent care of a Central hospital. Patients attended to 4 assessments: until 48 hours of the urgent care visit (T1) and 8 days (T2), 15 days (T3) and 45 days (T4) after the hospital visit. Patients' prescriptions included only pharmacological treatment and consisted in antibiotics (n=16; 44.4%), beta-adrenergic agonists (n=2; 5.6%), cholinergic antagonists (n=3; 8.3%), associations of bronchodilators with cholinergic antagonists (n=7; 19.4%), anti-inflammatory drugs (n=1; 2.8%), xanthines (n=1; 2.8%) and expectorants (n=6; 16.7%).

Activities-related dyspnoea (modified British Medical Research Council questionnaire – mMRC), dyspnoea and fatigue at rest (modified Borg Scale – MBS), cough, sputum and wheezing symptoms (11-point numerical rating scale) were registered in each assessment. FEV_1, using a portable spirometer, and quadriceps muscle strength (QMS), using a handheld dynamometer, were also collected.

The number of participants presenting symptoms, the severity of symptoms, FEV_1 and QMS were compared among T1, T2, T3 and T4 using the Cochran or Friedman tests, respectively. Changes in symptoms were correlated with changes in FEV_1 and QMS using the Spearman's correlation coefficient.

Results

Dyspnoea and cough were the most reported symptoms at the onset of AECOPD. The number of patients with dyspnoea at rest, assessed with the MBS (MBS>0), decreased significantly from T1 to T4 (22 vs. 16 vs. 15 vs. 13; p=0.040) (table 1). No significant differences were observed in the number of patients presenting activities-related dyspnoea, fatigue at rest, cough, sputum and wheezing symptoms. During the time course of the AECOPD, participants presented significantly more i) activities-related dyspnoea in T1, than in T3 (p=0.001) and T4 (p=0.028); ii) dyspnoea at rest in T1 than in T4 (p=0.016); iii) cough in T1 than in T2 (p=0.001), T3 (p<0.001) and T4 (p<0.001) and iii) wheezing in T1 than in T4 (p=0.022) (table 1).

Table 1. Clinical variables and symptoms variability during the course of an AECOPD.

	AECOPD (T1)	8 days (T2)	15 days (T3)	45 days (T4)	p-value
FEV_1, L	0.9 [0.7-1.4]	0.9 [0.7-1.3]	1.1 [0.7-1.6]	1.2 [0.8-1.6]	0.075
QMS, kgf	12.2 [9.2-20.1]	13.9 [10.9-18.6]	13.2 [11.2-21.8]	17.8* [13.3-24.7]	p<0.001
No. patients (mMRC>0)	35	31	32	30	0.091
mMRC	2.0 [2.0-3.0]	2.0 [2.0-2.8]	2.0 [1.0-2.0]*	1.5 [1.0-2.0]*	p<0.001
No. patients (MBS.d>0)	22	16	15	13*	0.040
MBS - dyspnoea	3.0 [0.0-4.0]	0.0 [0.0-2.8]	0.0 [0.0-2.8]	0.0 [0.0-1.8]*	p=0.001
No. patients (MBS.f>0)	17	15	17	11	0.249
MBS - fatigue	0.0 [0.0-3.0]	0.0 [0.0-3.0]	0.0 [0.0-3.0]	0.0 [0.0-2.0]	p=0.001
No. patients (NRS.cough>0)	24	23	21	23	0.056
Cough	8.0 [6.0-10.0]	4.0[2.0-5.0]*	3.0 [2.0-5.0]*	2.0 [0.0-4.0]*	p<0.001
No. patients (NRS.sputum>0)	22	23	21	24	0.392
Sputum	5.0 [2.0-7.5]	3.0 [1.5-6.0]	3.0 [2.0-4.0]	2.0 [0.5-5.0]	p=0.061
No. patients (NRS.wheezeing>0)	20	21	17	19	0.183
Wheezing	6.0 [2.5-10.0]	4.0 [1.0-8.0]	3.0 [0.0-5.5]	2.0 [0.0-4.0]*	p=0.006

Legend: Values are shown as number or median [interquartile range]; significant difference at p<0.05; * different from T1. FEV_1, forced expiratory volume in one second; mMRC, modified British Medical Research Council questionnaire; MBS.d, modified Borg scale – dyspnoea; MBS.f, modified Borg scale – fatigue; NRS, numerical rating scale; QMS, quadriceps muscle strength.

Changes occurring between T1 and T3 in mMRC correlated inversely with changes in QMS (r_s=-0.41; p=0.013) whilst changes in cough (r_s=0.47; p=0.021) correlated positively with QMS. Changes in MBS – dyspnoea (r_s=-0.47; p=0.004)

and fatigue (r_s=-0.34; p=0.046) correlated inversely with changes in FEV_1 (figure 1). No further correlations were found.
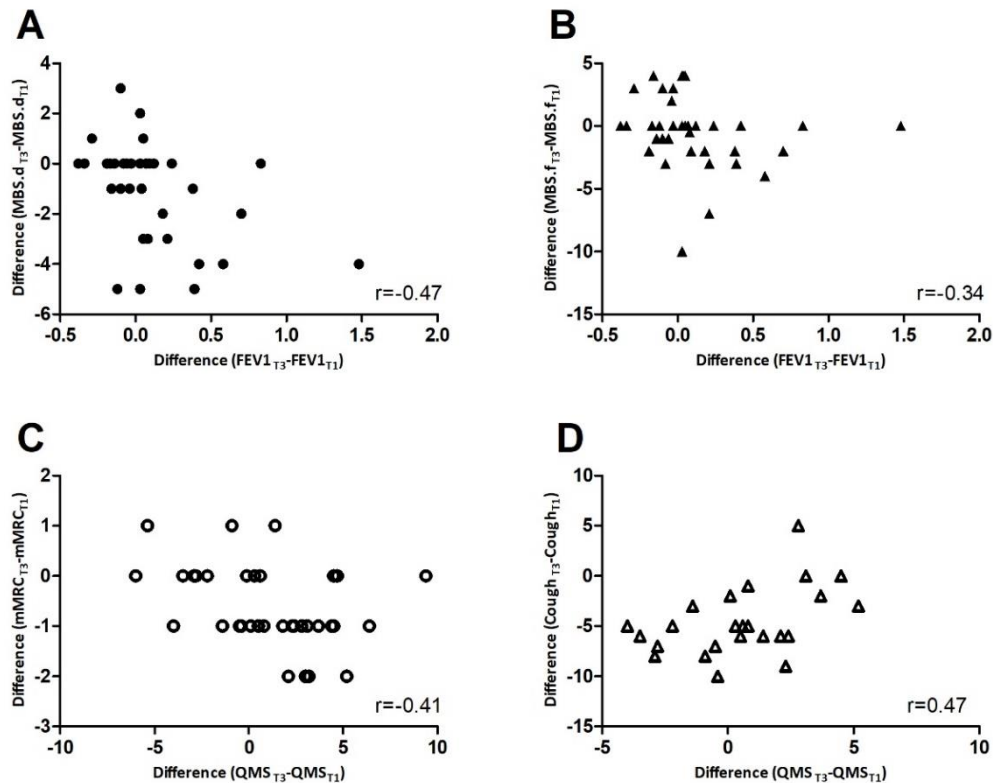

Figure 1. Correlations between changes from T1 to T3 in A) modified Borg scale – dyspnoea (MBS.d) and forced expiratory volume in 1 second (FEV_1); B) modified Borg scale – fatigue (MBS.f) and FEV_1; C) modified British Medical Research Council questionnaire (mMRC) and quadriceps muscle strength (QMS); D) Cough, assessed with the numerical scale, and QMS.

Discussion

Dyspnoea and cough were the most reported symptoms at the onset of AECOPD (Parker, Voduc, Aaron, Webb, & O'Donnell, 2005; Seemungal, Donaldson, Bhowmik, Jeffries, & Wedzicha, 2000). Dyspnoea was the most prevalent symptom. Its time-recovery matched previous reports (i.e., 6 to 30 days) (Parker et al., 2005; Seemungal et al., 2000). Cough was the symptom reported with the highest severity and the first to improve after treatment initiation. In COPD cough is the most common symptom for which individuals seek medical

attention and is a cardinal symptom in upper tract infections (Morice et al., 2014), one of the most common causes of AECOPD. Our results support the need of increasing awareness about cough severity and behaviour. Recognising the cough pattern may aid to guide patients' monitoring and interventions, reduce need for hospitalisation, recurrence of AECOPD and, consequently, costs and morbidity related with these events.

Differences in wheezing were only detected 45 days after the onset of the exacerbation, which differs from previous reports using computerised respiratory sound analysis (i.e., improvements 15 days after the AECOPD) (Oliveira, Rodrigues, & Marques, 2018). Lack of agreement between subjective and objective measures have already been reported for other outcomes, such as cough (Crook et al., 2017), and highlights the need for incorporating both patient-reported and clinical outcome measures in the assessment of patients with AECOPD.

Similar to other studies, associations between improvements in dyspnoea and higher expiratory flow rates were found, possibly due to the inflammatory aetiology of the acute exacerbation itself (i.e., reduction in inflammation during recovery from the AECOPD may influence the reduction of dyspnoea and increase expiratory flow rates) and/or reductions in lung hyperinflation (Parker et al., 2005). Nevertheless, both inflammation and hyperinflation were not directly studied in the present research and thus interpretations should be made carefully. A relationship between dyspnoea and QMS was also found, as previously reported in stable patients with COPD, due to the "downward disease spiral" of increased dyspnoea, decreased physical activity and deconditioning of locomotor muscles (Polkey & Moxham, 2006). During AECOPD, this downward spiral may be even more prominent as patients severely decrease their activities.

The positive correlation found between changes in cough severity and QMS was unexpected. Whilst cough severity showed significant improvements at day 15 of the AECOPD, QMS remained statistically unchanged during the same period, with 36% of the patients exhibiting decreases in their QMS. Similar

results have been found in hospitalised patients, where QMS decreased during the first 8 days of hospitalisation for AECOPD and only recovered at day 90 (Spruit et al., 2003). Thus, although both outcomes improved during an AECOPD, their timing of improvement differs, which may explain the positive correlation found between changes at T3-T1 between these two outcomes. Studies describing the pattern of QMS recovery in outpatients with AECOPD are needed to confirm these results and aid developing timely and personalised interventions.

Despite the novel findings in symptoms behaviour during AECOPD, this study has some limitations that need to be acknowledged. Treatment of exacerbations was not standardised, but rather prescribed according to the physician best judgment. Although the effects of therapies were not of interest in this study, it must be acknowledged that different combination of treatments might influence the recovery times and outcomes of individual patients. Characterisation of symptoms lack other important features, such as sputum purulence. These data can contribute to infer about the nature of the AECOPD (i.e., infective - viral and/or bacterial - or non-infective) and about the suitability of treatments prescribed. It is thus recommended to add sputum purulence to data collection in future study protocols.

In sum, this study showed that: i) dyspnoea is the most representative symptom at the onset of an AECOPD; ii) severity of cough is the first symptom to improve during the course of an AECOPD, and iii) changes in symptoms were correlated with FEV_1 and QMS, which are predictors of COPD hospitalisations and mortality. Our findings evidence that timely management of symptoms is essential for patients' recovery and should encourage health professionals to perform a comprehensive evaluation of outpatients with AECOPD using both patients reported symptoms and objective clinical outcome measures.

References

Crook, S., Busching, G., Schultz, K., Lehbert, N., Jelusic, D., Keusch, S., . . . Frei, A. (2017). A multicentre validation of the 1-min sit-to-stand test in patients with COPD. *European Respiratory Journal, 49*(3), 1601871.

Morice, A., Millqvist, E., Belvisi, M., Bieksiene, K., Birring, S., Chung, K., . . . Smith, J. (2014). Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *European Respiratory Journal, 44*(5), 1132-1148.

Oliveira, A., Rodrigues, J., & Marques, A. (2018). Enhancing our understanding of computerised adventitious respiratory sounds in different COPD phases and healthy people. *Respiratory Medicine, 138*, 57-63.

Parker, C., Voduc, N., Aaron, S., Webb, K., & O'Donnell, D. (2005). Physiological changes during symptom recovery from moderate exacerbations of COPD. *European Respiratory Journal, 26*(3), 420-428.

Polkey, M., & Moxham, J. (2006). Attacking the disease spiral in chronic obstructive pulmonary disease. *Clinical Medicine, 6*(2), 190-196.

Seemungal, T., Donaldson, G., Bhowmik, A., Jeffries, D., & Wedzicha, J. (2000). Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 161*(5), 1608-1613.

Spruit, M., 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.

Study V

_____

Enhancing our understanding of the time course of acute exacerbations of COPD managed on an outpatient basis.

Oliveira A, Afreixo V, Marques A.

Abstract

Purpose: Acute exacerbations of COPD (AECOPD) are associated with pulmonary/systemic changes; however, quantification of those changes during AECOPD managed on an outpatient basis and factors influencing recovery are lacking. This study aimed to characterise patients' changes during AECOPD and identify factors influencing their recovery.

Methods: Body mass index, the modified British Medical Research Council questionnaire, number of exacerbations in the previous year, and the Charlson comorbidity index (independent variables) were collected within 24–48 hours of hospital presentation (T0). Peripheral oxygen saturation (SpO_2), forced expiratory volume in one second, percentage predicted (FEV_1%predicted), maximum inspiratory pressure, quadriceps muscle strength, 5 times sit-to-stand, and COPD assessment test (CAT) (dependent variables) were collected at T0 and approximately at days 8 (T1), 15 (T2), and 45 (T3) after T0.

Results: A total of 44 outpatients with AECOPD ($31\male$; 68.2 ± 9.1 years; 51.1 ± 20.3 FEV_1%predicted) were enrolled. All variables improved overtime ($P<0.05$); however, at day 8, only SpO_2 and CAT ($P\leq0.001$) showed significant improvements. Changes in FEV_1 were not influenced by any independent measure, while changes in other outcome measures were influenced by at least one of the independent measures. Independently of the time of data collection, being underweight or overweight and having increased dyspnoea, previous exacerbations, and severe comorbidities negatively affected patients' outcomes.

Conclusion: FEV_1%predicted and SpO_2 were not influenced by any independent measure and, thus, seem to be robust measures to follow-up outpatients with AECOPD. No single indicator was able to predict patients' recovery for all measures; thus, a comprehensive assessment at the onset of the AECOPD is required to personalise interventions.

Introduction

COPD is frequently punctuated by acute exacerbations (acute exacerbations of COPD [AECOPD]), which account for more than half of the hospitalisations in COPD (Gulati & Wells, 2017) and are the main responsible for patients' clinical deterioration and increased health care costs (Anzueto, 2010). Globally, more than 50% of COPD-related costs are due to AECOPD (Celli & MacNee, 2004) and in USA, costs are estimated in $7.100 per patient/exacerbation (Guarascio, Ray, Finch, & Self, 2013).

Long-term consequences of AECOPD are known, such as clinical important physiological and functional deteriorations (Anzueto, 2010), resulting in significant declines in lung function, muscle strength, and quality of life and increased mortality (Anzueto, 2010; Spruit et al., 2003). AECOPD are also responsible for significant patients' clinical deterioration during its time course; however, most of the information available is on lung function and dyspnoea (Parker, Voduc, Aaron, Webb, & O'Donnell, 2005; Seemungal, Donaldson, Bhowmik, Jeffries, & Wedzicha, 2000; Seemungal et al., 1998) in hospitalised patients (Feliz-Rodriguez et al., 2013; Koutsokera et al., 2009; Mesquita, Donaria, Genz, Pitta, & Probst, 2013; Seemungal et al., 2000; Spruit et al., 2003). Little information is still available on more functional parameters, such as muscle strength, activities of daily living, and impact of the disease. Moreover, hospitalised patients differ from outpatients not only in their management but also in the disease severity (The Global Initiative for Chronic Obstructive Lung Disease, 2018), which may influence their pattern of recovery. Thus, understanding outpatients' recovery seems crucial to timely manage and appropriately plan their follow-ups.

Factors associated with the progression and prognosis of AECOPD during hospitalisations have already been studied and include patients' anthropometrics, stage of the disease (according to dyspnoea and number of AECOPD in the previous year), severity of comorbidities, and acute physiological derangements (Singanayagam, Schembri, & Chalmers, 2013). Such information is essential to

152

design management strategies and discharge plans during hospital stay. However, more than 80% of AECOPD are managed on an outpatient basis (The Global Initiative for Chronic Obstructive Lung Disease, 2018) and knowledge on factors influencing the time course of AECOPD managed in this setting is scarce. This unawareness impairs the standardisation, optimisation, and personalisation of the treatment and ultimately contributes to the existing high rate of AECOPD relapses (Adams, Melo, Luther, & Anzueto, 2000).

This study aimed to characterise patients' lung function, oxygen saturation, muscles strength, impact of the disease, and functionality during the time course of AECOPD managed on an outpatient basis. Additionally, it was aimed to identify the factors influencing this recovery period.

Methods

Study design and participants

A longitudinal observational study was conducted in non-hospitalised patients with AECOPD recruited from the urgent care of a Central Hospital. Inclusion criteria were the diagnosis of an AECOPD according to the GOLD criteria (The Global Initiative for Chronic Obstructive Lung Disease, 2018). Exclusion criteria were hospitalisation (defined as the need to be admitted as an inpatient at the respiratory or intensive care unit for further assessment/treatment after consultation with the urgency clinician); patients requiring emergency intubation and/or mechanical ventilation; and patients with compromised neurological status or hemodynamic instability or presence of severe co-existing respiratory, neurological (e.g., Parkinson's disease), cardiac (e.g., uncontrolled symptomatic heart failure), musculoskeletal (e.g., kyphoscoliosis), or signs of psychiatric impairments. Eligible patients were identified by clinicians and contacted by the researchers to schedule an appointment within 48 hours of the hospital visit.

Approval was obtained from the ethics committee of the Centro Hospitalar do Baixo Vouga (13NOV'1514:40065682) and from the National Data Protection

Committee (8828/2016). Written informed consent was obtained before data collection.

Sample size

In order to test the time effect (four measurements) over quantitative variables, a sample size estimation was performed to detect moderate effect sizes ($f=0.25$) as significant, with 80% power, 5% significance level. The minimum sample size estimated was 35 participants. In health-related longitudinal studies, dropout rates are of approximately 20%–45% (Bildt et al., 2001; Soyseth, Johnsen, & Kongerud, 2008); thus, 44 participants with AECOPD were aimed to be recruited.

Data collection

Patients were asked to attend to the following four assessment sessions: within 48 hours of the urgent care visit (T0, exacerbation onset) and approximately 8 days (T1, during exacerbation), 15 days (T2, following exacerbation),7 and 45 days after the hospital visit (T3, at stability postexacerbation). Data were collected at the urgent care, in the facilities of the University of Aveiro, or at patients' home.

Sociodemographic (age and gender), anthropometric (height, weight, and body mass index [BMI]), and general clinical (smoking habits, number of exacerbations in the previous year, medication, comorbidities, and dyspnoea) data were first collected. The severity of comorbid diseases was recorded and scored according to the Charlson comorbidity index (CCI) (Charlson, Pompei, Ales, & MacKenzie, 1987). Dyspnoea was assessed with the modified British Medical Research Council (mMRC) questionnaire (Doherty et al., 2006).

In each data collection moment, peripheral oxygen saturation (SpO_2), collected with a pulse oximeter (Pulsox 300i; Konica Minolta, Tokyo, Japan), lung function, respiratory muscle strength, quadriceps muscle strength (QMS), impact of the disease, and functionality were collected by a physiotherapist following the described standardised order.

Impact of the disease was measured with the COPD assessment test (CAT), a disease-specific questionnaire with eight items (i.e., cough, sputum, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep, and energy) (Jones et al., 2009).

Lung function was assessed with a portable spirometer (MicroLab 3535; CareFusion, Kent, UK) (Miller et al., 2005), and respiratory muscle strength was measured at the mouth as maximum inspiratory pressure (PImax) using an electronic pressure transducer (MicroRPM; Micromedical, Kent, UK) according to the American Thoracic Society, & European Respiratory Society (2002) guidelines.

QMS was measured as quadriceps peak torque during an isometric contraction of the quadriceps of the dominant side with a handheld dynamometer (microFET2; Hoggan Health, Salt Lake City, Utah) (Troosters et al., 2010). The best of three acceptable and reproducible manoeuvres was considered for analysis. Quadriceps peak torque was calculated in the percentage of predicted (QMS% predicted) (Bohannon, 1997).

Functionality was assessed with the 5 times sit-to-stand test (5STS). A straight-backed armless chair with a hard seat stabilised against a wall was used, and the protocol of Jones et al. (2013) was followed. The best of three acceptable and reproducible manoeuvres was considered for analysis.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA), and plots were created using GraphPad Prism 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at 0.05.

Descriptive statistics was used to describe the sample. The evolution of each dependent variable during AECOPD and the identification of variables that could influence the evolution of the dependent variables were analysed with generalised estimating equation' (GEE) models with a gama link function and

independent correlation structure. This method is an extension of generalised linear models to longitudinal data permitting the inclusion of time-dependent variables and the analysis of incomplete data (without imputing missing data), common in longitudinal health studies (Ma, Mazumdar, & Memtsoudis, 2012).

To explore the influence of time independently, a first analysis was performed using SpO_2, FEV_1 percentage predicted (FEV_1%predicted), PImax, QMS% predicted, CAT, and 5STS as dependent variables and time as the only independent variable. Then, to identify variables that could influence the evolution of the dependent variables, BMI (i.e., underweight <18.50, normal weight <24.99, and overweight ≥25.00) (World Health Organization, 2006), number of exacerbations in the previous year (i.e., 0–1 and ≥2) (The Global Initiative for Chronic Obstructive Lung Disease, 2018), comorbidities (mild: CCI ≤2, moderate: CCI ≤4, and severe: CCI≥5) (Charlson, Pompei, Ales, & MacKenzie, 1987), and dyspnoea (mild: mMRC<2 and severe: mMRC≥2) (The Global Initiative for Chronic Obstructive Lung Disease, 2018) were included as independent variables. A clinical criterion was used to select the dependent and independent variables included in the models (variables commonly reported and associated with the response to treatments in COPD and with AECOPD in the literature) (Guerra, Gaveikaite, Bianchi, & Puhan, 2017; Singanayagam et al., 2013; Spruit et al., 2015; Viniol & Vogelmeier, 2018).

Results

Participants

Seventy-eight non-hospitalised patients with AECOPD were referred for possible inclusion in the study. Of whom, 34 patients were excluded because at T0 they had a pulmonary function and clinical history incompatible with a diagnosis of COPD (n=22), did not meet the definition for AECOPD (n=1), presented lung neoplasia (n=2) and severe heart failure (n=1), were unable to comply with testing (n=3), and showed decline to participate in the study (n=5). Forty-four non-hospitalised patients with AECOPD (31♂; 68.18±9.09 years;

51.11±20.27 FEV$_1$% predicted) were invited and agreed to participate in the study. Participants' characteristics are summarised in Table 1.

Table 1. Sample characterisation.

Characteristics		Patients with AECOPD (n=44)
Age, years		68.18±9.09
Gender (male), n(%)		31 (70.5)
BMI (kg/m)^2		25.86±4.83
Smoking status, n(%)		
	Current	8 (18.2)
	Former	22 (50.0)
	Never	14 (31.8)
Packs/year		45.00 [22.00-67.25]
Exacerbations (previous year), n(%)		
	0	8 (18.2)
	1	11 (25.0)
	≥2	25 (56.8)
FEV$_1$, L		1.22±0.51
FEV$_1$, %predicted		51.11±20.27
FEV$_1$/FVC, %		50.47±13.64
GOLD stages, n(%)		
	A	6 (13.6)
	B	5 (11.4)
	C	5 (11.4)
	D	26 (59.1)
Medication, n(%)		
Antibiotics		28 (65.1)
Bronchodilators		
	SABA	9 (20.9)
	SAMA	6 (14.0)
	SABA/SAMA combination	6 (14.0)
	LABA	5 (11.6)
	LAMA	22 (51.2)
	LABA/LAMA combination	5 (11.6)
	ICS	7 (16.3)
	ICS/LABA combination	27 (62.8)
	Xanthines	16 (37.2)
	LTRA	4 (9.3)
Expectorants		20 (46.5)
Oral Corticosteroids		9 (20.9)
CCI		
	Mild	6 (14)
	Moderate	25 (57)
	Severe	13 (29)
mMRC		1 [0.5-2.0]

Notes: Values are presented as mean±SD (for normal distributed variables), or median (interquartile range) (for non-normal distributed variables) at T0, unless otherwise stated. FEV$_1$, at stability – T3; FVC, at stability – T3.

Abbreviations: AECOPD, acute exacerbations of COPD; BMI, body mass index; CCI, Charlson comorbidity index; ICS, Inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonist; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified British Medical Research Council questionnaire; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity.

Time course of AECOPD

The variation of each variable within the time course of the AECOPD is found in Figure 1. At day 8, only SpO_2 and CAT (P≤0.001) have shown significant improvements. At day 15, FEV_1%predicted (P=0.007) and 5STS (P<0.001) had improved from the onset of the AECOPD and at day 45, all variables presented significant improvements (P<0.05). A detailed description of the variables analysed per moment of data collection is found in Tables S1 and S2.
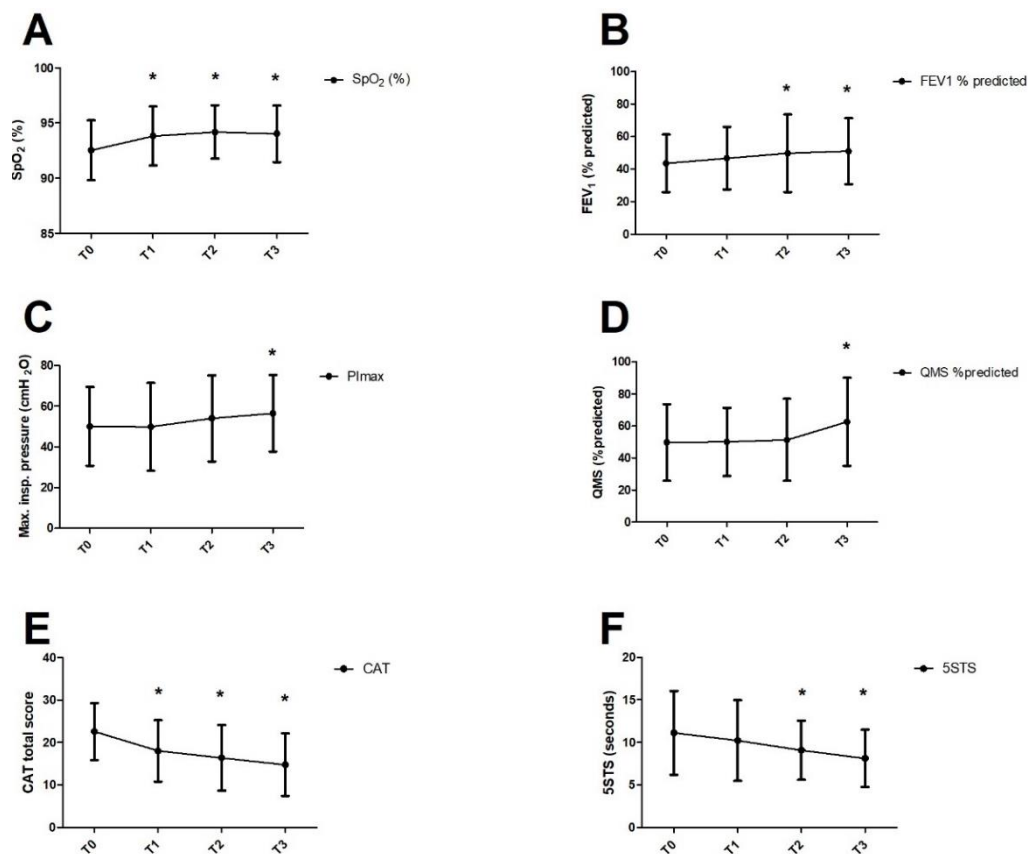

Figure 1. Changes in (A) peripheral oxygen saturation (SpO_2, %), (B) FEV_1%predicted, (C) PImax (cmH_2O), (D) QMS%predicted, (E) CAT, and (F) 5STS test (seconds).

Note: *Significantly different from T0 (P<0.05).

Abbreviations: CAT, COPD assessment test; PImax, maximum inspiratory pressure; QMS%predicted, quadriceps muscle strength percentage predicted; 5STS, 5 times sit-to-stand test.

Factors influencing recovery from AECOPD

Complete results of the independent variables' (i.e., BMI, number of exacerbations in the past year, CCI, and mMRC) effects in each of the dependent variables (i.e., SpO_2, FEV_1%predicted, PImax, QMS%predicted, CAT, and 5STS) are found in Table S3.

Peripheral oxygen saturation

No significant interactions were found between the independent variables and SpO_2 (P>0.05). However, patients presenting two or more AECOPD had mean values of SpO_2 lower than those with one or no AECOPD (mean difference -1.56%±0.53%; P=0.003) independently of the moment of data collection. Other independent variables were not found to significantly affect SpO_2 (P>0.05) (Figure S1).

FEV_1%predicted

No significant interactions were found between the independent variables and FEV_1%predicted (P>0.05). However, underweight patients presented lower FEV_1%predicted than overweight (mean difference -18.98%±4.49% predicted) and normal weight (mean difference -17.84%±4.15% predicted) patients, independently of the moment of data collection (P<0.001). Other independent variables were not found to significantly affect FEV_1%predicted (P>0.05) (Figure S2).

PImax

Significant interactions between time and number of exacerbations in the previous year (P=0.007), comorbidities (P=0.025), and dyspnoea (P=0.012) were found to affect changes in PImax during AECOPD. Other independent variables were not found to significantly affect PImax (P>0.05) (Figure S3).

QMS%predicted

Significant interactions between time and number of exacerbations in the previous year (P=0.035) and comorbidities (P=0.020) were found to affect changes in QMS%predicted during AECOPD. Additionally, QMS% predicted was

159

lower in more dyspnoeic patients (mMRC≥2) than in less dyspnoeic patients (mMRC<2; mean difference -24.27%±11.74% predicted; P=0.011), independently of the moment of data collection. Other independent variables were not found to significantly affect QMS%predicted (P>0.05) (Figure S4).

CAT

Significant interactions between time and BMI (P=0.039) were found to affect changes in CAT during AECOPD. Additionally, CAT scores were higher in overweight patients (BMI ≥25) than in patients with normal BMI (mean difference 4.59±1.77; P=0.042) and in more dyspnoeic patients (mMRC ≥2; mean difference 7.98±1.84; P<0.001), independently of the moment of data collection. Other independent variables were not found to significantly affect CAT (P>0.05) (Figure S5).

5STS

Significant interactions between time and BMI (P=0.008), comorbidities (P=0.001), and dyspnoea (P=0.003) were found to affect changes in 5STS during AECOPD. Additionally, patients with severe comorbidities took longer to complete the 5STS than those with mild (mean difference 2.72±1.35) and moderate (mean difference 2.73±1.14) comorbidities in the CCI independently of the moment of data collection (P=0.013). Other independent variables were not found to significantly affect 5STS (P<0.05) (Figure S6).

Discussion

This study added important findings on the time course of AECOPD managed on an outpatient basis, namely: 1) SpO_2 and CAT improve after 7 days of the onset of an AECOPD, FEV_1%predicted and 5STS improve after 15 days, and muscle strength improve after 45 days of the AECOPD; 2) changes in SpO_2 and FEV_1%predicted are not influenced by BMI, dyspnoea, previous AECOPD, or comorbidities; however, changes in other outcome measures were influenced by at least one independent variable; and 3) independently of the time of data

collection, low/high BMI, increased dyspnoea, previous exacerbations, and severe comorbidities significantly affect patients' outcomes during AECOPD.

Most burdensome symptoms and limitations perceived by each patient improved in the first week (difference of approximately five points in CAT), exceeding the minimal clinical important difference (MCID) of two points (Jones et al., 2012; Kon et al., 2014), and minor improvements were observed in the following weeks. These results matched those previously reported in hospitalised patients (Feliz-Rodriguez et al., 2013; Garcia-Sidro et al., 2015), in which major improvements have been obtained during the first 5 days of hospital admission (Feliz-Rodriguez et al., 2013). Improvements in CAT exceeding the MCID (from -3 to -10 (Kon et al., 2014; Miravitlles et al., 2013)) have been shown, with higher magnitudes observed in more severe exacerbations and in hospitalised patients (Feliz-Rodriguez et al., 2013). Assessment of CAT, especially in the first week following the AECOPD, is important, and different MCID might be needed for hospitalised and non-hospitalised patients with AECOPD. Additionally, a negative effect of overweight in CAT has been found, mimicking previous studies conducted in inpatients (Feliz-Rodriguez et al., 2013). These results shown that, independently of the setting of treatment, an excess of weight significantly impairs patients' improvements in their health status.

The use of SpO_2 and lung function to monitor patients with AECOPD have been controversial, as these measures have shown poor reliability and/or sensitivity to change (Al Rajeh & Hurst, 2016; Vestbo et al., 2013). Several studies have used SpO_2 as an outcome measure; however, the changes reported vary widely (Eaton et al., 2009; Parker et al., 2005; Torres-Sanchez et al., 2016) and, in the absence of an MCID for this parameter, it is not clear whether these changes are clinically significant, especially in patients not presenting hypoxemia at baseline assessment. Lung function measurements during AECOPD are not currently recommended by the GOLD (Vestbo et al., 2013); however, they are widely used (Mesquita et al., 2013; Parker et al., 2005; Seemungal et al., 2000). Results previously obtained are not homogeneous with some authors reporting

161

improvements in lung function, namely FEV_1 (Parker et al., 2005; Seemungal et al., 2000), and others finding no improvements after an AECOPD (Mesquita et al., 2013), which impairs conclusions regarding its usefulness and responsiveness during exacerbations. Using the minimal detectable difference recommended by the European Respiratory Society (i.e., increment of 9% in FEV_1%predicted) (Quanjer et al., 1993), important improvements in FEV_1 were only achieved at T3 (mean difference 9.3% from T0), meaning that, at stability, most patients may have achieved full recovery. These results should nonetheless be interpreted with caution as the minimal detectable difference used has only been established for bronchodilator responsiveness in stable patients with COPD (Quanjer et al., 1993). Nevertheless, our study showed that both SpO_2 and lung function are outcomes that can be simply obtained and seem not to be influenced by independent variables. Future studies are needed to further assess their adequacy to be used in monitoring AECOPD and establish their MCID.

Changes in muscle strength measures, such as PImax and QMS%predicted, were only significant after 45 days of AECOPD, and the pattern of their recovery was influenced by several independent measures, i.e., dyspnoea, previous exacerbations, and comorbidities. Recovery of physical parameters is often impaired during AECOPD and may never fully recover (Anzueto, 2010). In hospitalised patients, decreases in muscle strength occur even during the course of AECOPD (Spruit et al., 2003), which was not observed in this study, possibly because patients continued to perform their daily activities at home, even if at a slower pace. The inclusion of strengthening exercises in hospitalised patients during AECOPD has been recommended to further enhance their recovery (Spruit et al., 2003). This addition may be equally valid and fruitful in outpatients, since it may fasten patients' functional recovery to perform their daily and job-related activities.

Generally, more dyspnoeic patients, under-/overweight, with more exacerbations/year and more comorbidities, recovered slower, except for QMS and 5TST. These findings may be justified by the fact that these more fragile

patients presented poorer values at baseline and, thus, had more room for improvement. In the 5STS test, at T0 the overall sample completed the test in <10 seconds, leaving them a marginal room for progress (Bernabeu-Mora et al., 2016; Jones et al., 2013). This suggests that the 5STS presents a ceiling effect and may not be the most adequate outcome measure to monitor functionality in more functional patients but may be suitable for more severe and older patients.

Independently of the time of data collection, underweight patients presented more airway obstruction; overweight patients presented higher impacts of the disease; dyspnoeic patients presented lower QMS; frequent exacerbators presented lower oxygenation values; and patients with more comorbidities performed worse in 5STS. It is known that all of these parameters are potential predictors of COPD trajectory (Guerra et al., 2017), and thus, it was expected that they would also play a role during the recovery of AECOPD. Nevertheless, it was not possible to find one single independent variable that influenced and differentiated improvements in all outcome measures. These results further highlight the multidimensional and systemic component of AECOPD and the importance of studying the role of emerging biomarkers (Wan, 2018; Wang et al., 2016), together with clinical variables, to predict the trajectory of COPD, and specifically AECOPD.

Limitations

This study has some limitations that must be acknowledged. First, as effects of therapies were not of interest in this study, all patients were treated according to clinicians' best judgment. However, it must be acknowledged that different combinations of treatments might have influenced the outcomes of individual patients. Second, although a sample calculation has been computed to test the time effects in the dependent variables studied, the study was not powered for its secondary analysis (i.e., identify the factors influencing this recovery from AECOPD), resulting in a possible small sample size for this analysis. Consequently, patients' distribution among categories of independent variables (e.g., BMI – underweight, normal weight, and overweight) were not

homogeneous, which could have affected the results observed. Additionally, other variables that are known to influence COPD trajectory and that could also play a role in the time course of AECOPD, such as forced vital capacity, medication, and nature of previous exacerbations, could not been integrated in the models developed. Increasing the number of independent variables would have augmented the risk of having correlations among the variables and, thus, decreased the robustness and the accuracy of the models. Further studies, powered for a high number of variables, should clarify the role of the clinical variables explored and consider their potential interaction with other demographic, chemical, and biological variables to better understand the time course of AECOPD managed on an outpatient basis. Although this was not the main objective of the present article, our exploratory results are valuable, as they contributed to unravel the most promising variables to assess in clinical practice and may be used to compute appropriate sample sizes in future research. Third, most outcome measures used depend on patients' motivation and evaluator expertise. To minimise these influences, a trained physiotherapist conducted all data collection and only variations of less than 20% between the two better results (except for lung function and inspiratory muscle strength, where the European Respiratory Society and American Thoracic Society guidelines (2002; Miller et al., 2005) were followed) in each measurement were considered for analysis. Finally, patient's stable state prior to the exacerbation was not assessed and, thus, it is not known if patients returned or not to their baseline status. Still, information of the course of exacerbations managed on an outpatient basis is still provided and may be useful to personalise interventions in this population.

Conclusion

During an AECOPD managed on an outpatient basis, SpO_2 and CAT improve after 7 days of the onset, FEV_1%predicted and 5STS improve after 15 days, and muscle strength measures improved only after 45 days of the AECOPD. FEV_1%predicted and SpO_2 recovery are not influenced by independent patients' characteristics, such as BMI, dyspnoea, previous

AECOPD, or comorbidities and, thus, may be potentially useful to monitor AECOPD recovery. Low/high BMI, increased dyspnoea, previous exacerbations, and severe comorbidities significantly affect patients' outcomes during AECOPD. No single indicator was able to predict patients' recovery for all measures assessed; thus, a comprehensive assessment at the onset of the AECOPD is needed to personalise interventions to outpatients with AECOPD.

References

Adams, S., Melo, J., Luther, M., & Anzueto, A. (2000). Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. *Chest, 117*(5), 1345-1352.

Al Rajeh, A., & Hurst, J. (2016). Monitoring of Physiological Parameters to Predict Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review. *Journal of Clinical Medicine, 5*(12), 1-18.

American Thoracic Society, & European Respiratory Society. (2002). ATS/ERS Statement on respiratory muscle testing. *American Journal of Respiratory and Critical Care Medicine, 166*(4), 518-624.

Anzueto, A. (2010). Impact of exacerbations on COPD. *European Respiratory Review, 19*(116), 113-118.

Bernabeu-Mora, R., Medina-Mirapeix, F., Llamazares-Herran, E., Oliveira-Sousa, S., Sanchez-Martinez, M., & Escolar-Reina, P. (2016). The accuracy with which the 5 times sit-to-stand test, versus gait speed, can identify poor exercise tolerance in patients with COPD: A cross-sectional study. *Medicine, 95*(35), e4740.

Bildt, C., Alfredsson, L., Punnett, L., Theobald, H., Torgen, M., & Wikman, A. (2001). Effects of drop out in a longitudinal study of musculoskeletal disorders. *Occupational and Environmental Medicine, 58*(3), 194-199.

Bohannon, R. (1997). Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. *Archives of Physical Medicine and Rehabilitation, 78*(1), 26-32.

Celli, B., & MacNee, W. (2004). Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *European Respiratory Journal, 23*(6), 932-946.

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases, 40*(5), 373-383.

Doherty, D., Belfer, M., Brunton, S., Fromer, L., Morris, C., & Snader, T. (2006). Chronic obstructive pulmonary disease: consensus recommendations for early diagnosis and treatment. *Journal of Family Practice, 55*(11), S1-S1.

Eaton, T., Young, P., Fergusson, W., Moodie, L., Zeng, I., O'Kane, F., . . . Kolbe, J. (2009). Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. *Respirology, 14*(2), 230-238.

Feliz-Rodriguez, D., Zudaire, S., Carpio, C., Martinez, E., Gomez-Mendieta, A., Santiago, A., . . . Garcia-Rio, F. (2013). Evolution of the COPD Assessment Test score during chronic obstructive pulmonary disease exacerbations: determinants and prognostic value. *Canadian Respiratory Journal, 20*(5), e92-97.

Garcia-Sidro, P., Naval, E., Martinez Rivera, C., Bonnin-Vilaplana, M., Garcia-Rivero, J., Herrejon, A., . . . Miravitlles, M. (2015). The CAT (COPD Assessment Test) questionnaire as a predictor of the evolution of severe COPD exacerbations. *Respiratory Medicine, 109*(12), 1546-1552.

Guarascio, A., Ray, S., Finch, C., & Self, T. (2013). The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *ClinicoEconomics and Outcomes Research, 5*, 235-245.

Guerra, B., Gaveikaite, V., Bianchi, C., & Puhan, M. (2017). Prediction models for exacerbations in patients with COPD. *European Respiratory Review, 26*(143), 160061.

Gulati, S., & Wells, J. (2017). Bringing stability to the COPD patient: clinical and pharmacological considerations for frequent exacerbators. *Drugs, 77*(6), 651-670.

Jones, P., Harding, G., Berry, P., Wiklund, I., Chen, W-H., & Kline Leidy, N. (2009). Development and first validation of the COPD Assessment Test. *European Respiratory Journal, 34*(3), 648-654.

Jones, P., Harding, G., Wiklund, I., Berry, P., Tabberer, M., Yu, R., & Leidy, N. (2012). Tests of the responsiveness of the COPD assessment test following acute exacerbation and pulmonary rehabilitation. *Chest, 142*(1), 134-140.

Jones, S., Kon, S., Canavan, J., Patel, M., Clark, A., Nolan, C., . . . Man, W. (2013). The five-repetition sit-to-stand test as a functional outcome measure in COPD. *Thorax, 68*(11), 1015-1020.

Kon, S., Canavan, J., Jones, S., Nolan, C., Clark, A., Dickson, M., . . . Man, W. (2014). Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. *Lancet Respiratory Medicine, 2*(3), 195-203.

Koutsokera, A., Kiropoulos, T., Nikoulis, D., Daniil, Z., Tsolaki, V., Tanou, K., . . . Kostikas, K. (2009). Clinical, functional and biochemical changes during recovery from COPD exacerbations. *Respiratory Medicine, 103*(6), 919-926.

Ma, Y., Mazumdar, M., & Memtsoudis, S. (2012). Beyond repeated-measures analysis of variance: advanced statistical methods for the analysis of longitudinal data in anesthesia research. *Regional Anesthesia and Pain Medicine, 37*(1), 99-105.

Mesquita, R., Donaria, L., Genz, I., Pitta, F., & Probst, V. (2013). Respiratory muscle strength during and after hospitalization for COPD exacerbation. *Respiratory Care, 58*(12), 2142-2149.

Miller, M., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., . . . Gustafsson, P. (2005). Standardisation of spirometry. *European Respiratory Journal, 26*(2), 319-338.

Miravitlles, M., García-Sidro, P., Fernández-Nistal, A., Buendía, M., Espinosa de los Monteros, M., & Molina, J. (2013). Course of COPD assessment test (CAT) and clinical COPD questionnaire (CCQ) scores during recovery from exacerbations of chronic obstructive pulmonary disease. *Health and Quality of Life Outcomes, 11*(147), 1-9.

Parker, C., Voduc, N., Aaron, S., Webb, K., & O'Donnell, D. (2005). Physiological changes during symptom recovery from moderate exacerbations of COPD. *European Respiratory Journal, 26*(3), 420-428.

Quanjer, P. H., Tammeling, G. J., Cotes, J. E., Pedersen, O. F., Peslin, R., & Yernault, J. C. (1993). Lung volumes and forced ventilatory flows. *European Respiratory Journal, 6*(Suppl 16), 5-40.

Seemungal, T., Donaldson, G., Bhowmik, A., Jeffries, D., & Wedzicha, J. (2000). Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 161*(5), 1608-1613.

Seemungal, T., Donaldson, G., Paul, E., Bestall, J., Jeffries, D., & Wedzicha, J. (1998). Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 157*(5 Pt 1), 1418-1422.

Singanayagam, A., Schembri, S., & Chalmers, J. (2013). Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Annals of the American Thoracic Society, 10*(2), 81-89.

Soyseth, V., Johnsen, H., & Kongerud, J. (2008). Prediction of dropout from respiratory symptoms and airflow limitation in a longitudinal respiratory study. *Scandinavian Journal of Work, Environment & Health, 34*(3), 224-229.

Spruit, M., Augustin, I., Vanfleteren, L., Janssen, D., Gaffron, S., Pennings, H., . . . Franssen, F. (2015). Differential response to pulmonary rehabilitation in COPD: multidimensional profiling. *European Respiratory Journal, 46*(6), 1625-1635.

Spruit, M., 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.

The Global Initiative for Chronic Obstructive Lung Disease. (2018). Global Strategy for Diagnosis, Management, and Prevention of Chronic

Obstructive Pulmonary Disease - 2018 Report: The Global Initiative for Chronic Obstructive Lung Disease, Inc.

Torres-Sanchez, I., Valenza, M., Saez-Roca, G., Cabrera-Martos, I., Lopez-Torres, I., & Rodriguez-Torres, J. (2016). Results of a Multimodal Program During Hospitalization in Obese COPD Exacerbated Patients. *COPD, 13*(1), 19-25.

Troosters, T., Probst, V., Crul, T., Pitta, F., Gayan-Ramirez, G., Decramer, M., & Gosselink, R. (2010). Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 181*(10), 1072-1077.

Vestbo, J., Hurd, S., Agusti, A., Jones, P., Vogelmeier, C., Anzueto, A., . . . Rodriguez-Roisin, R. (2013). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *American Journal of Respiratory and Critical Care Medicine, 187*(4), 347-365.

Viniol, C., & Vogelmeier, C. (2018). Exacerbations of COPD. *European Respiratory Review, 27*(147), 170103.

Wan, E. (2018). Examining genetic susceptibility in acute exacerbations of COPD. *Thorax, 0*(0), 1-3.

Wang, Z., Bafadhel, M., Haldar, K., Spivak, A., Mayhew, D., Miller, B., . . . Brown, J. (2016). Lung microbiome dynamics in COPD exacerbations. *European Respiratory Journal, 47*(4), 1082-1092.

World Health Organization. (2006). BMI classification. Retrieved May 24, 2018, from http://apps.who.int/bmi/index.jsp?introPage=intro_3.html

Chapter IV

Discussion

_____

General discussion

This research work has focused on two main areas of increasing research and clinical interest in AECOPD: i) the adequacy of outcome measures used to assess outpatients with AECOPD and ii) the time course of AECOPD treated on an outpatient-basis. Although discussion of these areas has been presented in each study, an overall discussion, aiming at providing a comprehensive perspective, is followed.

Outcome measures in outpatients with AECOPD

The **Systematic review,** developed during the course of this research, provides a comprehensive overview of the measurement properties of the outcome measures most used in pulmonary rehabilitation during AECOPD and that can be easily applied in outpatients' settings. Twenty-three PROMs and 18 clinical outcome measures were identified; however, measurement properties could only be synthesised for 22 PROMs and 7 clinical outcome measures. The methodological quality to assess measurement properties of most studies was poor, and the results obtained were indeterminate. These results clarify that whilst a large number of outcome measures are available to assess patients with AECOPD in outpatients' settings, investigation of their measurement properties have not been adequately adressed. Thus, the use of those measures may compromise the validity and applicability of the results achieved after pulmonary rehabilitation and contribute to the conflicting results found in the literature (Puhan, Gimeno-Santos, Cates, & Troosters, 2016; Wedzicha et al., 2017; Wilson et al., 2018) regarding the effects of pulmonary rehabilitation during AECOPD. This **Systematic review** further contributed to answer to a research question raised by the official *American Thoracic Society/ European Respiratory Society statement: research questions in COPD* (Celli et al., 2015), by identifying the CAT and SpO_2 as the outcome measures exhibiting the most appropriate measurement properties to assess patients with AECOPD. It also evidenced critical knowledge gaps that need to be bridged to further clarify the role of pulmonary rehabilitation in outpatients with AECOPD. It is of special importance

173

to establish the measurement properties (i.e., reliability, validity and responsiveness) of commonly used outcome measures (e.g., MBS, mMRC, FEV_1 and six-minute walking test) using robust methodologies, such as the COSMIN standards (Terwee et al., 2012). In order to address this gap in the literature, the empirical Studies, developed during the course of this research, concerning measurement properties (**Studies I and II**), followed this international methodology.

Studies I and **II** explored the measurement properties of respiratory outcome measures to assess patients with AECOPD. A measure should reflect the construct that one intends to measure (i.e., validity) and remain unchanged for as long as the clinical state of the patient remains stable (i.e., reliability), to confidently be used as an outcome measure (Mokkink, Prinsen, Bouter, Vet, & Terwee, 2016). Thus, before being recommended as an outcome measure for AECOPD, the validity and reliability of computerised respiratory sounds were explored in stable patients with COPD in **Study I**.

Although discreetly, the number of inspiratory crackles recorded from the posterior chest was the respiratory sound parameter that correlated the most with the patient's severity of airway obstruction, represented by the FEV_1%predicted. FEV_1 mainly expresses obstruction in larger airways (McNulty & Usmani, 2014), whilst COPD pathogenesis primarily targets small airways (The Global Initiative for Chronic Obstructive Lung Disease, 2019). In contrast, crackles are an acoustic phenomenon that, when heard over distal lung regions, are associated with inflammation or oedema of smaller airways (Piirila & Sovijarvi, 1995). Thus, whilst high correlations between these outcome measures were not expected, the significant correlations found highlight the potential of crackles to indicate peripheral airway obstruction in patients with COPD. Several other studies have reported on the ability of lung auscultation to discriminate among patients with different severity grades of airway obstruction (Anderson, Aitken, Carter, MacLeod, & Moran, 1990; Leuppi et al., 2006; Malmberg et al., 1994; Spence, Bentley, Evans, & Morgan, 1992). Crackles, identified with conventional

auscultation, have been found to be the respiratory sounds most related with decreases in lung function (odds ratio of 0.995 (95% CI 0.991–0.999); p=0:039) of patients assessed in an emergency department (Leuppi et al., 2006). **Study I**, further highlights and establishes the clinical relevance of crackles to detect airway obstruction, by presenting a cut-off of 1 crackle to differentiate between mild-to-moderate and severe-to-very severe obstructions. Nevertheless, our findings differ from previous literature that has mainly found relationships between F50 and FEV_1 (Anderson et al., 1990; Malmberg et al., 1994; Spence et al., 1992). The different methodologies used across studies, i.e., performing forced expiratory manoeuvres or using chemical substances that cause airway obstruction during respiratory sound recordings, might explain this incongruence and raise attention to the need of standardising respiratory sounds recordings to advance knowledge in this field. Similar to correlations found with FEV_1%predicted, correlations with patient-reported outcomes were small or absent. Therefore, it seems fair to argue that computerised respiratory sounds should not be used isolated, but rather integrated with other clinical outcome measures and PROM, as they may fill the gap of assessing small airways and contribute towards a patient's comprehensive evaluation.

Regarding to reliability, results from **Study I** were similar but slightly lower than those previously reported by Jácome and Marques (2015) when exploring within-day reliability of computerised respiratory sounds using standardised respiratory flows at 0.4-0.6L/s ($ICC_{1,3}$ from 0.65 to 0.99). This was expected, as it is known that better reliability is achieved when repeated tests are performed within short periods of time (Shin, Ro du, Lee, Oh, & Kim, 2012) and at target air flows (Vlemincx, Van Diest, & Van den Bergh, 2012). The flow, but also volume, dependence of respiratory sounds (Pasterkamp, Kraman, & Wodicka, 1997), has motivated the development of research using standardised, controlled and/or target air flows (Hadjileontiadis, 2018; Jácome & Marques, 2017; Malmberg, Pesu, & Sovijärvi, 1995; Reyes et al., 2018). This methodology is essential to infer about the genesis and mechanisms of respiratory sounds propagation in basic science research, however it may not be feasible to implement in real life

studies and clinical practice. The **Study I** of this document and the study of Jácome and Marques (2015) have shown that, even without flow and/or volume standardisation, moderate-to-excellent between days reliability exists, meaning that computerised respiratory sounds may be confidently used for clinical purposes even when respiratory flow and volume cannot be standardised.

The **Systematic review** and **Study I** explored and described the measurement properties of the most used and promising respiratory outcome measures to assess AECOPD. Building on that knowledge, **Study II** pooled the MDD and MID for the MBS, the mMRC, FEV_1 and FEV_1%predicted, SpO_2 and computerised adventitious respiratory sounds (i.e., crackles and wheezes). Overall, the established MDD and MID were comparable to those previously reported for patients with stable COPD following pharmacological treatment (Donohue, 2005; Jones et al., 2014; Quanjer et al., 1993; Ries, 2005). Similar results have been reported for health-related questionnaires, such as the CAT and the CCQ (Alma et al., 2018). These results suggest that the MIDs established for COPD following pharmacological treatments may be used interchangeably during stable and exacerbation periods. Thus, sparing health professionals from having to consider two different MIDs according to patients' clinical state and increasing their applicability in clinical practice. Nevertheless, one aspect should be taken into consideration, that is the time needed to achieve the MID and/or the MDD, which was shorter in patients with AECOPD (approximately 45 days), than the 2 to 12 months of treatment commonly used in stable patients (Crisafulli & Clini, 2010; Jones et al., 2014; Ries, 2005). Due to the lack of correlation with the anchor chosen, MIDs could not be established for the FEV_1%predicted, SpO_2 and computerised adventitious respiratory sounds. As showed in the **Systematic review**, some of these outcome measures have been extensively used to assess the effects of pulmonary rehabilitation and other interventions (Laue, Reierth, & Melbye, 2015; McCrory & Brown, 2002; Mukerji et al., 2015; Walters et al., 2014) in patients with AECOPD, however little is known about their measurement properties and interpretability in these patients. Given their great potential to be used at bedside of patients with AECOPD, as they are simple, non-invasive and

widely available, it is advisable that future studies build on knowledge from the results of this research and find relevant anchors to established MID for $FEV_1\%$predicted, SpO_2 and computerised adventitious respiratory sounds.

Time course of AECOPD treated on an outpatient-basis

Studies III, **IV** and **V** described the time course of a variety of patient-reported and clinical outcome measures during AECOPD treated on an outpatient setting. Overall, the results found matched those previously reported in hospitalised patients, with all outcomes improving significantly over the course of 45 days following an AECOPD, but exibiting different patterns of improvement (Feliz-Rodriguez et al., 2013; Nishimura et al., 2018; Seemungal, Donaldson, Bhowmik, Jeffries, & Wedzicha, 2000; The Global Initiative for Chronic Obstructive Lung Disease, 2019; Zhou et al., 2018). Patient reported outcome measures, such as the CAT, the mMRC and the numerical rating scale to assess cough showed statistical significant improvements after 7 to 15 days of the AECOPD, as well as some clinical measures, such as the SpO_2, $FEV_1\%$predicted, 5STS and computerised inspiratory wheezes. On the other hand, quadriceps muscle strength, computerised inspiratory crackles and rest dyspnoea, assessed with the MBS, only evidenced significant improvements after 45 days of the acute event. No improvements were found for patients' fatigue and sputum assessed with the numerical rating scale. However, when considering the MID established for each measure in COPD, this pattern differed slightly. Initial improvements in dyspnoea at rest (MBS) (i.e., -1 unit) (Jones et al., 2014; Ries, 2005) were observed after 15 days of the AECOPD and in the $FEV_1\%$predicted (i.e., 9%) (Quanjer et al., 1993) only after 45 days of the AECOPD. Nevertheless, the CAT questionnaire (i.e., -2 units) (Kon et al., 2014) and the 5STS test (i.e., -1.7s) (Jones et al., 2013) still showed significant and clinical improvements after 15 days of the AECOPD. No comparisons could be established for the remaining outcome measures, due to lack of MIDs. Similar results can be found in the study of Koutsokera et al. (2009), where statistically significant improvements were observed in the $FEV_1\%$predicted at day 10 post AECOPD. However when we considering the MID of 9% (Quanjer et al., 1993),

clinically improvements were not observed during the total course of the study (i.e., 40 days) (Koutsokera et al., 2009). These findings reveal how vastly interpretations can differ if statistical or clinical significance is considered and should call the attention of health professionals and researchers for how these differences may influence decision-making in clinical practice and ultimatly affect patients' treatment. Nevertheless, it is important to note that, with the exception of the CAT questionnaire, the MIDs used are those established for stable patients, as MIDs for patients with AECOPD are lacking. Considering the MID of the CAT, **Study V** found that after only 7 days of pharmacological treatment, the difference in CAT already exceeded in approximately 3 points the current established MID, supporting what has been reported in the literature (Feliz-Rodriguez et al., 2013; Nishimura et al., 2018; Zhou et al., 2018). Overall, these results support the establishment of MID for outcome measures used to assess patients with AECOPD, but also highlight the need of revising the existing MIDs (Alma et al., 2018) as they may not accurtely represent the recovery process of patients treated on an outpatient basis.

Considering other patient reported outcomes, such as symptoms, **Study IV** contributed to show the importance of cough during AECOPD, as this was the symptom reported with the highest severity and the first to improve after initiation of treatment. In COPD, cough is the most common symptom for which individuals seek medical attention and is a cardinal symptom in respiratory tract infections (Morice et al., 2014), one of the most common triggers of AECOPD (Wedzicha & Donaldson, 2003). Our results support the need of increasing awareness of patients, families and health professionals about cough severity and behaviour to guide patients' monitoring and interventions.

Regarding to clinical outcome measures, **Studies IV and V** found that, although some patients presented a decrease in quadriceps muscle strength, as observed in hospitalised patients (Spruit et al., 2003), an overall pattern of decrease was not observed in outpatients with AECOPD. Rather, quadriceps muscle strength tended to remain stable. Conversely to hospitalised patients,

outpatients decrease less their levels of physical activity (Donaldson, Wilkinson, Hurst, Perera, & Wedzicha, 2005; Esteban et al., 2016), as they tend to quickly return to outdoors activities (Donaldson et al., 2005) or may continue to perform their daily activities at home, even if at a slower pace. The inclusion of physical activity and exercise programmes (Spruit et al., 2003), including strengthening, in hospitalised patients during AECOPD has been recommended to further enhance patients' recovery (Spruit et al., 2003). The results of this research work suggest that these additions may be equally valid and fruitful in outpatients, since they seem to be more predispose to physical activities. Such programmes could be developed using patients' daily life activities, thus little affecting their routine, and may fasten patients' functional recovery and behaviour changing towards physical activity in stable stages of the disease.

Study V also showed that some clinical outcome measures, such as the 5STS test, may not be the most adequate to monitor functionality in patients with AECOPD treated in an outpatient setting. This measure has been widely used in fragile older populations (Alcazar et al., 2018; Goldberg, Chavis, Watkins, & Wilson, 2012; Makizako et al., 2017) and recently it has been adapted to patients with stable COPD, showing to be feasible, reliable, valid and responsive (Bui, Nyberg, Maltais, & Saey, 2017). Nevertheless, previous studies have mainly enrolled patients with severe to very severe airway obstruction, which performance is highly reduced (i.e., mean of 13.5 to 15.4 seconds) (Crook et al., 2017; Jones et al., 2013) when compared with patients with AECOPD with moderate airway obstruction and treated on an outpatient setting (i.e., mean of 11.11 seconds). The high performance presented by outpatients with AECOPD leave them with a marginal room for progress and suggest a ceiling effect of the 5STS test in this population. Recently, Morita et al. (2018) have compared multiple sit-to-stand tests in stable patients with COPD and reach to the conclusion that the 1-minute sit-to-stand test may be the best sit-to-stand test to evaluate subjects with COPD. This test was choosen as the best, due to its potential to generate high hemodynamic demands and high association with important clinical outcomes such as functional exercise capacity, functional

status, and physical activity. Sit-to-stand tests present significant advantages to be used in outpatients settings, since they require little space and minimal resources to be implemented. Thus it is advisable for future research to test the feasibility and measurement properties of the 1-min sit-to-stand test to be used as an outcome measure in outpatients with AECOPD.

The use of both patient-reported and clinical outcome measures allowed to clarify the need of a comprehensive patients' assessment at the onset of the AECOPD. **Study V** showed that low and high body mass index, increased dyspnoea, previous exacerbations, and severe comorbidities, assessed at the onset of the AECOPD, significantly affected patients' self-reported, physical and functional outcomes during the recovery process, except for SpO_2 and FEV_1%predicted. Thus, whilst oximetry and lung function may be potentially useful to monitor AECOPD recovery, as recently reported by Fernandez-Villar et al. (2018), a comprehensive assessment at the onset of the AECOPD including patients' body mass index, dyspnoea, previous exacerbations and comorbidities may be needed to develop personalised interventions**. Studies III** and **IV** also found significant differences in objective and self-reported perception of wheezing, a common symptom experience during AECOPD. Decreases in self-reported wheezing were only perceived by patients 45 days after the onset of the exacerbation, whilst decreases using computerised respiratory sound analysis were found after 15 days of the onset. Lack of agreement between subjective and objective measures have already been reported for other outcomes, such as cough (Crooks et al., 2017), and further highlight the need for incorporating both patient-reported and clinical outcome measures in the assessment of patients with AECOPD.

Limitations

The interpretation of the findings of this research work should be tempered considering a number of limitations.

The first aspect that might be considered as a limitation of this research is the use of the COSMIN methodological recommendations in the **Systematic Review** and in **Studies I** and **II** to evaluate the quality of the outcome measures assessed. The COSMIN was originally developed for health-related PROM, such as questionnaires (Terwee et al., 2007). Therefore, the application of the COSMIN as a tool for guiding methodology of studies testing clinical outcome measures can be questioned. Nonetheless, in the absence of guidelines specifically designed to conduct such studies, the COSMIN is indicated as an adequate alternative tool (Bartels, de Groot, & Terwee, 2013).

Secondly, flows and/or volumes were not controlled during respiratory sounds recordings in **Studies I**, **II** and **III** and it is known that respiratory sound acoustics depends on volume and rate of respiratory manoeuvres (Pasterkamp et al., 1997). However, flow and/or volume control is not current practice during auscultation as it requires expensive and little portable equipment (e.g., pneumotacographs, calibration syringes and heating elements), may be poorly tolerated by dyspnoeic and anxious patients and requires trained professionals. A previous study has demonstrated that even without airflow control, respiratory sounds present adequate reliability (ICC>0.70) and are almost as reliable as during recordings at controlled flows (Jácome & Marques, 2015). Thus, in the methodology of this research work it was chosen not to implement flow and/or volume measurements to maximise the potential of directly translating our results to clinical practice.

Thirdly, the complex set up used to record computerised sounds in **Studies I**, **II** and **III** may be perceived as a limitation to their use in the clinical practice. Given computerised respiratory sounds potential to monitor patients

with AECOPD, future research should focus in developing technologies for acquiring high quality data at bedside with minimal setup.

The fourth main limitation of this research work is the lack of treatment standardisation for AECOPD in **Studies II**, **III**, **IV** and **V**. Patients' were treated according to the physician best judgment, using pharmacology as the standard treatment. Although the effects of therapies were not of interest in this research work, it must be acknowledged that different combination of treatments could have influenced patient's recovery.

Fifthly, a sample size calculation was not performed for some research questions explored in **Studies II**, **IV** and **V**, which may have resulted in a small sample size for the analyses conducted. Particularly in **Study V**, the lack of sample size calculation resulted in an unbalanced patients' distribution among categories of the independent variables (e.g., body mass index – underweight, normal weight, and overweight), which could have affected the results observed.

Finally, **Studies III**, **IV** and **V** lack patient's stable state prior to the exacerbation, as patients were only contacted if they were diagnosed with AECOPD. Inclusion of such data would have allowed to conclude about patients' fully recovery, or not, to their baseline status following the AECOPD and thus enhance the findings of this research work.

Implications for future research and clinical practice

From this research work, a number of implications for future research and clinical practice can be highlighted.

1. There is a need to continue conducting research on the measurement properties of patient reported and clinical outcome measures, suitable to be used in outpatients with AECOPD. These measures have been identified in our Systematic Review but it is important that further research, using the available established methodologies, such as the COSMIN standards, follows. This will not only allow to establish comparisons among measures performance but will also

increase the degree of confidence in interpreting results of interventional studies in AECOPD.

2. Another important avenue to pursue in future studies is to potentiate the use of the outcome measures identified as more adequate to monitor outpatients with AECOPD and their MID in clinical practice. This includes improving the access to promising outcome measures, such as computerised respiratory sounds, by developing technological solutions for their acquisition with minimal setup, but also disseminating of the results of this research work through academic, research and clinical communities. Dissemination of these results have been conducted throughout the timeframe of this research work by presenting them in scientific and clinical publications, seminars, courses and congresses in the respiratory field. However, further dissimination should follow by integrating the developed knowledge in new research studies and clinical settings and contexts.

3. It is also important to personalise and optimise the length of treatment and timing of appropriate follow-up in outpatients with AECOPD. The information provided on the timing of improvement of each patient-reported and clinical outcome may aid health professionals to plan their follow-ups according to the time needed to observe effects in a specific outcome of interest, as well as to more accurately monitor the effects of their intervention.

4. Much also needs to be investigated to enhance our knowledge on the time course of AECOPD managed on an outpatient setting and factors influencing patients' recovery. This includes conducting longitudinal research with optimised treatment plans from patients' stable state to recovery from AECOPD. Future work should also be appropriately powered for determining interactions among variables during the recovery of AECOPD, including other demographic, chemical, and biological variables that were left out of the scope of this research.

5. Finally, more research in alternative interventions to manage outpatients with AECOPD is recommended. This includes further research from blind

randomised controlled trials defining the feasibility, effectiveness and cost-effectiveness of the standard care (pharmacological), explored in this research work, against potential interventions, such as pulmonary rehabilitation, to improve patients' functionality in outpatients settings.

Summary

The Studies conducted within the scope of this research contributed to clarify the adequacy of the outcome measures most currently used to assess patients with AECOPD treated on an outpatient basis, as well as to establish the time course, pattern of recovery and interactions of several outcomes and outcome measures during these events. This chapter presented an integrated discussion of the findings of the different Studies in the light of the most recent literature in the field, the limitations identified through the course of the reserach and the implications of the results achieved for future clinical and research practices.

Chapter V

Conclusion

_____

General conclusion

This research work contributes with new evidence on the measurement properties of outcome measures used to assess patients with AECOPD treated on an outpatient basis and on the time course of their recovery during these events. It has been found that few outcome measures with sound-evidence measurement properties (i.e., reliability, validity and responsiveness) exist to assess patients with AECOPD (Systematic review). Computerised respiratory sounds, namely the number of crackles acquired from the posterior region, were found to be reliable and valid to assess patients with COPD (Study I) and minimal detectable and clinical differences have been established for this and other respiratory outcome measures (Study II). During the course of an AECOPD, PROMs, such as the CAT, the mMRC and the numerical rating scale to assess cough, significantly improved after 7 to 15 days of the AECOPD onset (Studies III and V), as well as some clinical measures, such as the SpO_2, FEV_1%predicted, 5STS test and computerised inspiratory wheezes (Studies III and IV). On the other hand, quadriceps muscle strength, computerised inspiratory crackles and dyspnoea at rest, assessed with the MBS, only evidenced significant improvements after 45 days of the onset of the AECOPD (Studies III, IV and V). Except for SpO_2 and FEV_1%predicted, the recovery from an AECOPD treated on an outpatient basis was negatively affected by patients' low and high body mass index, increased dyspnoea, previous exacerbations, and severe comorbidities assessed at the onset of the AECOPD (Study III). Thus, whilst oximetry and lung function may be potentially useful to monitor recovery from AECOPD, a comprehensive assessment is needed to determine patients' progression and personalise interventions. Further research with standardised methodologies, larger samples and longitudinal pre-post exacerbation designs is warranted to consolidate these preliminary findings and increase the scope of knowledge on the time course of AECOPD treated on an outpatient basis.

References

_____

Aaron, S., Vandemheen, K., Clinch, J., Ahuja, J., Brison, R., Dickinson, G., & Hebert, P. (2002). Measurement of short-term changes in dyspnea and disease-specific quality of life following an acute COPD exacerbation. *Chest, 121*(3), 688-696.

Adams, S., Melo, J., Luther, M., & Anzueto, A. (2000). Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. *Chest, 117*(5), 1345-1352.

Adeloye, D., Chua, S., Lee, C., Basquill, C., Papana, A., Theodoratou, E., . . . Rudan, I. (2015). Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *Journal of Global Health, 5*(2), 020415.

Alcazar, J., Losa-Reyna, J., Rodriguez-Lopez, C., Alfaro-Acha, A., Rodriguez-Manas, L., Ara, I., . . . Alegre, L. (2018). The sit-to-stand muscle power test: An easy, inexpensive and portable procedure to assess muscle power in older people. *Experimental Gerontology, 112*, 38-43.

Alma, H., de Jong, C., Tsiligianni, I., Sanderman, R., Kocks, J., & van der Molen, T. (2018). Clinically relevant differences in COPD health status: systematic review and triangulation. *European Respiratory Journal, 52*(3), 1800412.

Anderson, K., Aitken, S., Carter, R., MacLeod, J. E., & Moran, F. (1990). Variation of breath sound and airway caliber induced by histamine challenge. *American Review of Respiratory Disease, 141*(5 Pt 1), 1147-1150.

Anzueto, A. (2010). Impact of exacerbations on COPD. *European Respiratory Review, 19*(116), 113-118.

Araújo, A. (2016). *11º Relatório - Prevenir as doenças respiratórias, acompanhar e reabilitar os doentes.* Lisboa: Observatório Nacional das Doenças Respiratórias.

Bartels, B., de Groot, J., & Terwee, C. (2013). The six-minute walk test in chronic pediatric conditions: a systematic review of measurement properties. *Physical Therapy, 93*(4), 529-541.

Boer, L., Bischoff, E., Borgijink, X., Vercoulen, J., Akkermans, R., Kerstjens, H., . . . Schermer, T. (2018). 'Exacerbation-free time'to assess the impact of exacerbations in patients with chronic obstructive pulmonary disease (COPD): a prospective observational study. *NPJ Primary Care Respiratory Medicine, 28*(1), 12.

Bohadana, A., Izbicki, G., & Kraman, S. (2014). Fundamentals of lung auscultation. *New England Journal of Medicine, 370*(8), 744-751.

Bui, K., Nyberg, A., Maltais, F., & Saey, D. (2017). Functional Tests in Chronic Obstructive Pulmonary Disease, Part 2: Measurement Properties. *Annals of the American Thoracic Society, 14*(5), 785-794.

Celli, B., & MacNee, W. (2004). Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *European Respiratory Journal, 23*(6), 932-946.

Celli, B., Decramer, M., Wedzicha, J., Wilson, K., Agusti, A., Criner, G., . . . ZuWallack, R. (2015). An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. *European Respiratory Journal, 45*(4), 879-905.

Chabot, F., Zysman, M., Perrin, J., Mercy, M., Guillaumot, A., Gomez, E., . . . Chaouat, A. (2014). Impact of COPD: from disability to exacerbations. *La Presse Medicale, 43*(12 Pt 1), 1353-1358.

Cook, C., Paul, M., & Wyatt, V. (2014). Potential caveats in the use of interpretability of outcome measures. *Physical Therapy Reviews, 19*(3), 158-162.

Coster, W. (2013). Making the Best Match: Selecting Outcome Measures for Clinical Trials and Outcome Studies. *American Journal of Occupational Therapy, 67*(2), 162-170.

Crisafulli, E., & Clini, E. (2010). Measures of dyspnea in pulmonary rehabilitation. *Multidisciplinary Respiratory Medicine, 5*(3), 202-210.

Crook, S., Busching, G., Schultz, K., Lehbert, N., Jelusic, D., Keusch, S., . . . Frei, A. (2017). A multicentre validation of the 1-min sit-to-stand test in patients with COPD. *European Respiratory Journal, 49*(3), 1601871.

Crooks, M., den Brinker, A., Hayman, Y., Williamson, J., Innes, A., Wright, C., . . . Morice, A. (2017). Continuous Cough Monitoring Using Ambient Sound Recording During Convalescence from a COPD Exacerbation. *Lung, 195*(3), 289-294.

de Vet, H., Terwee, C., Ostelo, R., Beckerman, H., Knol, D., & Bouter, L. (2006). Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. *Health and Quality of Life Outcomes, 4*(54), 1-5.

Direção-Geral da Saúde. (2015). *Plano nacional de saúde: revisão e extensão a 2020*. Retrieved from http://www2.insa.pt/sites/INSA/Portugues/ComInf/Noticias/Documents/2015/Junho/PNS-2020.pdf.

Direção-Geral da Saúde. (2016). *PORTUGAL: Doenças Respiratórias em Números – 2015*. Lisboa: Direção-Geral da Saúde. Retrieved from https://www.dgs.pt/estatisticas-de-saude/estatisticas-de-saude/publicacoes/portugal-doencas-respiratorias-em-numeros-20151.aspx.

Direção-Geral da Saúde. (2017). *Programa Nacional para as Doenças Respiratórias 2017*. Lisboa: Direção-Geral da Saúde. Retrieved from https://www.dgs.pt/portal-da-estatistica-da-saude/diretorio-de-informacao/diretorio-de-informacao/por-serie-880758-pdf.aspx?v=11736b14-73e6-4b34-a8e8-d22502108547.

Donaldson, G., Wilkinson, T., Hurst, J., Perera, W., & Wedzicha, J. (2005). Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 171*(5), 446-452.

Donohue, J. (2005). Minimal clinically important differences in COPD lung function. *COPD, 2*(1), 111-124.

Esteban, C., Quintana, J., Garcia-Gutierrez, S., Anton-Ladislao, A., Gonzalez, N., Baré, M., . . . Rivas-Ruiz, F. (2016). Determinants of change in physical activity during moderate-to-severe COPD exacerbation. *International Journal of Chronic Obstructive Pulmonary Disease, 11*, 251-261.

European Respiratory Society. (2013). The economic burden of lung disease. In G. Gibson, R. Loddenkemper, Y. Sibille & B. Lundbäck (Eds.), *The European Lung White Book* (pp. 16-27). Sheffield: European Respiratory Society.

Evensen, A. (2010). Management of COPD exacerbations. *American Family Physician, 81*(5), 607-613.

Feliz-Rodriguez, D., Zudaire, S., Carpio, C., Martinez, E., Gomez-Mendieta, A., Santiago, A., . . . Garcia-Rio, F. (2013). Evolution of the COPD Assessment Test score during chronic obstructive pulmonary disease exacerbations: determinants and prognostic value. *Canadian Respiratory Journal, 20*(5), e92-97.

Fernandez-Granero, M., Sanchez-Morillo, D., & Leon-Jimenez, A. (2018). An artificial intelligence approach to early predict symptom-based exacerbations of COPD. *Biotechnology & Biotechnological Equipment, 32*(3), 778-784.

Fernandez-Villar, A., Represas-Represas, C., Mouronte-Roibas, C., Ramos-Hernandez, C., Priegue-Carrera, A., Fernandez-Garcia, S., & Lopez-Campos, J. (2018). Reliability and usefulness of spirometry performed during admission for COPD exacerbation. *PLoS One, 13*(3), e0194983.

Forum of International Respiratory Societies. (2013). Respiratory diesease in the world: Realities of Today - Opportunities for Tomorrow. (pp. 1-34). Sheffield: European Respiratory Society.

Gavriely, N., Nissan, M., Cugell, D. W., & Rubin, A. H. (1994). Respiratory health screening using pulmonary function tests and lung sound analysis. *European Respiratory Journal, 7*(1), 35-42.

GBD 2015 DALYs and HALE Collaborators. (2016). Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet, 388*(10053), 1603-1658.

Goldberg, A., Chavis, M., Watkins, J., & Wilson, T. (2012). The five-times-sit-to-stand test: validity, reliability and detectable change in older females. *Aging Clinical and Experimental Research, 24*(4), 339-344.

Guarascio, A., Ray, S., Finch, C., & Self, T. (2013). The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *ClinicoEconomics and Outcomes Research, 5*, 235-245.

Guerra, B., Gaveikaite, V., Bianchi, C., & Puhan, M. (2017). Prediction models for exacerbations in patients with COPD. *European Respiratory Review, 26*(143), 160061.

Hadjileontiadis, L. (2018). Continuous wavelet transform and higher-order spectrum: combinatory potentialities in breath sound analysis and electroencephalogram-based pain characterization. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, 376*(2126), 20170249.

Hadjileontiadis, L. (2018). Current Techniques for Breath Sound Analysis. In K. Priftis, L. Hadjileontiadis & M. Everard (Eds.), *Breath Sounds - From Basic Science to Clinical Practice* (pp. 139-177). Switzerland: Springer International Publishing.

Halpin, D., Miravitlles, M., Metzdorf, N., & Celli, B. (2017). Impact and prevention of severe exacerbations of COPD: a review of the evidence. *International Journal of Chronic Obstructive Pulmonary Disease, 12*, 2891-2908.

Hurst, J., Vestbo, J., Anzueto, A., Locantore, N., Mullerova, H., Tal-Singer, R., . . . Wedzicha, J. (2010). Susceptibility to exacerbation in chronic obstructive pulmonary disease. *New England Journal of Medicine, 363*(12), 1128-1138.

Ioannidis, J., Greenland, S., Hlatky, M., Khoury, M., Macleod, M., Moher, D., . . . Tibshirani, R. (2014). Increasing value and reducing waste in research design, conduct, and analysis. *Lancet, 383*(9912), 166-175.

Jácome, C., & Marques, A. (2015). Computerized Respiratory Sounds Are a Reliable Marker in Subjects With COPD. *Respiratory Care, 60*(9), 1264-1275.

Jácome, C., & Marques, A. (2017). Computerized Respiratory Sounds: Novel Outcomes for Pulmonary Rehabilitation in COPD. *Respiratory Care, 62*(2), 199-208.

Jácome, C., Oliveira, A., & Marques, A. (2017). Computerized respiratory sounds: a comparison between patients with stable and exacerbated COPD. *The Clinical Respiratory Journal, 11*(5), 612-620.

Jaeschke, R., Singer, J., & Guyatt, G. H. (1989). Measurement of health status. Ascertaining the minimal clinically important difference. *Controlled Clinical Trials, 10*(4), 407-415.

Jerosch-Herold, C. (2005). An Evidence-Based Approach to Choosing Outcome Measures: A Checklist for the Critical Appraisal of Validity, Reliability and Responsiveness Studies. *British Journal of Occupational Therapy, 68*(8), 347-353.

Jones, P., Beeh, K., Chapman, K., Decramer, M., Mahler, D., & Wedzicha, J. (2014). Minimal clinically important differences in pharmacological trials. *American Journal of Respiratory and Critical Care Medicine, 189*(3), 250-255.

Jones, S., Kon, S., Canavan, J., Patel, M., Clark, A., Nolan, C., . . . Man, W. (2013). The five-repetition sit-to-stand test as a functional outcome measure in COPD. *Thorax, 68*(11), 1015-1020.

Kahya, Y. (2018). Breath Sound Recording. In K. Priftis, L. Hadjileontiadis & M. Everard (Eds.), *Breath Sounds - From Basic Science to Clinical Practice* (pp. 105-118). Switzerland: Springer International Publishing.

Kerkhof, M., Freeman, D., Jones, R., Chisholm, A., & Price, D. (2015). Predicting frequent COPD exacerbations using primary care data. *International Journal of Chronic Obstructive Pulmonary Disease, 10*, 2439-2450.

Kessler, R., Ståhl, E., Vogelmeier, C., Haughney, J., Trudeau, E., Löfdahl, C., & Partridge, M. (2006). Patient Understanding, Detection, and Experience of COPD Exacerbations: An Observational, Interview-Based Study. *Chest, 130*(1), 133-142.

Kim, V., & Aaron, S. (2018). What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement. *European Respiratory Journal, 52*(5), 1801261.

Kiyokawa, H., & Pasterkamp, H. (2002). Volume-dependent variations of regional lung sound, amplitude, and phase. *Journal of Applied Physiology, 93*(3), 1030-1038.

Kon, S., Canavan, J., Jones, S., Nolan, C., Clark, A., Dickson, M., . . . Man, W. (2014). Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. *Lancet Respiratory Medicine, 2*(3), 195-203.

Korpershoek, Y., Vervoort, S., Nijssen, L., Trappenburg, J., & Schuurmans, M. (2016). Factors influencing exacerbation-related self-management in patients with COPD: a qualitative study. *International Journal of Chronic Obstructive Pulmonary Disease, 11*, 2977-2990.

Koutsokera, A., Kiropoulos, T., Nikoulis, D., Daniil, Z., Tsolaki, V., Tanou, K., . . . Kostikas, K. (2009). Clinical, functional and biochemical changes during recovery from COPD exacerbations. *Respiratory Medicine, 103*(6), 919-926.

Laue, J., Reierth, E., & Melbye, H. (2015). When should acute exacerbations of COPD be treated with systemic corticosteroids and antibiotics in primary care: a systematic review of current COPD guidelines. *NPJ Primary Care Respiratory Medicine, 25*, 15002.

Leuppi, J., Dieterle, T., Wildeisen, I., Martina, B., Tamm, M., Koch, G., . . . Leimenstoll, B. (2006). Can airway obstruction be estimated by lung auscultation in an emergency room setting? *Respiratory Medicine, 100*(2), 279-285.

Macfarlane, J. T., Colville, A., Guion, A., Macfarlane, R. M., & Rose, D. H. (1993). Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet, 341*(8844), 511-514.

Makizako, H., Shimada, H., Doi, T., Tsutsumimoto, K., Nakakubo, S., Hotta, R., & Suzuki, T. (2017). Predictive Cutoff Values of the Five-Times Sit-to-Stand Test and the Timed "Up & Go" Test for Disability Incidence in Older People Dwelling in the Community. *Physical Therapy, 97*(4), 417-424.

Malmberg, L. P., Sovijarvi, A. R., Paajanen, E., Piirila, P., Haahtela, T., & Katila, T. (1994). Changes in frequency spectra of breath sounds during histamine challenge test in adult asthmatics and healthy control subjects. *Chest, 105*(1), 122-131.

Malmberg, L., Pesu, L., & Sovijärvi, A. (1995). Significant differences in flow standardised breath sound spectra in patients with chronic obstructive pulmonary disease, stable asthma, and healthy lungs. *Thorax, 50*(12), 1285-1291.

McCrory, D., & Brown, C. (2002). Anti-cholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(4), Art. No.: CD003900.

McNulty, W., & Usmani, O. (2014). Techniques of assessing small airways dysfunction. *European Clinical Respiratory Journal, 1*(1), 25898.

Mesquita, R., Donaria, L., Genz, I., Pitta, F., & Probst, V. (2013). Respiratory muscle strength during and after hospitalization for COPD exacerbation. *Respiratory Care, 58*(12), 2142-2149.

Miravitlles, M., Anzueto, A., Legnani, D., Forstmeier, L., & Fargel, M. (2007). Patient's perception of exacerbations of COPD-the PERCEIVE study. *Respiratory Medicine, 101*(3), 453-460.

Miravitlles, M., Murio, C., & Guerrero, T. (2001). Factors associated with relapse after ambulatory treatment of acute exacerbations of chronic bronchitis. DAFNE Study Group. *European Respiratory Journal, 17*(5), 928-933.

Mokkink, L., Prinsen, C., Bouter, L., Vet, H., & Terwee, C. (2016). The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) and how to select an outcome measurement instrument. *Brazilian Journal of Physical Therapy, 20*(2), 105-113.

Mokkink, L., Terwee, C., Patrick, D., Alonso, J., Stratford, P., Knol, D., . . . de Vet, H. (2010). The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *Journal of Clinical Epidemiology, 63*(7), 737-745.

Morice, A., Millqvist, E., Belvisi, M., Bieksiene, K., Birring, S., Chung, K., . . . Smith, J. (2014). Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *European Respiratory Journal, 44*(5), 1132-1148.

Morita, A., Bisca, G., Machado, F., Hernandes, N., Pitta, F., & Probst, V. (2018). Best Protocol for the Sit-to-Stand Test in Subjects With COPD. *Respiratory Care, 63*(8), 1040-1049.

Mukerji, S., Shahpuri, B., Clayton-Smith, B., Smith, N., Armstrong, P., Hardy, M., . . . Marsh, E. (2015). Intravenous magnesium sulphate as an adjuvant therapy in acute exacerbations of chronic obstructive pulmonary disease: a single centre, randomised, double-blinded, parallel group, placebo-controlled trial: a pilot study. *New Zealand Medical Journal, 128*(1425), 34-42.

National Clinical Guideline Centre. (2010). Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Institute for Health and Clinical Excellence: Guidance.

Niewoehner, D., Collins, D., & Erbland, M. (2000). Relation of FEV(1) to clinical outcomes during exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *American Journal of Respiratory and Critical Care Medicine, 161*(4 Pt 1), 1201-1205.

Nishimura, K., Nakamura, S., Kusunose, M., Nakayasu, K., Sanda, R., Hasegawa, Y., & Oga, T. (2018). Comparison of patient-reported outcomes during acute exacerbations of chronic obstructive pulmonary disease. *BMJ Open Respiratory Research, 5*(1), e000305.

Oliveira, A., Munha, J., Bugalho, A., Guimaraes, M., Reis, G., & Marques, A. (2017). Identification and assessment of COPD exacerbations. *Pulmonology, 24*(1), 42-47.

Parker, C., Voduc, N., Aaron, S., Webb, K., & O'Donnell, D. (2005). Physiological changes during symptom recovery from moderate exacerbations of COPD. *European Respiratory Journal, 26*(3), 420-428.

Pasterkamp, H., Kraman, S., & Wodicka, G. (1997). Respiratory sounds. Advances beyond the stethoscope. *American Journal of Respiratory and Critical Care Medicine, 156*(3 Pt 1), 974-987.

Patel, J., Nagar, S., & Dalal, A. (2014). Indirect costs in chronic obstructive pulmonary disease: a review of the economic burden on employers and individuals in the United States. *International Journal of Chronic Obstructive Pulmonary Disease, 9*, 289-300.

Piirila, P., & Sovijarvi, A. (1995). Crackles: recording, analysis and clinical significance. *European Respiratory Journal, 8*(12), 2139-2148.

Pramono, R., Bowyer, S., & Rodriguez-Villegas, E. (2017). Automatic adventitious respiratory sound analysis: A systematic review. *PLoS One, 12*(5), e0177926.

Price, D., Freeman, D., Cleland, J., Kaplan, A., & Cerasoli, F. (2011). Earlier diagnosis and earlier treatment of COPD in primary care. *Primary Care Respiratory Journal, 20*(1), 15-22.

Puhan, M., Gimeno-Santos, E., Cates, C., & Troosters, T. (2016). Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews, 12*, Art. No.: CD005305.

Quanjer, P. H., Tammeling, G. J., Cotes, J. E., Pedersen, O. F., Peslin, R., & Yernault, J. C. (1993). Lung volumes and forced ventilatory flows. *European Respiratory Journal, 6*(Suppl 16), 5-40.

Reyes, B., Olvera-Montes, N., Charleston-Villalobos, S., González-Camarena, R., Mejía-Ávila, M., & Aljama-Corrales, T. (2018). A Smartphone-Based System for Automated Bedside Detection of Crackle Sounds in Diffuse Interstitial Pneumonia Patients. *Sensors, 18*(11), 3813.

Ries, A. (2005). Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. *COPD, 2*(1), 105-110.

Sanchez Morillo, D., Astorga Moreno, S., Fernandez Granero, M., & Leon Jimenez, A. (2013). Computerized analysis of respiratory sounds during COPD exacerbations. *Computers in Biology and Medicine, 43*(7), 914-921.

Seemungal, T., Donaldson, G., Bhowmik, A., Jeffries, D., & Wedzicha, J. (2000). Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 161*(5), 1608-1613.

Seemungal, T., Donaldson, G., Paul, E., Bestall, J., Jeffries, D., & Wedzicha, J. (1998). Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 157*(5 Pt 1), 1418-1422.

Shin, S., Ro du, H., Lee, O., Oh, J., & Kim, S. (2012). Within-day reliability of shoulder range of motion measurement with a smartphone. *Manual Therapy, 17*(4), 298-304.

Sovijärvi, A., Dalmasso, F., Vanderschoot, J., Malmberg, L., Righini, G., & Stoneman, S. (2000). Definition of terms for applications of respiratory sounds. *European Respiratory Review, 10*(77), 597-610.

Spence, D., Bentley, S., Evans, D., & Morgan, M. (1992). Effect of methacholine induced bronchoconstriction on the spectral characteristics of breath sounds in asthma. *Thorax, 47*(9), 680-683.

Spencer, S., Calverley, P., Sherwood Burge, P., & Jones, P. (2001). Health status deterioration in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 163*(1), 122-128.

Spruit, M., 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.

Terwee, C., Bot, S., de Boer, M., van der Windt, D., Knol, D., Dekker, J., . . . de Vet, H. (2007). Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of Clinical Epidemiology, 60*(1), 34-42.

Terwee, C., Mokkink, L., Knol, D., Ostelo, R., Bouter, L., & de Vet, H. (2012). Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Quality of Life Research, 21*(4), 651-657.

The Global Initiative for Chronic Obstructive Lung Disease. (2019). Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease - 2019 Report: The Global Initiative for Chronic Obstructive Lung Disease, Inc.

Toy, E., Gallagher, K., Stanley, E., Swensen, A., & Duh, M. (2010). The economic impact of exacerbations of chronic obstructive pulmonary disease and exacerbation definition: a review. *COPD, 7*(3), 214-228.

Tsai, C., Hodder, R., Page, J., Cydulka, R., Rowe, B., & Camargo, C. A. (2008). The short-form chronic respiratory disease questionnaire was a valid, reliable, and responsive quality-of-life instrument in acute exacerbations of chronic obstructive pulmonary disease. *Journal of Clinical Epidemiology, 61*(5), 489-497.

Viniol, C., & Vogelmeier, C. (2018). Exacerbations of COPD. *European Respiratory Review, 27*(147), 170103.

Vlemincx, E., Van Diest, I., & Van den Bergh, O. (2012). Imposing respiratory variability patterns. *Applied Psychophysiology and Biofeedback, 37*(3), 153-160.

Walters, J., Tan, D., White, C., Gibson, P., Wood-Baker, R., & Walters, E. (2014). Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(9), Art. No.: CD001288.

Wedzicha, J., & Donaldson, G. (2003). Exacerbations of chronic obstructive pulmonary disease. *Respiratory Care, 48*(12), 1204-1213.

Wedzicha, J., Miravitlles, M., Hurst, J., Calverley, P., Albert, R., Anzueto, A., . . . Krishnan, J. (2017). Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *European Respiratory Journal, 49*(3), 1600791.

Weldam, S., Schuurmans, M., Liu, R., & Lammers, J. (2013). Evaluation of Quality of Life instruments for use in COPD care and research: a systematic review. *International Journal of Nursing Studies, 50*(5), 688-707.

Wilkinson, T., Donaldson, G., Hurst, J., Seemungal, T., & Wedzicha, J. (2004). Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 169*(12), 1298-1303.

Wilson, K., Krishnan, J., Sliwinski, P., Criner, G., Miravitlles, M., Hurst, J., . . . Wedzicha, J. (2018). Pulmonary rehabilitation for patients with COPD during and after an exacerbation-related hospitalisation: back to the future? *European Respiratory Journal, 51*(1), 1702577.

World Health Organization. (2007). *Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach*. Geneva: World Health Organization.

World Health Organization. (2008). *2008–2013 Action plan for the global strategy for the prevention and control of non communicable diseases.* Geneva: World Health Organization.

Zhou, A., Zhou, Z., Peng, Y., Zhao, Y., Duan, J., & Chen, P. (2018). The role of CAT in evaluating the response to treatment of patients with AECOPD. *International Journal of Chronic Obstructive Pulmonary Disease, 13*, 2849-2858.

Appendices

_____

Appendix 1. List of publications within the scope of the Thesis

_____

List of publications

Publications in Peer-Reviewed Journals

Citations: 0
[IF: 1.731]
RESPIRATORY
SYSTEM: Q4

Oliveira A, Marques A. Understanding symptoms variability in outpatients with AECOPD. Pulmonology 24(6): 357-360. doi: https://doi.org/10.1016/j.pulmoe.2018.09.007
Letter to the Editor

Citations: 0
[IF: 2.604]
REHABILITATION:
Q3

Oliveira A, Machado A, Marques A. (2018) Minimal important and detectable differences of respiratory measures in AECOPD. COPD 2018; 15(5): 479-488 doi: 10.1080/15412555.2018.1537366

Citations: 0
[IF: 2.917]
RESPIRATORY
SYSTEM: Q2

Oliveira A, Afreixo V, Marques A. (2018) Enhancing our understanding of the time course of acute exacerbations of COPD managed on an outpatient basis. International Journal of Chronic Obstructive Pulmonary Disease 13: 3759-37663. doi: https://doi.org/10.2147/COPD.S175890

Citations: 2
[IF: 3.230]
RESPIRATORY
SYSTEM: Q2

Oliveira A, Rodrigues J, Marques A. (2018) Enhancing our understanding of computerised adventitious respiratory sounds in different COPD phases and healthy people. Respiratory Medicine 138: 57-63. doi: 10.1016/j.rmed.2018.03.023.

Citations: 1
[IF: 2.356]
RESPIRATORY
SYSTEM: Q2

Oliveira A, Lage S, Rodrigues J, Marques A. (2018) Reliability, validity, and minimal detectable change of computerised respiratory sounds in patients with Chronic Obstructive Pulmonary Disease. The Clinical Respiratory Journal 12(5): 1838-48. doi: 10.1111/crj.12745

Citations: 1
[IF: 2.764]
REHABILITATION:
Q1

Oliveira A., Marques A. (2018) Outcome measures used in pulmonary rehabilitation in patients with Acute Exacerbation of COPD – a systematic review. Physical Therapy. 98(3):191-204. doi: 10.1093/ptj/pzx122
Editor's Choice for free access publication

Invited publications

Citations: 0

Oliveira A, Marques A, (2018) Instrumentos de de avaliação nas exacerbações da Doença Pulmonar Obstrutiva Crónica. Newsletter of Linde AirCare Center

Abstracts in Conference Proceedings

[IF: 12.242]

Oliveira A, Afreixo V, Valente C, Andrade L, Marques A, (2018) "Enhancing the understanding of the time course of AECOPD" European Respiratory Journal; 52: Suppl. 62, PA3837. 28th European Respiratory Society (ERS) International Congress, 14-19 September 2018, Paris, France (poster discussion)

[IF: Not available]

Oliveira A, Lage S, Rodrigues, J, Ferreira D, Neves J, Marques A. Criterion, construct and predictive validity of computerised respiratory sounds in COPD. Abstract book of the International Primary Care Respiratory Group (IPCRG) 9th World Conference & 1st Ibero-American Conference. Applied Clinical Research &Implementation Science. pp. 30. 31 May-2 June, Porto, Portugal (oral communication)

[IF: 1.843]

Oliveira A, Rebelo P, Andrade L, Valente C, Marques A (2018) "Computerised respiratory sounds during acute exacerbations of Chronic Obstructive Pulmonary Disease" BMC Health Services Research; 18(Suppl. 2):684, pp. 16. 4th IPLeiria International Health Congress, 11-12 May, Leiria, Portugal (oral communication)

[IF: 10.569]

Oliveira A, Marques A (2017) "Outcome measures used in pulmonary rehabilitation of Acute Exacerbation of COPD" European Respiratory Journal; 50: Suppl. 61, PA2509. 27th European Respiratory Society (ERS) International Congress, 9-13 September 2017, Milan, Italy (thematic poster)

[IF: 10.569]

Oliveira A, Valente C, Marques A (2017) "Measurement properties of muscle strength tests in AECOPD" European Respiratory Journal; 50: Suppl. 61, PA4706. 27th European Respiratory Society (ERS) International Congress, 9-13 September 2017, Milan, Italy (poster discussion)

[IF: 10.569]

Oliveira A, Andrade L, Marques A (2017) "Minimal clinically important difference and predictive validity of the mMRC and mBorg in acute exacerbations of COPD" European Respiratory Journal; 50: Suppl. 61, PA4705. 27th European Respiratory Society (ERS) International Congress, 9-13 September 2017, Milan, Italy (poster discussion).

[IF: Not available]

Oliveira A, Lage S, Neves J, Marques A (2017) "Reliability and validity of computerised respiratory sounds in COPD" Proceeding of the 42nd Annual Conference of the International Lung Sound Association, 182:12 ISBN: 978-82-8378-003-1. 42nd Annual Conference of the International Lung Sound Association, 15-16 September 2017, Tromson, Norway (oral communication)

Communications by invitation

May, 31 2018   Oliveira, A. Lung auscultation properties in patients with stable & exacerbated COPD. International Primary Care Respiratory Group (IPCRG) 9th World Conference & 1st Ibero-American Conference "The value of lung sounds in the assessment of patients with respiratory conditions", Porto, Portugal

May, 26 2017   Oliveira, A. Incidence and prevalence of respiratory infections in patients with COPD and its personal, social and economic impacts. 2ª Jornada Dr. Egas Moniz "Prevenção e controlo da infeção", Avanca, Portugal

April, 8 2017   Oliveira, A. Assessment of respiratory rehabilitation in acute conditions. Are we using the proper measures? 2ª Jornada de Estudo do CNFt'2017 "Fisioterapia Cardiorrespiratória: Contributos para uma prática efetiva". Aveiro, Portugal

Appendix 2. Ethics approval letters

_____

CENTRO HOSPITALAR DO BAIXO VOUGA, E.P.E. / AVEIRO

Avenida Artur Ravara – 3814-501 AVEIRO
Tel. 234 378 300 – Fax 234 378 395
sec-geral@chbv.min-saude.pt
Matrícula na Conservatória do Registo Comercial
de Aveiro
Capital Social 40.284.651 €
Pessoa Colectiva nº 510 123 210

Exma. Senhora

Ana Luísa Araújo Oliveira
Rua Central do Bairro, nº 62
4760-066 Famalicão

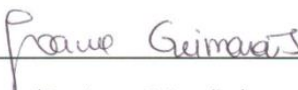| S/ Ref.ª	S/ Comunicação de	N/ Ref.ª	Aveiro, 11-11-2015
		13 NOV'15 14:40 065682	

ASSUNTO: Resposta ao V/ Pedido de autorização de realização de estudo no CHBV, E.P.E.

Em resposta à V/ solicitação para realização de estudo no âmbito de doutoramento em Fisioterapia da Faculdade de Desporto da Universidade do Porto, subordinado ao tema "Sons respiratórios computorizados – Uma medida emergente na avaliação de doentes com Doença Pulmonar Obstrutiva Crónica", vimos, pelo presente, informar que por deliberação do Conselho de Administração, nesta data, se encontra autorizado o pedido formulado.

Quando concluído, deverá ser enviado um relatório final ao Serviço de Investigação e Formação do CHBV, E.P.E.

Com os melhores cumprimentos,

A Diretora do Serviço de Investigação e Formação

(Dra. Joana Guimarães)

CHBV – 347

CONSELHO DE ÉTICA

PROCESSO N.º 8/2015.
REQUERENTE: Doutora Alda Sofia Pires de Dias Marques.
DESIGNAÇÃO DO PROJETO: "Sons respiratórios computorizados – Uma medida emergente na avaliação de doentes com Doença Pulmonar Obstrutiva Crónica".
INVESTIGADOR RESPONSÁVEL: Doutora Alda Sofia Pires de Dias Marques.
RELATOR: Professor António José Arsénia Nogueira.
RELATORES ADJUNTOS: Professor Armando Pinho, Professor A. Rocha Andrade, Professor Paula Cristina Pereira e Professor Jorge Arroteia.

PARECER

A. Fundamentação

1. O estudo submetido a parecer da Comissão Permanente do Conselho de Ética e Deontologia tem como requerente uma Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro, Diretora de Curso da Licenciatura em Fisioterapia. Com este projeto, pretende explorar a utilização de sons respiratórios computorizados na avaliação de doentes com Doença Pulmonar Obstrutiva Crónica

2. O estudo apresentado tem como objetivos:

2.1. Caracterizar os sons respiratórios computorizados em pacientes com DPOC estável, exacerbação de DPOC e população saudável

2.2. Estabelecer as características psicométricas dos sons respiratórios computorizados em doentes

3. Para se alcançarem os objetivos mencionados em 2.1. e 2.2. recorrer-se-á ao recrutamento de 30-50 indivíduos pertencentes a três grupos distintos: indivíduos saudáveis, indivíduos com DPOC e de DPOC e população saudável

4. Segundo está declarado na documentação apresentada:

4.1. Os participantes serão previamente informados de todos os procedimentos, a eles cabendo a decisão de participar ou não no estudo. Os que decidam participar darão por escrito o seu consentimento informado, podendo a qualquer momento desistir;

4.2. Os dados recolhidos nos questionários e nas folhas de registo serão codificados sem identificação

4.3. As declarações de consentimento informado serão entregues à investigadora principal e guardados à parte dos formulários onde se fez o registo dos dados, de modo a proteger a confidencialidade de todos os registos e garantir o anonimato da informação a ser analisada;

4.4. Está previsto que toda a documentação com informação sensível (declarações de consentimento e registo dos dados recolhidos) será destruída (queimada ou triturada) 5 anos após a realização do estudo

B. Sugestões e recomendações

Concluída a leitura e análise de todos os documentos que descrevem, fundamentam e explicam os objetivos, métodos e procedimentos que a investigação pretende seguir:
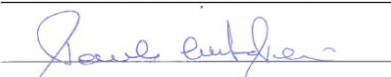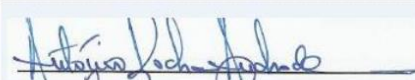
CONSELHO DE ÉTICA

Recomenda-se, de modo particular, que se proceda ao esclarecimento prévio de todos os participantes e se obtenha o seu consentimento informado de acordo com os procedimentos.
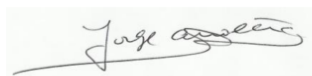
C. Conclusão

De acordo com o anteriormente assinalado e os princípios seguidos pelo CED é emitido o seguinte parecer:

1. a Comissão Permanente do Conselho de Ética, constituída pelos ora Relatores, após a apreciação conjunta da documentação recebida e atendendo a que os procedimentos descritos no estudo de investigação apresentado fundamentam e explicam os objetivos, métodos e procedimentos que a investigação pretende seguir;

2. asseguram a não utilização de qualquer método invasivo e asseguram que os participantes serão oportunamente informados e esclarecidos sobre as condições em que vão decorrer as observações e recolha de dados;

3. garantem que os dados recolhidos serão tratados de maneira a permanecerem confidenciais e anónimos;

4. Cumpridos os procedimentos descritos, respeitadas as recomendações e assegurada a proteção do anonimato dos dados recolhidos, entende-se que ficam salvaguardados os direitos dos participantes e se verifica a conformidade do estudo com os princípios e as normas éticas aplicáveis. Por ser assim, a Comissão Permanente do CED, dá parecer favorável, por unanimidade, na condição de que a obtenção dos consentimentos informados seja feita por termo, recolhida em folha separada, no qual devem constar as assinaturas do participante e do responsável pelo projeto à realização do estudo "Sons respiratórios computorizados – Uma medida emergente na avaliação de doentes com Doença Pulmonar Obstrutiva Crónica", desde que a obtenção dos consentimentos informados seja feita por termo, recolhida em folha separada, no qual deve constar a assinatura do participante e a assinatura do responsável pelo projeto.

Os Relatores:

CONSELHO DE ÉTICA

(assinatura)

_____

D. Decisão

Submetido ao CED o parecer da sua Comissão Permanente, este Conselho em sua reunião plenária de 13 de Abril de 2016, por entender que ficam salvaguardadas as exigências éticas e os princípios da justiça e da autonomia e bem-estar dos participantes, concorda por unanimidade com o mesmo, em razão do que, verificada a condição referida no parecer da CP-CED, dá parecer favorável à realização do projeto intitulado: "Sons respiratórios computorizados – Uma medida emergente na avaliação de doentes com Doença Pulmonar Obstrutiva Crónica".
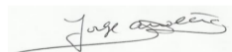
Aveiro, 13 de Abril de 2016.

Conselho de ética e Deontologia da Universidade de Aveiro.

Presidente: _____

Vice - Presidente: _____

Secretário: _____

De: **Alda Marques** amarques@ua.pt 📎
Assunto: FW: Estudo Clínico intitulado "GENIAL - Marcadores genéticos e clínicos na trajectória do DPOC
Data: 18 de julho de 2017, 15:22
Para: **Ana Machado** filipamachado@ua.pt, **Cátia Paixão** catia.paixao@ua.pt, **Hélder Melro** heldermelro@ua.pt, **Ana Oliveira** alao@ua.pt, **Sara Miranda** sara.souto@ua.pt

From: hdff [mailto:hdff@hdfigueira.min-saude.pt]
Sent: 18 de julho de 2017 10:59
To: Alda Marques <amarques@ua.pt>
Cc: Maria Manuela Lourenço Lopes <manuelalopes@hdfigueira.min-saude.pt>; Direção Clinica <dir.clinica@hdfigueira.min-saude.pt>
Subject: Estudo Clínico intitulado "GENIAL - Marcadores genéticos e clínicos na trajectória do DPOC

Dra. Alda Pires de Dias Marques,

Encarrega-me o Dr. José Albino e Silva, Presidente do Conselho de Administração de informar que o Conselho de Administração deliberou aprovar o pedido apresentado para a realização do Estudo Clínico intitulado "GENIAL – Marcadores genéticos e clínicos na trajectória do DPOC".

Com os meus cumprimentos,

Ana Maria Rodrigues
Secretariado do Conselho de Administração

Appendix 3. National Data Protection Committee letter of approval

_____

Autorização n.º 8828/ 2016

Universidade de Aveiro , NIPC 501461108, notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de realizar um Estudo Clínico com Intervenção, denominado GENIAL - Marcadores Genéticos e Clínicos na Trajetória da DPOC .

Existe justificação específica, validada pela Comissão de Ética Competente (CEC), para o tratamento do dado pessoal raça/etnia.

O participante é identificado por um código especificamente criado para este estudo, constituído de modo a não permitir a imediata identificação do titular dos dados; designadamente, não são utilizados códigos que coincidam com os números de identificação, iniciais do nome, data de nascimento, número de telefone, ou resultem de uma composição simples desse tipo de dados. A chave da codificação só é conhecida do(s) investigador(es).

É recolhido o consentimento expresso do participante ou do seu representante legal.

A informação é recolhida diretamente do titular e indiretamente do processo clínico.

As eventuais transmissões de informação são efetuadas por referência ao código do participante, sendo, nessa medida, anónimas para o destinatário.

A CNPD já se pronunciou na Deliberação n.º 1704/2015 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios aplicáveis para o correto cumprimento da Lei n.º 67/98, de 26 de outubro, alterada pela Lei n.º 103/2015, de 24 de agosto, doravante LPD, bem como sobre as condições e limites aplicáveis ao tratamento de dados efetuados para a finalidade de investigação clínica.

No caso em apreço, o tratamento objeto da notificação enquadra-se no âmbito daquela deliberação e o responsável declara expressamente que cumpre os limites e condições aplicáveis por força da LPD e da Lei n.º 21/2014, de 16 de abril, alterada pela Lei n.º 73/2015, de 27 de junho – Lei da Investigação Clínica –, explicitados na Deliberação n.º 1704/2015.

O fundamento de legitimidade é o consentimento do titular.

A informação tratada é recolhida de forma lícita, para finalidade determinada, explícita e legitima e não é excessiva – cf. alíneas a), b) e c) do n.º 1 do artigo 5.º da LPD.

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, da alínea a) do n.º 1 do artigo 28.º e do artigo 30.º da LPD, bem como do n.º 3 do artigo 1.º e do n.º 9 do artigo 16.º ambos da Lei de Investigação Clínica, com as condições e limites explicitados na Deliberação da CNPD n.º 1704/2015, que aqui se dão por reproduzidos, autoriza-se o presente tratamento de dados pessoais nos seguintes termos:

Responsável – Universidade de Aveiro

Finalidade – Estudo Clínico com Intervenção, denominado GENIAL - Marcadores Genéticos e Clínicos na Trajetória da DPOC

Categoria de dados pessoais tratados – Código do participante; idade/data de nascimento; género; raça/etnia; dados antropométricos; sinais vitais; dados da história clínica; dados dados de exame físico; dados de meios complementares de diagnóstico; medicação prévia concomitante; genéticos; dados de cuidadores/acompanhantes (apenas os relacionados com as necessidades do participante); dados de qualidade de vida/efeitos psicológicos

Exercício do direito de acesso – Através dos investigadores, presencialmente

Comunicações, interconexões e fluxos transfronteiriços de dados pessoais identificáveis no destinatário – Não existem

Prazo máximo de conservação dos dados – A chave que produziu o código que permite a identificação indireta do titular dos dados deve ser eliminada 5 anos após o fim do estudo.

Da LPD e da Lei de Investigação Clínica, nos termos e condições fixados na presente Autorização e desenvolvidos na Deliberação da CNPD n.º 1704/2015, resultam obrigações que o responsável tem de cumprir. Destas deve dar conhecimento a todos os que intervenham no tratamento de dados pessoais.

Lisboa, 23-08-2016

A Presidente

Filipa Calvão

Appendix 4. Permissions to reproduce the published materials

_____

OXFORD UNIVERSITY PRESS LICENSE
TERMS AND CONDITIONS

Jan 02, 2019

This Agreement between Mrs. Ana Oliveira ("You") and Oxford University Press ("Oxford University Press") consists of your license details and the terms and conditions provided by Oxford University Press and Copyright Clearance Center.

License Number	4500841085756
License date	Jan 02, 2019
Licensed content publisher	Oxford University Press
Licensed content publication	Physical Therapy
Licensed content title	Outcome Measures Used in Pulmonary Rehabilitation in Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review
Licensed content author	Oliveira, Ana L; Marques, Alda S
Licensed content date	Dec 6, 2017
Type of Use	Thesis/Dissertation
Institution name	
Title of your work	Emergent measures and patterns of recovery during acute exacerbations of Chronic Obstructive Pulmonary Disease
Publisher of your work	University of Porto
Expected publication date	Mar 2019
Permissions cost	0.00 EUR
Value added tax	0.00 EUR
Total	0.00 EUR
Title	Emergent measures and patterns of recovery during acute exacerbations of Chronic Obstructive Pulmonary Disease
Institution name	University of Porto
Expected presentation date	Mar 2019
Order reference number	1
Portions	The entire article is to be included inthe document of the PhD thesis.
Requestor Location	Mrs. Ana Oliveira Campus Universitário de Santiago Agras do Crasto, Edíficio 30
	Aveiro, Select 3810-193 Portugal Attn: Mrs. Ana Oliveira
Publisher Tax ID	GB125506730
Billing Type	Invoice
Billing Address	Mrs. Ana Oliveira Campus Universitário de Santiago Agras do Crasto, Edíficio 30
	Aveiro, Portugal 3810-193 Attn: Mrs. Ana Oliveira
Total	0.00 EUR
Terms and Conditions	

ccxxxi

STANDARD TERMS AND CONDITIONS FOR REPRODUCTION OF MATERIAL FROM AN OXFORD UNIVERSITY PRESS JOURNAL

1. Use of the material is restricted to the type of use specified in your order details.

2. This permission covers the use of the material in the English language in the following territory: world. If you have requested additional permission to translate this material, the terms and conditions of this reuse will be set out in clause 12.

3. This permission is limited to the particular use authorized in (1) above and does not allow you to sanction its use elsewhere in any other format other than specified above, nor does it apply to quotations, images, artistic works etc that have been reproduced from other sources which may be part of the material to be used.

4. No alteration, omission or addition is made to the material without our written consent. Permission must be re-cleared with Oxford University Press if/when you decide to reprint.

5. The following credit line appears wherever the material is used: author, title, journal, year, volume, issue number, pagination, by permission of Oxford University Press or the sponsoring society if the journal is a society journal. Where a journal is being published on behalf of a learned society, the details of that society must be included in the credit line.

6. For the reproduction of a full article from an Oxford University Press journal for whatever purpose, the corresponding author of the material concerned should be informed of the proposed use. Contact details for the corresponding authors of all Oxford University Press journal contact can be found alongside either the abstract or full text of the article concerned, accessible from www.oxfordjournals.org Should there be a problem clearing these rights, please contact journals.permissions@oup.com

7. If the credit line or acknowledgement in our publication indicates that any of the figures, images or photos was reproduced, drawn or modified from an earlier source it will be necessary for you to clear this permission with the original publisher as well. If this permission has not been obtained, please note that this material cannot be included in your publication/photocopies.

8. While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by Oxford University Press or by Copyright Clearance Center (CCC)) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and Oxford University Press reserves the right to take any and all action to protect its copyright in the materials.

9. This license is personal to you and may not be sublicensed, assigned or transferred by you to any other person without Oxford University Press's written permission.

10. Oxford University Press reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

11. You hereby indemnify and agree to hold harmless Oxford University Press and CCC, and their respective officers, directors, employs and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

12. Other Terms and Conditions:

v1.4

Questions? customercare@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.

ccxxxii

ccxxxiii

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS

Jan 02, 2019

This Agreement between Mrs. Ana Oliveira ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number	4500851301960
License date	Jan 02, 2019
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	Clinical Respiratory Journal
Licensed Content Title	Reliability, validity and minimal detectable change of computerized respiratory sounds in patients with chronic obstructive pulmonary disease
Licensed Content Author	Ana Oliveira, Susan Lage, João Rodrigues, et al
Licensed Content Date	Dec 18, 2017
Licensed Content Volume	12
Licensed Content Issue	5
Licensed Content Pages	11
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic
Portion	Full article
Will you be translating?	No
Title of your thesis / dissertation	Emergent measures and patterns of recovery during acute exacerbations of Chronic Obstructive Pulmonary Disease
Expected completion date	Mar 2019
Expected size (number of pages)	1
Requestor Location	Mrs. Ana Oliveira Campus Universitário de Santiago Agras do Crasto, Edíficio 30 Aveiro, Select 3810-193 Portugal Attn: Mrs. Ana Oliveira
Publisher Tax ID	EU826007151
Total	0.00 EUR
Terms and Conditions	

TERMS AND CONDITIONS

CCXXXV

Terms and Conditions

- The materials you have requested permission to reproduce or reuse (the "Wiley Materials") are protected by copyright.

- You are hereby granted a personal, non-exclusive, non-sub licensable (on a stand-alone basis), non-transferable, worldwide, limited license to reproduce the Wiley Materials for the purpose specified in the licensing process. This license, **and any CONTENT (PDF or image file) purchased as part of your order,** is for a one-time use only and limited to any maximum distribution number specified in the license. The first instance of republication or reuse granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before the end date may be distributed thereafter). The Wiley Materials shall not be used in any other manner or for any other purpose, beyond what is granted in the license. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Wiley Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Wiley Material. Any third party content is expressly excluded from this permission.

- With respect to the Wiley Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Wiley Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Wiley Materials without the prior permission of the respective copyright owner.**For STM Signatory Publishers clearing permission under the terms of the STM Permissions Guidelines only, the terms of the license are extended to include subsequent editions and for editions in other languages, provided such editions are for the work as a whole in situ and does not involve the separate exploitation of the permitted figures or extracts,** You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Wiley Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Wiley Materials on a stand-alone basis, or any of the rights granted to you hereunder to any other person.

- The Wiley Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc, the Wiley Companies, or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Wiley Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Wiley Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto

- NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY, INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED

ccxxxvi

BY YOU.

- WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.

- You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.

- IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

- Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

- The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

- This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.

- Any fee required for this permission shall be non-refundable after thirty (30) days from receipt by the CCC.

- These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

- In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

ccxxxvii

- WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

- This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

- This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

WILEY OPEN ACCESS TERMS AND CONDITIONS
Wiley Publishes Open Access Articles in fully Open Access Journals and in Subscription journals offering Online Open. Although most of the fully Open Access journals publish open access articles under the terms of the Creative Commons Attribution (CC BY) License only, the subscription journals and a few of the Open Access Journals offer a choice of Creative Commons Licenses. The license type is clearly identified on the article.
The Creative Commons Attribution License
The Creative Commons Attribution License (CC-BY) allows users to copy, distribute and transmit an article, adapt the article and make commercial use of the article. The CC-BY license permits commercial and non-
Creative Commons Attribution Non-Commercial License
The Creative Commons Attribution Non-Commercial (CC-BY-NC)License permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.(see below)

Creative Commons Attribution-Non-Commercial-NoDerivs License
The Creative Commons Attribution Non-Commercial-NoDerivs License (CC-BY-NC-ND) permits use, distribution and reproduction in any medium, provided the original work is properly cited, is not used for commercial purposes and no modifications or adaptations are made. (see below)
Use by commercial "for-profit" organizations
Use of Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee.
Further details can be found on Wiley Online Library
http://olabout.wiley.com/WileyCDA/Section/id-410895.html

Other Terms and Conditions:

v1.10 Last updated September 2015

ccxxxviii

Taylor & Francis
Taylor & Francis Group

Our Ref: P011619-02/ICOP

16/01/2019

Dear Ana Oliveira on Behalf of the University of Porto,

Material requested: Ana Oliveira, Ana Machado & Alda Marques (2018)
Minimal Important and Detectable Differences of Respiratory Measures
in Outpatients with AECOPD[†]
COPD: Journal of Chronic Obstructive Pulmonary Disease, 15 (5): 479-488:
DOI: 10.1080/15412555.2018.1537366

Thank you for your correspondence requesting permission to publish and post the above mentioned
Author's Original Manuscript in or on your institutions intranet or within the Institutional Repository
of your institution **for your dissertation.**

As you are the author of the above article, we are pleased to grant you permission to include your
article as it was originally submitted to the journal on the condition that you make the following
acknowledgement:

You will also need to obtain permission from any co-author's of this article.

This is an Author's Original Manuscript of an article published by Taylor & Francis Group in the
[Journal Title] **on [Date of Online Publication],** available online**:** (Using a real DOI will form a link
to the Version of Record on www.tandfonline.com/

Please note we are unable to grant you permission to include the final published version within the
(12) month embargo period.

Thank you very much for your interest in Taylor & Francis publications. Should you have any questions
or require further assistance, please feel free to contact me directly.

Sincerely,

Mary Ann Muller

Permissions Coordinator

E-mail: maryann.muller@taylorandfrancis.com

Telephone: 215.606.4334

RightsLink®

Home   Account Info   Help

Title: Enhancing our understanding of computerised adventitious respiratory sounds in different COPD phases and healthy people

Author: Ana Oliveira,João Rodrigues,Alda Marques

Publication: Respiratory Medicine

Publisher: Elsevier

Date: May 2018

© 2018 Elsevier Ltd. All rights reserved.

Logged in as:
Ana Oliveira

LOGOUT

BACK   CLOSE WINDOW

ccxli

Copyright Clearance Center

Confirmation Number: 11778518
Order Date: 01/02/2019

Customer Information

Customer: Ana Oliveira
Account Number: 3001386981
Organization: Ana Oliveira
Email: alao@ua.pt
Phone: +351 913937469
Payment Method: Invoice

This is not an invoice

Order Details

International Journal of Chronic Obstructive Pulmonary Disease

	Billing Status: **N/A**

Order detail ID:	71745656	**Permission Status:** ✅ **Granted**
ISSN:	1178-2005	**Permission type:** Republish or display content
Publication Type:	e-Journal	**Type of use:** Republish in a thesis/dissertation
Volume:		**Order License Id:** 4500861059925
Issue:		
Start page:		**Requestor type** — Author of requested content
Publisher:	DOVE Medical Press	

Format	Print, Electronic
Portion	chapter/article
The requesting person/organization	Ana Oliveira
Title or numeric reference of the portion(s)	Enhancing our understanding of the time course of acute exacerbations of COPD managed on an outpatient basis
Title of the article or chapter the portion is from	Enhancing our understanding of the time course of acute exacerbations of COPD managed on an outpatient basis
Editor of portion(s)	N/A
Author of portion(s)	Oliveira A, Afreixo V, Marques A
Volume of serial or monograph	2018
Issue, if republishing an article from a serial	13
Page range of portion	
Publication date of portion	20 November 2018
Rights for	Main product
Duration of use	Life of current and all future editions
Creation of copies for the disabled	no
With minor editing privileges	no
For distribution to	Worldwide
In the following language(s)	Original language of publication

ccxliii

With incidental promotional use	no
Lifetime unit quantity of new product	Up to 499
Title	Emergent measures and patterns of recovery during acute exacerbations of Chronic Obstructive Pulmonary Disease
Institution name	University of Porto
Expected presentation date	Mar 2019

Note: This item was invoiced separately through our **RightsLink service.** More info   **$ 0.00**

Total order items: 1   **Order Total: $0.00**

About Us | Privacy Policy | Terms & Conditions | Pay an Invoice

ccxliv

Confirmation Number: 11778518

Special Rightsholder Terms & Conditions
The following terms & conditions apply to the specific publication under which they are listed

International Journal of Chronic Obstructive Pulmonary Disease
Permission type: Republish or display content
Type of use: Republish in a thesis/dissertation

TERMS AND CONDITIONS

The following terms are individual to this publisher:

None

Other Terms and Conditions:

STANDARD TERMS AND CONDITIONS

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

3.1 All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

3.2 General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the Order Confirmation, the license is automatically revoked and is null and void, as if it had never been issued, if complete payment for the license is not received on a timely basis either from User directly or through a payment agent, such as a credit card company.

3.3 Unless otherwise provided in the Order Confirmation, any grant of rights to User (i) is "one-time" (including the editions and product family specified in the license), (ii) is non-exclusive and non-transferable and (iii) is subject to any and all limitations and restrictions (such as, but not limited to, limitations on duration of use or circulation) included in the Order Confirmation or invoice and/or in these terms and conditions. Upon completion of the licensed use, User shall either secure a new permission for further use of the Work(s) or immediately cease any new use of the Work(s) and shall render inaccessible (such as by deleting or by removing or severing links or other locators) any further copies of the Work (except for copies printed on paper in accordance with this license and still in User's stock at the end of such period).

3.4 In the event that the material for which a republication license is sought includes third party materials (such as photographs, illustrations, graphs, inserts and similar materials) which are identified in such material as having been used by permission, User is responsible for identifying, and seeking separate licenses (under this Service or otherwise) for, any of such third party materials; without a separate license, such third party materials may not be used.

3.5 Use of proper copyright notice for a Work is required as a condition of any license granted under the Service. Unless otherwise provided in the Order Confirmation, a proper copyright notice will read substantially as follows: "Republished with permission of [Rightsholder's name], from [Work's title, author, volume, edition number and year of copyright]; permission conveyed through Copyright Clearance Center, Inc. " Such notice must be provided in a reasonably legible font size and must be placed either immediately adjacent to the Work as used (for example, as part of a by-line or footnote

ccxlv

but not as a separate electronic link) or in the place where substantially all other credits or notices for the new work containing the republished Work are located. Failure to include the required notice results in loss to the Rightsholder and CCC, and the User shall be liable to pay liquidated damages for each such failure equal to twice the use fee specified in the Order Confirmation, in addition to the use fee itself and any other fees and charges specified.

3.6 User may only make alterations to the Work if and as expressly set forth in the Order Confirmation. No Work may be used in any way that is defamatory, violates the rights of third parties (including such third parties' rights of copyright, privacy, publicity, or other tangible or intangible property), or is otherwise illegal, sexually explicit or obscene. In addition, User may not conjoin a Work with any other material that may result in damage to the reputation of the Rightsholder. User agrees to inform CCC if it becomes aware of any infringement of any rights in a Work and to cooperate with any reasonable request of CCC or the Rightsholder in connection therewith.

4. Indemnity. User hereby indemnifies and agrees to defend the Rightsholder and CCC, and their respective employees and directors, against all claims, liability, damages, costs and expenses, including legal fees and expenses, arising out of any use of a Work beyond the scope of the rights granted herein, or any use of a Work which has been altered in any unauthorized way by User, including claims of defamation or infringement of rights of copyright, publicity, privacy or other tangible or intangible property.

5. Limitation of Liability. UNDER NO CIRCUMSTANCES WILL CCC OR THE RIGHTSHOLDER BE LIABLE FOR ANY DIRECT, INDIRECT, CONSEQUENTIAL OR INCIDENTAL DAMAGES (INCLUDING WITHOUT LIMITATION DAMAGES FOR LOSS OF BUSINESS PROFITS OR INFORMATION, OR FOR BUSINESS INTERRUPTION) ARISING OUT OF THE USE OR INABILITY TO USE A WORK, EVEN IF ONE OF THEM HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. In any event, the total liability of the Rightsholder and CCC (including their respective employees and directors) shall not exceed the total amount actually paid by User for this license. User assumes full liability for the actions and omissions of its principals, employees, agents, affiliates, successors and assigns.

6. Limited Warranties. THE WORK(S) AND RIGHT(S) ARE PROVIDED "AS IS". CCC HAS THE RIGHT TO GRANT TO USER THE RIGHTS GRANTED IN THE ORDER CONFIRMATION DOCUMENT. CCC AND THE RIGHTSHOLDER DISCLAIM ALL OTHER WARRANTIES RELATING TO THE WORK(S) AND RIGHT(S), EITHER EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. ADDITIONAL RIGHTS MAY BE REQUIRED TO USE ILLUSTRATIONS, GRAPHS, PHOTOGRAPHS, ABSTRACTS, INSERTS OR OTHER PORTIONS OF THE WORK (AS OPPOSED TO THE ENTIRE WORK) IN A MANNER CONTEMPLATED BY USER; USER UNDERSTANDS AND AGREES THAT NEITHER CCC NOR THE RIGHTSHOLDER MAY HAVE SUCH ADDITIONAL RIGHTS TO GRANT.

7. Effect of Breach. Any failure by User to pay any amount when due, or any use by User of a Work beyond the scope of the license set forth in the Order Confirmation and/or these terms and conditions, shall be a material breach of the license created by the Order Confirmation and these terms and conditions. Any breach not cured within 30 days of written notice thereof shall result in immediate termination of such license without further notice. Any unauthorized (but licensable) use of a Work that is terminated immediately upon notice thereof may be liquidated by payment of the Rightsholder's ordinary license price therefor; any unauthorized (and unlicensable) use that is not terminated immediately for any reason (including, for example, because materials containing the Work cannot reasonably be recalled) will be subject to all remedies available at law or in equity, but in no event to a payment of less than three times the Rightsholder's ordinary license price for the most closely analogous licensable use plus Rightsholder's and/or CCC's costs and expenses incurred in collecting such payment.

8. **Miscellaneous.**

8.1 User acknowledges that CCC may, from time to time, make changes or additions to the Service or to these terms and conditions, and CCC reserves the right to send notice to the User by electronic mail or otherwise for the purposes of notifying User of such changes or additions; provided that any such changes or additions shall not apply to permissions already secured and paid for.

8.2 Use of User-related information collected through the Service is governed by CCC's privacy policy, available online here: http://www.copyright.com/content/cc3/en/tools/footer/privacypolicy.html.

8.3 The licensing transaction described in the Order Confirmation is personal to User. Therefore, User may not assign or transfer to any other person (whether a natural person or an organization of any kind) the license created by the Order Confirmation and these terms and conditions or any rights granted hereunder; provided, however, that User may assign such license in its entirety on written notice to CCC in the event of a transfer of all or substantially all of User's rights in the new material which includes the Work(s) licensed under this Service.

8.4 No amendment or waiver of any terms is binding unless set forth in writing and signed by the parties. The Rightsholder and CCC hereby object to any terms contained in any writing prepared by the User or its principals, employees, agents or affiliates and purporting to govern or otherwise relate to the licensing transaction described in the Order Confirmation, which terms are in any way inconsistent with any terms set forth in the Order Confirmation and/or in these terms and conditions or CCC's standard operating procedures, whether such writing is prepared prior to, simultaneously with or subsequent to the Order Confirmation, and whether such writing appears on a copy of the Order Confirmation or in a separate instrument.

8.5 The licensing transaction described in the Order Confirmation document shall be governed by and construed under the law of the State of New York, USA, without regard to the principles thereof of conflicts of law. Any case, controversy, suit, action, or proceeding arising out of, in connection with, or related to such licensing transaction shall be brought, at CCC's sole discretion, in any federal or state court located in the County of New York, State of New York, USA, or in any federal or state court whose geographical jurisdiction covers the location of the Rightsholder set forth in the Order Confirmation. The parties expressly submit to the personal jurisdiction and venue of each such federal or state court.If you have any comments or questions about the Service or Copyright Clearance Center, please contact us at 978-750-8400 or send an e-mail to info@copyright.com.

v 1.1

ccxlvi

Close

ccxlvii

ccxlviii

Appendix 5. Consent forms

_____

Termo de Consentimento Livre e Esclarecido

Título do Projeto: Sons respiratórios computorizados – Uma medida emergente na avaliação de doentes com Doença Pulmonar Obstrutiva Crónica.

Nome da Orientadora: Prof. Doutora Alda Sofia Pires de Dias Marques
Nome da aluna de Doutoramento: Ana Luísa Araújo Oliveira

Por favor leia e assinale com uma cruz (X) os quadrados seguintes.

1. Eu confirmo que percebi a informação que me foi dada e tive a oportunidade de questionar e de me esclarecer. ☐

2. Eu percebo que a minha participação é voluntária e que sou livre de desistir, em qualquer altura, sem dar nenhuma explicação, sem que isso afete qualquer serviço de saúde que me é prestado. ☐

3. Eu concordo que as recolhas de dados sejam fotografadas com o objetivo de ajudar no planeamento de futuros estudos e publicação em Revistas Científicas ou Congressos na área. ☐

4. Eu compreendo que os dados recolhidos durante o estudo são confidenciais e que só a aluna de doutoramento e sua orientadora terão acesso a eles. Portanto, dou autorização para que os mesmos tenham acesso a esses dados. ☐

5. Eu compreendo que os dados recolhidos durante o estudo podem ser utilizados para publicação em Revistas Científicas e usados noutras investigações, sem que haja qualquer quebra de confidencialidade. Portanto, dou autorização para a utilização dos dados para esses fins. ☐

_____ _____ _____

Nome da pessoa   Data   Assinatura

_____ _____ _____

Nome do Investigador(a)   Data   Assinatura

ccli