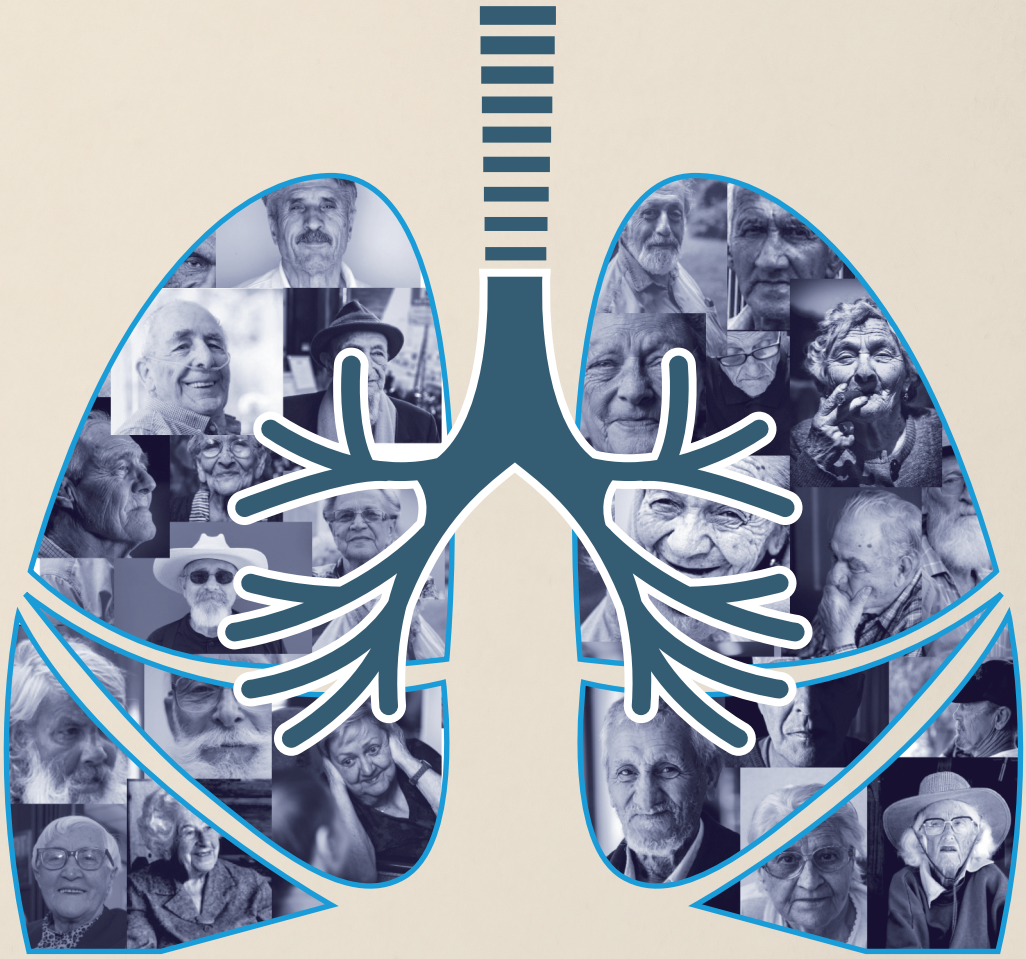

Geriatric Rehabilitation for older patients with COPD

Integration of rehabilitation and palliative care

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A thing of beauty is a joy forever, it's loveliness increases and will never pass into nothingness. *From 'Endymion' by John Keats, 1818*

CONTENTS

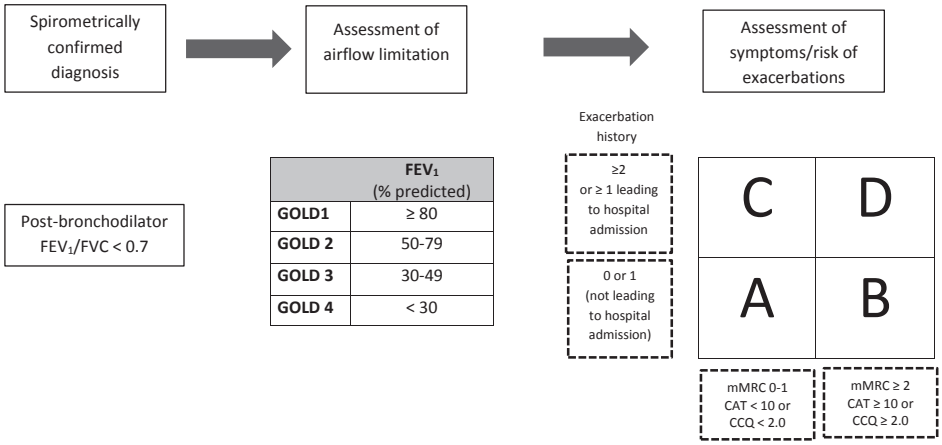
General introduction

1

COPD

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease. It is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1] Tobacco smoking is the main risk factor for COPD, but other environmental exposures, such as air pollution and biomass fuel exposure, may also contribute. Furthermore, host factors, such as genetic factors and accelerated aging, predispose individuals to develop COPD.[1]
Both the prevalence and burden of COPD is rising worldwide. COPD accounts for 6% of all deaths globally and is projected to become the third leading cause of morbidity and mortality worldwide by 2030.[2] In the Netherlands, the prevalence of COPD is estimated to be around 2% across all ages. However, as COPD is strongly related to age, estimated prevalences rise up to more than 10% in those aged 40 years and older. As a result of the ageing population and changes in demographics, the prevalence of COPD in the Netherlands is expected to increase by 36% between 2010 and 2040. COPD already accounts for more than 6,000 deaths and 22,000 hospital admissions each year, thereby representing a substantial and growing burden for individual patients and for the Dutch society in terms of healthcare organisation and costs.[3]
Diagnosis of COPD is based on clinical symptoms (dyspnoea, cough and sputum production are the most common symptoms) and patient characteristics (age > 40 years, history of exposure to risk factors), in combination with spirometry.[2] Traditionally, disease severity was solely based on the degree of persistent airflow obstruction (obtained by spirometry) and classified according to the global initiative for chronic obstructive lung disease (GOLD) classification. However, more recent evidence shows that lung function alone does not correlate well with patient's experience of disease severity and quality of life.[2,4] Although the degree of persistent airflow obstruction remains the cornerstone of diagnosis, GOLD guidelines now recommend that disease severity is determined by a combined assessment of airflow obstruction, exacerbation frequency and symptom burden (Figure 1).[1]
Furthermore, several extra-pulmonary symptoms (e.g. limited functional status and exercise capacity, poor nutritional status, co-morbidity) negatively influence quality of life and prognosis in individual patients. Many of these extra-pulmonary symptoms of COPD can also be seen as characteristics of older, geriatric patients in general. Therefore, they can accumulate in older patients with COPD, ultimately leading to a vicious circle of deteriorating health status and poor prognosis.[5-7]
Acute exacerbations in COPD, defined as an acute worsening of respiratory symptoms that result in additional therapy, play a key role. These exacerbations

Figure 1. GOLD categorisation of COPD based on a combined ABCD assessment.



Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: global initiative for chronic obstructive lung disease; CAT: COPD assessment test; CCQ: Clinical COPD questionnaire; mMRC: modified Medical Research Council dyspnoea scale

represent a major burden for individual patients, are the most frequent reason for hospital admission and death among patients with COPD, and negatively influence quality of life and exercise capacity, often leading to readmissions, further decline of health status and high mortality rates.[7-10] In patients who lack sufficient recovery during hospital stay, and in patients with frequent exacerbations and hospital readmissions, pulmonary rehabilitation is recommended.[9]

Pulmonary rehabilitation after hospital admission for acute exacerbations (i.e. postacute pulmonary rehabilitation) has proven to be an effective treatment with positive effects on quality of life, exercise capacity, hospital readmissions and mortality.[9] However, despite proven benefits, many older patients with COPD do not receive postacute pulmonary rehabilitation in daily practice.[11] Several reasons for this underuse have emerged. First, many physicians do not recommend postacute pulmonary rehabilitation to their older patients; this lack of referral can be related to the more impaired clinical and functional status of these older patients, who are more likely to present with frailty, higher burden of co-morbidities, and disability. Secondly, patients that are referred are less likely to participate, also mainly due to poor health status and other age-related problems.[12] This is also caused by (temporary) care dependency after hospital admission which requires a specific setting for rehabilitation, including support and training of activities of daily living and a fluent transition from hospital admission to rehabilitation setting. Finally, in many older patients hospitalised for an acute exacerbation of COPD, palliative care methods and advance care planning are indicated because of their poor quality of

life and prognosis.[13] However, palliative care is still scarcely received by patients with severe COPD, and integration of palliative care into (postacute) pulmonary rehabilitation is recommended but not yet implemented in practice.[14]

To summarise, COPD is a significant and growing problem among older adults. Exacerbations play a key role in terms of quality of life, prognosis and costs. Although postacute rehabilitation is effective and recommended, older patients with more advanced COPD often have additional specific age-related problems and needs that render referral and uptake of pulmonary rehabilitation difficult. Therefore, there is a need for specifically designed postacute rehabilitation programs for older patients with COPD.

Geriatric rehabilitation

Geriatric rehabilitation can be an interesting option for older patients hospitalised for an acute exacerbation of COPD. Geriatric rehabilitation has emerged as a relatively young but important and evolving field of interest in both clinical practice and scientific research. Geriatric rehabilitation is defined as "*evaluative, diagnostic and therapeutic interventions whose purpose is to restore functional ability or enhance residual functional capability in older people with disabling impairments*".[15] In the Netherlands, geriatric rehabilitation is provided as a form of postacute rehabilitation, offered at skilled nursing facilities, usually situated in nursing homes, and organised as structured-care pathways in close collaboration with several medical departments of adjacent hospital(s). Geriatric rehabilitation does not differ from rehabilitation medicine in its approach and aims, but patients admitted for geriatric rehabilitation generally have specific characteristics, problems and needs associated with ageing. For example, they often have complex health issues due to co-morbidities, and may suffer from limited functional status, sarcopenia and cognitive problems. Furthermore, loneliness due to loss of social role or work and spiritual questions, including advance care planning, are common. In this sense, geriatric rehabilitation operates at the cross-roads of geriatric medicine, rehabilitation medicine and palliative care.[16]

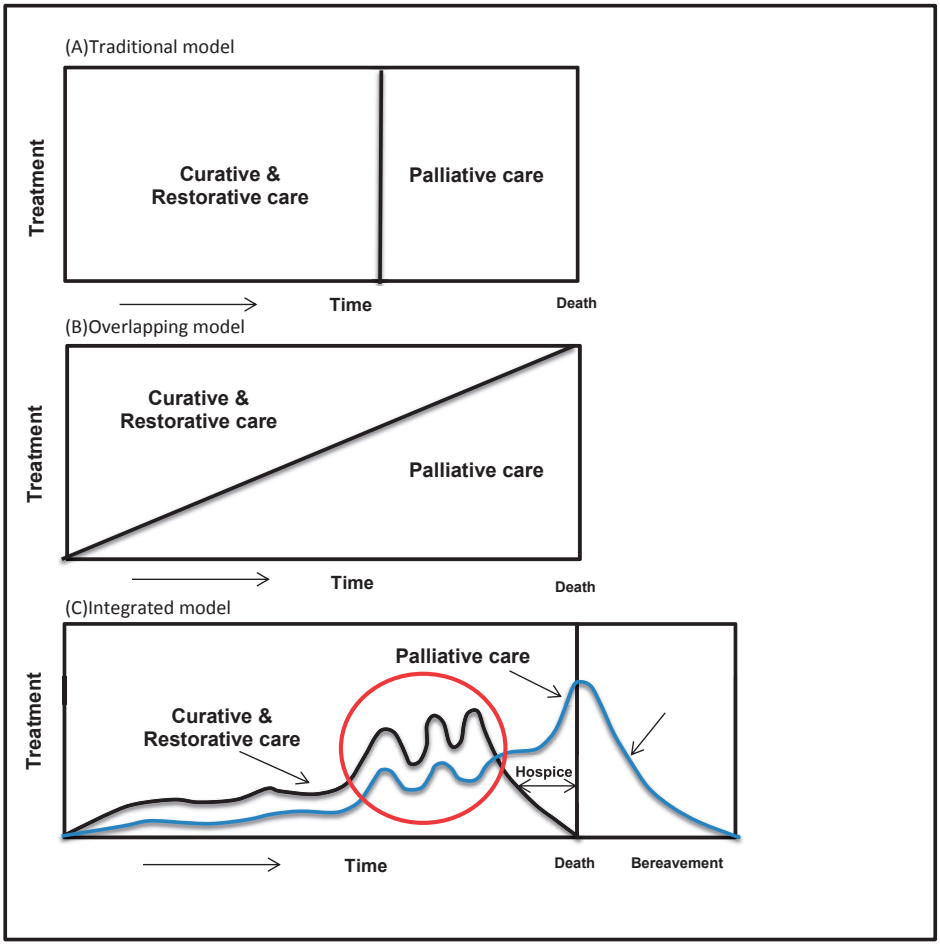
Geriatric rehabilitation can improve outcomes related to function, nursing home admissions, and mortality.[16] However, until now, evidence of this could only be acquired from two types of geriatric rehabilitation programs, i.e. general and orthopaedic geriatric rehabilitation.[16] Studies on the effectiveness of rehabilitation programs specifically designed for geriatric patients in other clinical specialties (e.g. pulmonary, cardiac or stroke) are still lacking. This indicates the need and importance for the development, implementation and evaluation of other types of

geriatric rehabilitation programs, since they may have the potential to change clinical practice in the future.[16]
In view of the ageing populations worldwide, appropriate rehabilitation programs for older patients are needed. On the other hand, increasing healthcare costs also call for appropriate and cost-effective use of rehabilitation resources.[17,18] This implies screening or case finding of patients (e.g. with COPD) who are most likely to benefit from geriatric rehabilitation, and selecting the most appropriate setting for each patient, since the goal is to provide the right type of care, at the right moment, in the right setting, to the right patient.

Palliative care in COPD

In many older patients with more advanced COPD, optimal pharmacologic therapy produces only moderate or incomplete relief from symptoms, resulting in significantly impaired quality of life.[19] Considering the poor quality of life and prognosis in these patients, palliative care is indicated and should start early in the disease trajectory, combined with active and restorative treatments, such as rehabilitation (Figure 2).[13] In fact, it is advocated that integration of palliative care into pulmonary rehabilitation, and vice versa, is warranted.[20,21] However, in daily practice such integration can be challenging since rehabilitation medicine and palliative care are usually organised as two separate domains in health care. In geriatric rehabilitation, however, rehabilitation and palliative care methods are already combined.[16]
Adequate symptom management is considered to be a key part of palliative care and is also important to achieve optimal effect of rehabilitation. Patients with advanced COPD suffer from many symptoms, of which dyspnoea, cough and sputum production are the most commonly known. Recent literature indicated that pain is also a significant, but largely unrecognised, underestimated and undertreated symptom in patients with COPD.[22,23] Furthermore, in patients with COPD, other symptoms, like dyspnoea, anxiety, depression and insomnia, seem to be associated with pain.[24] These multiple concurrent symptoms can cluster and aggravate each other, causing what has been called the '*vicious COPD circle*'.[23] In this concept, pain was described as "tying up the body", which makes breathing difficult, thereby leading to more breathlessness and pain. Pain also induced anxiety, depression and insomnia, causing more pain and psychological problems.[23] In COPD, pain is also related to diminished quality of life.[25] Subsequently, pain might negatively influence outcomes of postacute pulmonary rehabilitation in COPD. On the other hand, postacute pulmonary rehabilitation can also be seen as a possible non-pharmacological intervention to reduce pain in COPD, as it might counteract the

Figure 2. Care models illustrating three different concepts of palliative care versus curative and restorative care.



Model adapted from Lanken et al[13]. The third (C), individually integrated model is recommended as the preferred approach, in which patients receive palliative care (blue line) when they become symptomatic, concurrently with curative and restorative treatment, such as rehabilitation (black line), in an individualised manner, based on their symptoms and disease trajectory. The red circle indicates the position of geriatric rehabilitation within this model.

pain-related vicious circles in COPD.[23] As pain management is preferably undertaken using multi-domain strategies (e.g. psychological, physical, behavioural and pharmacological), it might be a separate goal in postacute pulmonary rehabilitation by means of improving muscle strength, exercise capacity and coping. However, studies on this topic are lacking, as are investigations on the effect of integrating standard pain assessment and treatment into rehabilitation programs.

The GR_COPD program

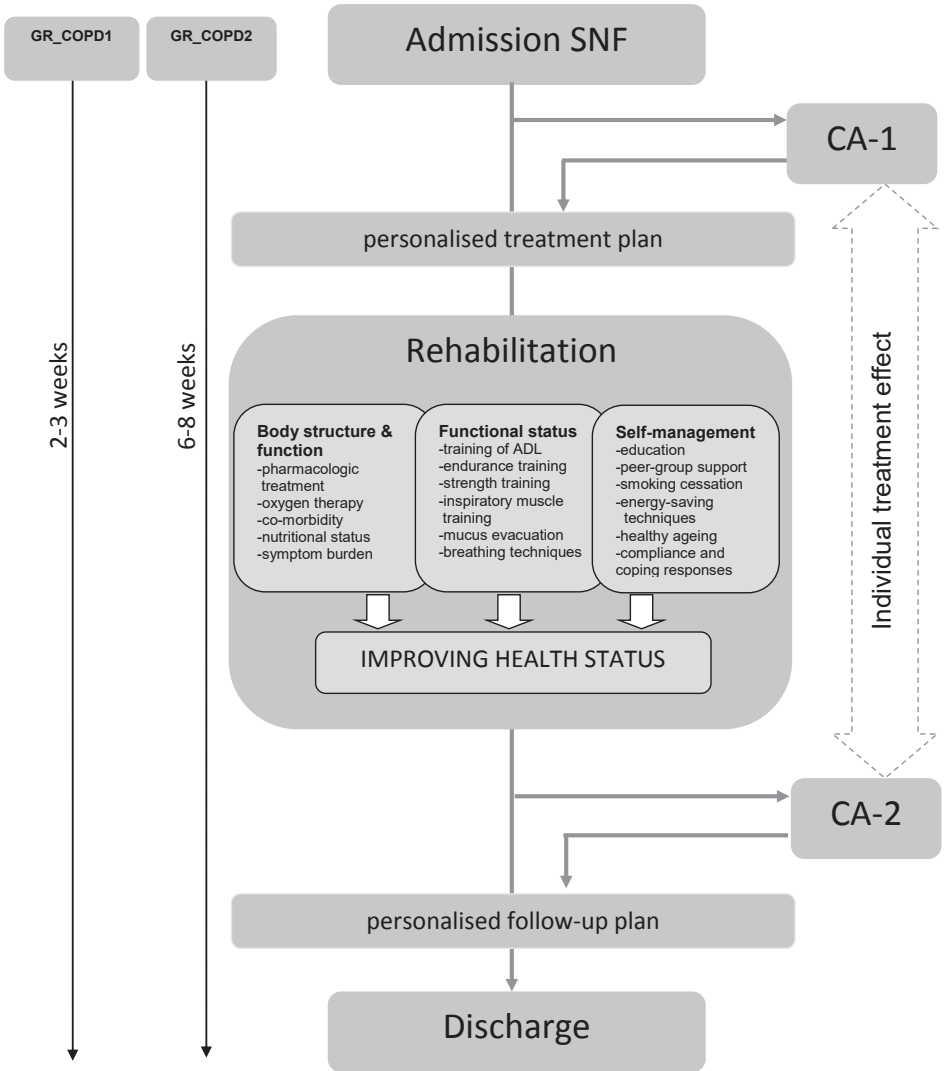
In view of the above issues related to COPD in older patients, geriatric rehabilitation and palliative care, the GR_COPD program was developed and implemented as a structured-care pathway in clinical practice (Figure 3). This new program offers multidisciplinary patient-centred rehabilitation that integrates palliative care methods, to older patients with COPD who have been hospitalised for an acute exacerbation. The program aims to counteract or stabilise the gradual decline in health status, achieve sustainable improvements in functional status, quality of life and self-management, and prevent hospital readmissions. As the feasibility and effectiveness of such a program for this specific group (i.e. older patients with advanced COPD) in this specific setting (geriatric rehabilitation) are unknown, research was needed. After describing the specific characteristics of the program, the feasibility of the program had to be established, the outcome measurements to be used in these patients had to be determined, and the effectiveness of the GR_COPD program had to be investigated.

Aims and outline of this thesis

The primary aim of this thesis was to investigate the feasibility and effectiveness of the GR_COPD program; a geriatric rehabilitation program that integrated palliative care aspects, for older patients with advanced COPD hospitalized for an acute exacerbation. Therefore, four studies, that included two different study populations and a systematic review and meta-analysis of the literature, were developed and executed.

Part one of this thesis focusses on the GR_COPD program itself, the feasibility study, and the GR_COPD study that examined the effectiveness of the GR_COPD program. In **chapter 2** the characteristics of the GR_COPD program are described, illustrated by three case studies of patients that were admitted to the GR_COPD program. The three cases that are presented illustrate why integration of rehabilitation and palliative care methods is needed and how this can be implemented into clinical practice. **Chapter 3** presents the results of the feasibility study. The feasibility study consisted of a retrospective real-life case series of patients receiving the GR_COPD program. Aim of this study was to investigate feasibility in terms of patient characteristics, suitability, safety and preliminary evaluation of patient response to the GR_COPD program. Furthermore, defining a suitable, valid and reliable outcome measure that is also sensitive to change in response to the program, in this specific group and setting, was needed. Therefore, **chapter 4** presents

Figure 3. Flowchart of the GR_COPD program



Abbreviations: SNF, skilled nursing facility; ADL, activities of daily living; CA, comprehensive assessment

results from the feasibility study that investigated the responsiveness of the clinical COPD questionnaire (CCQ) in this specific group and setting. After completion of the feasibility study, the subsequent GR_COPD study was developed and aimed to investigate the effectiveness of the GR_COPD program on health status, as measured with the CCQ, as primary outcome. Results of the GR_COPD study, a real-life prospective cohort study with a follow-up period of three months, are presented in **chapter 5**.

Part two of this thesis focuses on the palliative care aspects in COPD, with a more specific focus on symptom burden in general, and pain in patients with COPD, in particular. **Chapter 6** presents the results of the systematic review and meta-analysis study on pain in COPD, that aimed to systematically investigate published reports on the prevalence of pain, the characteristics of pain and factors related to pain, in patients with COPD. **Chapter 7** provides the results of cross-sectional data from the GR_COPD study, that investigated the prevalence of pain and its characteristics and relationships in patients with COPD, hospitalized for an acute exacerbation and indicated for the GR_COPD program.

In **chapter 8**, the summary and general discussion of this thesis, the main findings emerging from this work are presented and are placed into a broader perspective. Methodological considerations of the four studies are addressed and interpreted in terms of their clinical relevance and recommendations are made for future research.

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Geriatric Rehabilitation for patients with advanced COPD: programme characteristics and case studies

2

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Abstract

Considering the worldwide ageing population, there is a growing need for rehabilitation programmes especially designed for geriatric patients. The authors developed and implemented a post-acute geriatric rehabilitation programme in a skilled nursing facility for patients with advanced chronic obstructive pulmonary disease (COPD); the GR-COPD programme. This paper describes the characteristics of the programme and presents three case studies to illustrate its possible benefits for individual patients. The case studies show that integration of rehabilitation and palliative care components is essential, as patients with advanced COPD admitted to the hospital for an acute exacerbation often suffer from high symptom burden, deteriorating quality of life, and poor prognosis. Development and implementation of a post-acute GR-COPD programme is feasible and can offer substantial benefits for patients with advanced COPD admitted to the hospital for an acute exacerbation.

Background

Considering the worldwide ageing population with increasing numbers of frail older people with chronic diseases, there is a growing need for rehabilitation programmes specifically designed for geriatric patients. Geriatric patients often have specific problems and needs associated with ageing: multiple comorbidities and polypharmacy, cognitive dysfunction, frailty and the need to talk about end of life decisions. Due to this complexity, disabilities in geriatric patients are often multicausal.[1] Geriatric rehabilitation (GR) has emerged as a promising field of interest and has been defined as "*evaluative, diagnostic and therapeutic interventions whose purpose is to restore functional ability or enhance residual functional capability in elderly people with disabling impairments*".[2]

In a recent systematic review on the effects of inpatient GR programs Bachmann et al concluded that GR has the potential to improve outcomes related to function, admission to nursing homes and mortality in elderly patients.[1] Interestingly, they found only two types of GR programs in their meta-analysis: general and orthopaedic (for hip fracture). They found no study in any other clinical specialty, such as pulmonary, cardiac or stroke that was specifically designed for geriatric patients. This emphasizes the need for development and research for other types of GR programmes.

One of the fields in which development of disease specific programmes for geriatric patients can be meaningful is that of progressive organ failure such as chronic obstructive pulmonary disease (COPD). COPD is a progressive airway disease with rising prevalence, morbidity and mortality rates worldwide.[3] The prevalence of advanced COPD worldwide ranges from 0.1 to 0.7% in the general population and is strongly related to age.[4] In the Netherlands, 18% of all COPD patients suffer from severe COPD, i.e. Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III disease, to very severe COPD, i.e. GOLD stage IV disease (Table 1). It is expected that the prevalences of advanced COPD, i.e. GOLD stages III and IV, will rise by 30% and 120%, respectively in the next decade.[5]

Health status is severely impaired in advanced COPD. Patients have high symptom burden, deteriorating functional capacity, declining quality of life, and poor prognosis.[6,7] Pulmonary rehabilitation (PR) has emerged as a recommended standard of care for patients with symptomatic COPD and is effective in all stages of COPD.[8] PR after an acute exacerbation is a highly effective and safe by means of reducing the risk of readmission and mortality.[9] However, in geriatric patients suffering from severe or end-stage COPD, training capacity is often limited and patients experience too many restrictions in daily functioning to undertake such an intensive programme.

Table 1. GOLD staging of COPD

Stage	Severity	FEV_1 % predicted[#]
I	Mild COPD	>80%
II	Moderate COPD	50-80%
III	Severe COPD	30-50%
IV	Very severe COPD	<30%

#: Recommended simplified spirometry thresholds from the *Global Initiative for Chronic Obstructive Lung Disease (GOLD)*.[19] All values are based on post-bronchodilator FEV_1.
Abbreviations: FEV_1: Forced expiratory volume in the first second as % of predicted value.

Poor health status and prognosis in advanced COPD also call for implementation of palliative care methods. Palliative care should start early in the disease trajectory (when patients become symptomatic) and should be combined with active treatment and life-prolonging care.[10] This recommendation is supported by the Official American Thoracic Society.[11] However, although the palliative care needs of patients with severe or end-stage COPD are increasingly being recognized, palliative care is still scarcely received by patients with advanced COPD.[12] This might be due to the difficult disease trajectory of severe COPD, a phenomenon that was recently described as 'prognostic paralysis'.[13]

Integration of rehabilitation and palliative care has been recognized as an interesting option for patients with advanced COPD.[14] Rehabilitation and palliative care programmes already show many common characteristics. They are both integrated, patient-centred, and multidisciplinary programs primarily focused on symptom control, functional capacity, quality of life, and participation. In patients with progressive disease, incorporation of rehabilitation into palliative care, and vice versa, can offer a strong model for collaboration. Such collaboration can also facilitate the gradual transition from curative management to palliative care.[15] This approach is in line with the model presented by the American Thoracic Society in which patients receive palliative care concurrently with curative/restorative care (including rehabilitation) in an individualized manner.[11]

However, the implementation of such collaboration and integration in daily practice remains challenging. The authors proposed that a post-acute GR programme for patients with severe or end-stage COPD (a GR-COPD programme) could be a solution to the problems, as GR already combines rehabilitation and palliative care aspects. The paper describes the characteristics of this GR-COPD programme. To illustrate the methodology of the programme and its possible benefits for patients, three case studies are reported.

Geriatric Rehabilitation in Dutch nursing homes

In the Netherlands, GR is provided at skilled nursing facilities (SNF), usually situated in nursing homes. An SNF offers post-acute restorative treatment with a multidisciplinary patient-centred approach in a therapeutic environment. GR does not differ from rehabilitation medicine in its approach. However, patients admitted to GR programmes do have different characteristics that those admitted for standard rehabilitation do not: higher age, substantial comorbidity and frailty. Due to their comorbidity and frailty, patients' training capacity is sometimes severely limited, and they often suffer from concurrent diseases and complications interfering with the rehabilitation treatment. In this sense, GR operates at the intersection of geriatric medicine, rehabilitation medicine, and palliative care.

In the Netherlands, 55,000 patients are admitted for GR each year.[16] Almost all of these (93%) are admitted to an SNF for GR after hospital admission. Nearly half are admitted following a hip fracture or other orthopaedic surgery, 24% after stroke, and 31% after any other acute disabling disease or surgery, such as chronic or acute cardiopulmonary or neurological (other than stroke) diseases or abdominal surgery.[16]

SNFs in the Netherlands offer an inpatient rehabilitation programme with an average length of admission (LoA) of 42 days and a maximum LoA of 3 months. On specific indication the inpatient rehabilitation programme can be prolonged for another 3 months (usually for stroke). Each patient receives a weekly average of 18-22 hours of nursing care and 4 hours of individual therapy.[16]

SNFs have a specialized multidisciplinary team including an elderly care physician,[17] a skilled nurse, a physiotherapist, a psychologist, an occupational therapist, a speech and language pathologist, a dietician, and social worker.

In the first week after admission to the SNF a comprehensive geriatric assessment (CGA) is conducted.[18] This comprises a general medical assessment of disease severity, medication, and comorbidity; obtaining (hetero) anamnestic information on symptoms and functional capacity and psychosocial functioning; clinimetric tests; assessment of activities of daily living (ADL) status; assessment of health status; psychosocial screening; and intake by the social worker. Based on the CGA, an individual multidisciplinary GR programme is designed by the elderly care physician. Goal setting is tailored to the individual patient and the GR programme is evaluated weekly and adjusted as needed by the multidisciplinary team. The elderly care physician and the skilled nurse visit all patients weekly (family can be present) to evaluate their progress and adjust goals when needed.

Characteristics of the GR-COPD programme

Patients with GOLD stage III or IV COPD who are admitted to the hospital with an acute exacerbation are signed up for the GR-COPD programme by a pulmonologist. GR-COPD is considered appropriate when patients suffer from high symptom burden and a substantial decline in functional capacity without sufficient recovery during their hospital stay. Furthermore, a multidisciplinary programme must be deemed necessary to achieve functional recovery (not only physiotherapy).
Two 'standard' GR-COPD treatment programmes were developed (Boxes 1 and 2). Differentiation between these two programmes is based on the patients' medical history, health status before hospital admission, and training capacity. Both programmes are individually tailored to the patients' needs and possibilities, based on the CGA.

Box 1. GR-COPD1

- Chronic obstructive pulmonary disease (COPD) Global Initiative for Chronic Obstructive Lung Disease (GOLD)[19] stage III and IV
- History: stable course of health status
- Aim: restore patient to their pre-hospitalisation functional level
- Training capacity: relatively good
- Programme: focus on exercise and strength training (physiotherapy), optimal pharmacological therapy, nutritional advice and patient education

Box 2. GR-COPD2

- Chronic obstructive pulmonary disease (COPD) Global Initiative for Chronic Obstructive Lung Disease (GOLD)[19] stage III and IV
- History: frequent exacerbations and/or hospital admissions, gradual decline of health status, multiple disabling comorbidities
- Aim: to counteract or stabilize the gradual decline of health status and optimize quality of life
- Training capacity: limited
- Programme: rehabilitation and palliative care methods are integrated

Programme content

The GR-COPD programmes consists of several modules concerning different aspects of rehabilitation and palliative care: optimizing pulmonary medication use and inhalation techniques; chronic use of oxygen; smoking cessation; control of symptoms (mostly dyspnoea, cough, pain, fatigue, insomnia, and anorexia);

physiotherapy (endurance and strength training, inspiratory muscle training, relaxation techniques, breathing regulation skills and mucus evacuation techniques); occupational therapy (regulation of pace, use of walking aids); nutritional status and dietary supplementation; speech, breathing and swallowing techniques; psychosocial intervention (mostly aimed at depression, anxiety or adverse coping strategies); self-management strategies and peer support contact; spiritual needs; advance care planning. During the last part of the programme, focus is on discharge and strategies to maintain the attained physical and psychosocial levels of functioning. Patients follow a standardised daily programme and assignment to therapies is stringent. Patients who lack motivation or patients with prominent psychiatric or cognitive dysfunction are not included in the programme and are instead discharged back to their place of residence.

Case studies

Mrs A

Mrs A was 69 years old when she was admitted to the SNF for the GR-COPD1 programme. She had been diagnosed with COPD GOLD stage III in 2008 by her GP and had been unwilling to undergo further evaluation and treatment since. She was admitted to the hospital for 5 days because of progressive dyspnoea due to an acute viral infection. Her medical history showed no other chronic diseases or disabilities. She smoked 40 cigarettes per day. In the past few months her health status had declined significantly and she could walk only small distances, taking several pauses along the way.

On admission to the GR-COPD ward she had a high symptom burden, with dyspnoea at rest, cough, and phlegm, all present during most days. Furthermore she suffered from impaired functional capacity, fatigue, impaired nutritional status, and anorexia. Table 2 shows the outcomes of several tests and questionnaires that were conducted in her CGA.

An individual multidisciplinary rehabilitation programme was designed. Primary interventions were to give education, to support smoking cessation, to analyse and to give advice concerning her diet and to restore functional capacity by means of lower- and upper-body exercise and strength training. During her stay Mrs A recovered very well and stopped smoking, and she could be discharged back home after 30 days. At discharge her functional- and exercise capacity, health- and nutritional status had all improved (Table 2). She continued physiotherapy twice a week. Three months after discharge she was seen by her pulmonologist. She was doing very well, maintaining her functional capacity with daily 1-hour walks and

physiotherapy once a week, and referred to herself as being ‘a different person’. Smoking cessation had been successful. She experienced no restrictions in daily functioning at all and her nutritional status had improved considerably.

Mrs B

Mrs B, 82 years old, widowed, and living alone, had suffered from GOLD stage III COPD since 2005 and had a cardiac history including hypertension, an acute myocardial infarction in 2007, and a coronary artery bypass graft in 2008. She was admitted to the hospital owing to progressive dyspnoea and care dependency. In the past few weeks she had presented twice to the emergency care unit, once with atypical thoracic pain and once with a collapse without evident cause. She was apparently anxious, living alone, and feeling that she had lost control over her life. She was transferred to the SNF after 3 days of hospitalisation.

During the first week an CGA was conducted (Table 2). Based on the CGA an individual GR-COPD2 programme was designed, the goals of which were: to optimize ADL independency; improve functional capacity, nutritional status and coping strategies; and restore her feelings of security and control. To achieve these goals the GR-COPD programme included the following rehabilitation and palliative care modules: physiotherapy (standard endurance and strength training, relaxation techniques and breathing regulation skills), occupational therapy (regulation of pace and advice concerning all ADL and a walking aid), analysis of diet and dietary supplementation, analyses of and intervention regarding a possible anxiety disorder and/or depression by a psychologist, and weekly conversations with the social worker concerning her feeling of insecurity and loss of control due to her progressive limitations and care dependency .

During her stay Mrs B showed good progress in daily functioning, her adaptation and coping strategies improved, and her symptoms diminished remarkably (Table 2). Nevertheless, she remained very insecure, needing constant reassurance. The psychologist concluded that, although there was no specific anxiety disorder or depression present, Mrs B was indeed very frail in both her physical and her psychosocial functioning. The multidisciplinary team foresaw that, considering her frailty and the feeling of insecurity, discharge back home would probably cause a relapse. This was discussed with Mrs B and her children and it was concluded that moving to a residential care home was indicated. After 10 weeks of admission she was discharged back home and a few weeks later she was able to move to the residential care home of her choice.

Mr C

Mr C, 60 years old, was admitted to the hospital with an acute exacerbation without signs of infection. In the past few months he had been treated for several exacerbations by his GP and had been admitted to the hospital three times. His medical history showed, besides GOLD stage IV COPD, Dupeytren's disease in both hands. Mr C was married and lived with his wife. 18 months prior to his most recent hospital admission he had followed the GR-COPD1 programme and after discharge had been stable for more than a year without exacerbations or hospital admissions. On admission to the GR-COPD ward he was mostly bed-bound and could walk only small distances in his room. He used oxygen 1 l/minute continuously because of chronic respiratory failure. A CGA was conducted during the first days of admission (Table 2).

An individual GR-COPD2 programme was designed and included physiotherapy (endurance and strength training) and occupational therapy focusing on improving Mr C's daily functioning so he would be able to function at home without help,

Table 2. Comprehensive geriatric assessment on admission and discharge

	Mrs A		Mrs B		Mr C
	Admission	Discharge	Admission	Discharge	Admission
FEV_1	32%		47%		21%
BMI	21.2 kg/m^2	23.1 kg/m^2	19.5 kg/m^2	21.4 kg/m^2	23.5 kg/m^2
FFMI	12.8 kg/m^2		13.3 kg/m^2		14.2 kg/m^2
HADS-A	4		14		8
HADS-D	5		15		3
CCQ	5.1	1.2	3.9	1.7	3.3
BI	18	20	20	20	14
6MWT	253 m	342 m	168 m	287 m	76 m

Abbreviations: FEV_1: Forced expiratory volume in the first second as % of predicted; BMI: Body mass index , calculated as weight/height^2 (kg/m^2); FFMI: Fat-free Mass Index, was measured during hospital stay using the bioelectrical impedance analysis; HADS: Hospital Anxiety and Depression Score is a screening instrument for symptoms of anxiety and depression with two seven-item subscales, one for anxiety (HADS-A) and one for depression (HADS-D). A score of 8 points or higher on either subscale indicates a higher risk for the presence of a clinically relevant anxiety disorder or depression; CCQ: Clinical COPD Questionnaire is a 10-item, self-administered questionnaire measure of health status. Higher scores indicate a worse health status. The minimal clinically important difference (MCID) of the CCQ total score is ±0.4;[20] BI: Barthel Index , measures activities of daily living. Total score ranges from 0 to 20, with 20 representing complete functional independence. Its MCID is +1.8;[21] 6MWT: the six-minute walking test is a widely used instrument to measure exercise capacity in patients with chronic obstructive pulmonary disease (COD). The MCID for the 6MWT in general for COPD patients is +54 meter. In patients with severe COPD the MCID is +26m.[22]

considering that he was alone at home most of the time because his wife still worked. He was also treated by the dietician for losing weight and by the language and speech therapist regarding breathing and relaxation techniques, and he participated in the education and peer support group run by the psychologist.
During the first month of his stay Mr C suffered from insomnia and recurrent thoracic pains. He described the pain as being unbearable and used Oramorph 2.5 mg as needed with moderate effect. Long-acting morphine and promethazine were prescribed. There was no progress in his functional status and the physiotherapist reported that his exercise capacity was very limited, mostly due to deep desaturation during exercise training, even though oxygen therapy was then temporarily enhanced. In fact, physiotherapy now seemed to have an adverse effect, leading to more exhaustion and pain.
All of this was discussed within the team and with Mr C, his wife and children. It was concluded that the aim of the programme should now be focussed on control of his symptoms of pain and insomnia. End-of-life care communication and advance care planning (do not attempt cardiopulmonary resuscitation, no more admissions to the hospital, discussion of the possibility of palliative sedation) seemed to lift a lot of weight from his shoulders and diminished his fear of dying from suffocation. During the weeks that followed Mr C's insomnia improved and pain was sufficiently controlled with long-acting morphine, 15 mg twice a day. He had 'good and bad days', as he called them, and enjoyed visits from his grandchildren very much. After a few weeks, the elderly care physician was called one evening because Mr C experienced acute progression of dyspnoea and extreme anxiety. After physical examination, diminished unilateral breathing sounds were heard, indicating a possible pneumothorax on the left side, and palliative sedation was started with subcutaneous morphine and midazolam. On this Mr C became unconscious quickly and died the next morning in the presence of his wife and children.

Discussion and conclusion

These case studies show that a GR-COPD programme can offer substantial benefits and can integrate aspects of rehabilitation and palliative care. For some patients the focus is primarily on rehabilitation; restoring functional capacity and improving symptom burden, nutritional status and psychosocial functioning. The case of Mrs A demonstrates the possible effects on functional capacity and quality of life. In the case of Mrs B, adaptation to and acceptation of her loss of independence had a crucial role. Without focusing on this part of the problem, the effects of the GR-COPD programme probably would not have lasted long and relapse

would have been expected. In other patients, as for Mr C, rehabilitation cannot be the primary goal anymore and focus must primarily be on palliative care: symptom control, quality of life and advance care planning.

As literature on this topic is very scarce, further research is essential. This should focus on defining appropriate outcome measurements to identity which patient outcomes can be achieved and sustained. Furthermore, there is a need to identify patient characteristics that can predict which patients are most likely to benefit from a GR-COPD programme.

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3

Geriatric rehabilitation for patients with advanced chronic obstructive pulmonary disease: A naturalistic prospective cohort study on feasibility and course of health status

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Abstract

In view of the worldwide aging population, disease-specific geriatric rehabilitation (GR) programs are needed. Therefore, we developed and implemented a postacute GR program for patients with advanced chronic obstructive pulmonary disease (COPD) (the GR-COPD program). The aim of this study is to investigate the feasibility of the GR-COPD program and to present clinical data on patient characteristics and course of functional capacity and health status. This is a naturalistic prospective cohort study of patients with advanced COPD. A total of 61 patients entered the GR-COPD program and were eligible to participate in this study. All patients suffered from advanced COPD, and comorbidities were frequent. On admission, functional capacity and health status were severely limited but showed significant and clinically relevant improvement during the GR-COPD program. Patients with advanced COPD admitted to hospital for an acute exacerbation suffer from severely impaired functional capacity and poor health status. Development and implementation of a postacute GR program for these patients are feasible and likely to offer substantial improvements. Further research is essential and should focus on designing a controlled intervention trial to investigate the efficacy of the program.

Introduction

Geriatric rehabilitation (GR) has emerged as a promising field of interest, showing that it has the potential to improve outcome measurements related to morbidity and mortality in elderly people.[1] GR is usually organized as a form of integrated care and does not differ from rehabilitation medicine in its multidisciplinary, patient-centered approach. However, geriatric patients differ in many ways from younger patients that need rehabilitation. Besides having multimorbidity, their disabilities are usually multi-causal. Pre-existent functional limitations are not only caused by comorbidity but also by physiological conditions, such as sarcopenia.[2] Furthermore, patients admitted for GR often suffer from concurrent diseases and complications interfering with the rehabilitation treatment. In this sense, GR operates at the crossroads of geriatric medicine and rehabilitation medicine.[2] Considering the worldwide aging population, there is a growing need for programs designed for geriatric patients. However, studies on development, implementation and evaluation of disease-specific GR programs (other than orthopedic and general), are lacking.[1]

One field in which development of disease-specific GR programs can be meaningful is that of progressive organ failure, such as chronic obstructive pulmonary disease (COPD). Prevalence of COPD is rising worldwide and disease severity is strongly related to age.[3] Patients with advanced COPD suffer from a high symptom burden, deteriorating functional capacity and declining quality of life; moreover, their prognosis is poor, especially after hospital admission for an acute exacerbation.[4-6]

Pulmonary rehabilitation (PR) has emerged as a recommended standard of care for patients with symptomatic COPD and is effective in advanced and both stable and postacute COPD in reducing the risk for readmission and mortality and improving health related quality of life (HRQoL) and exercise capacity.[7,8] Poor health status and prognosis in patients with advanced COPD also call for implementation of palliative care methods. Palliative care should start early in the disease trajectory (when patients become symptomatic) and should be combined with active treatment and life-prolonging care.[9]

In clinical practice however, availability of PR programs is limited and patients with advanced COPD are often excluded from these programs because of their limited training capacity and frequent concurrent diseases and complications due to comorbidity, all interfering with the rehabilitation program. Furthermore, although the palliative care needs of patients advanced COPD are increasingly being recognized, palliative care is still scarcely received by patients with advanced COPD.[10] A disease specific GR program that is more adjusted to the needs and possibilities of this group of patients could be an interesting option. Besides offering an adjusted,

low intensity program, GR in the Netherlands is coordinated by an elderly care physician, who is specialized in rehabilitation of frail, often elderly, patients with complex disabilities and multimorbidity.[11] The importance of medical practitioners as an essential part of GR and their findings about causes, comorbidity and prognosis being incorporated into the rehabilitation plan, was recently stated.[12] Furthermore, integration of rehabilitation medicine and palliative care is common practice in GR, and patients with advanced COPD might benefit from this integrated approach.[13] Considering these facts, our group developed and implemented an postacute GR program for patients with advanced COPD (the GR-COPD program).[14] Aim of the present study is to investigate feasibility of the program and to present clinical data on patient characteristics course of functional capacity and health status.

Methods

Design

This is a naturalistic prospective cohort study of patients with advanced COPD admitted to a postacute GR program in a skilled nursing facility (SNF). Baseline data (T0) were collected within 3 days after admission to the SNF. Patient and disease characteristics, functional capacity, nutritional status, psychosocial functioning and health status were registered. At discharge from the SNF (T1), functional capacity, nutritional status and health status were measured again. Data were collected from May 2009 until January 2011.

Setting and study population

Patients with severe (Global Initiative for Chronic Obstructive Lung Disease (GOLD)[15] stage 3) to very severe (GOLD stage 4) COPD, admitted to the hospital for an acute exacerbation were selected for the GR-COPD program by a pulmonologist. Indication for the GR-COPD program was considered appropriate when patients suffered from high symptom burden and/or a substantial decline in functional capacity without sufficient recovery during hospital stay. Furthermore, a multidisciplinary approach was required to achieve improvement in functional capacity and health status instead of physical therapy alone and patients had to be motivated. Patients who lacked motivation, or patients with prominent psychiatric or cognitive dysfunction interfering with rehabilitation, were excluded from the program. All patients admitted to the GR-COPD program were eligible to participate in this study. Data were collected from the patient's file by the patient's physician and transferred to an anonymous data file using Statistical Package for the Social Sciences software (SPSS 20; SPSS, Chicago, Illinois, USA).

The GR-COPD program

In the Netherlands, GR is organized as a form of integrated and transmural care and is provided at SNFs, usually situated in nursing homes.[16] SNFs offer post-acute restorative treatment with a multidisciplinary patient-centred approach in a therapeutic living environment.[16] During the study period, GR was funded by the government's Exceptional Medical Expenses Act (AWBZ), which offers a weekly average of 18–22 h of nursing care and 4 h of individual therapy. The SNF at which the current study was conducted has a multidisciplinary team that offers pulmonary, orthopedic, neurological and general GR. It is situated at a separate ward of the nursing home and has a capacity of 60 beds. On average, 350 patients are admitted to the GR ward each year with a mean length of admission (LOA) of 39 days. The GR-COPD program was developed in 2009 by the multidisciplinary team of the SNF in close collaboration with the pulmonologist and physiotherapist from the pulmonary department of the local hospital. Development of the program was based on national and international guidelines on pulmonary rehabilitation and palliative care.[9,17] The multidisciplinary team of the SNF consists of an elderly care physician, a skilled nurse, a physiotherapist, a psychologist, an occupational therapist, a speech and language pathologist, a dietician, and a social worker. During development and implementation each member of the team received specific training on pulmonary rehabilitation techniques within their own field of interest. A detailed description of the program has recently been published.[14] The GR-COPD program contains several modules concerning different aspects of rehabilitation and palliative care: optimizing pulmonary medication use and inhalation techniques, support smoking cessation, adequate symptom control, physiotherapy (endurance and strength training, inspiratory muscle training, relaxation techniques, breathing regulation skills and mucus evacuation techniques), occupational therapy, analysis of nutritional status and dietary supplementation, analysis of speech, breathing and swallowing techniques, psychosocial intervention (mostly aimed at depression, anxiety or adverse coping strategies), education focusing on self-management strategies, peer support contact and advance care planning. Goal setting is tailored to the individual patient and the program is weekly evaluated and adjusted (as needed) by the multidisciplinary team and the pulmonologist, who makes monthly visits to all patients. All patients follow a standardized 6-week program and assignment to therapies is stringent. The program contains a minimum of six 40-min physiotherapy sessions per week, usually three endurance- and three strength training sessions. Group sessions are combined with individual training. Furthermore, training of breathing-, huffing- and relaxation techniques is offered once a week. Occupational therapy is given once or twice a week in 30- to 45-min sessions and analysis and evaluation of nutritional status is done by the dietician

every week. Patients participate in weekly group sessions, which are supervised by the psychologist, and are aimed at education of patients and relatives on self-management strategies and peer support contact.

Measurements and instruments

The following patient and disease characteristics were registered: age, sex, marital status, disease severity (GOLD stage, forced expiratory volume in 1 s as percentage of predicted (FEV_1 % pred)), long-term oxygen therapy (LTOT) (yes/no), smoking status (smoker/nonsmoker), LOA during hospital stay and LOA during rehabilitation. Comorbidity was assessed using the modified Cumulative Illness Rating Scale (CIRS);[18] The CIRS consists of 13 items (organ or disease systems) with a severity scale ranging from 0 to 4 for each item. Total score is the sum of all items (range 0 to 56), with scores > 10 indicating severe impairment.

Nutritional status was measured by the body mass index (BMI) and the fat-free mass index (FFMI). The BMI was calculated as weight/height^2 (kg/m^2) and was categorized in two groups: underweight (< 21 kg/m^2) and no underweight (≥ 21 kg/m^2).[19] The FFMI was measured during hospital stay using bioelectrical impedance analysis. Depletion was considered when the FFMI was ≤ 16 kg/m^2 in men and ≤ 15 kg/m^2 in women.[19]

Functional capacity

The modified 20-point Barthel Index (BI) measures activities of daily living and is a valid, reliable and widely used instrument to assess improvement during rehabilitation programs.[20] The total score ranges from 0 to 20, with 20 representing complete functional independence. The minimal clinically important difference (MCID) for the BI is not well established for COPD patients. In stroke patients, the MCID of the BI is +1.85.[21]

The 6-minute walk test (6MWT) is a practical, easy to perform and widely used instrument to measure exercise capacity in COPD patients. The MCID for the 6MWT in patients with severe COPD is +26 (± 2) m.[22]

Peripheral muscle strength was measured as hand-grip force (HF) using a hand dynamometer. Total scores (right + left hand) are given in kilogram force, and normative data are age and sex dependent.[23]

Psychosocial functioning

The Hospital Anxiety and Depression Scale (HADS) is a valid and reliable screening instrument for symptoms of anxiety and depression. It has two 7-item subscales, one for anxiety and the other for depression. A score of 8 points or higher on either

subscale indicates a higher risk for the presence of a clinically relevant anxiety disorder or depression.[24]

Health status

Health status was measured using the Clinical COPD Questionnaire (CCQ).[25] The CCQ is a validated and reliable 10-item, self-administered questionnaire. Items are scored on a Likert scale from 0 to 6. The final score is the sum of all items divided by 10; higher scores indicate a worse health status. The CCQ consists of the subdomains symptoms, functional status and mental status, and scores for these three domains can be calculated separately. The MCID of the CCQ total score is ±0.4.[26]

Statistical analysis

All data were processed using SPSS (SPSS 20.0). Descriptive analyses were used for general baseline patient characteristics, disease characteristics and data from measurements on admission. Categorical variables are described as frequencies, while continuous variables were tested for normality and are presented as mean and SD or median and interquartile range (IQR) in case of skewed data. Continuous variables were compared between T0 and T1 using a paired samples t-test or Mann-Whitney test, as appropriate. We defined statistical significance at $p \leq 0.05$ (two-sided level of significance).

Results

General patient characteristics

Of the 63 consecutive patients who entered the program during the period from May 2009 until January 2011, 2 were excluded from this study because of a different diagnosis (1 due to asthma and 1 due to small airway disease). One patient dropped out due to lack of motivation and was discharged back home. Two patients died during the program; in both patients it was concluded that rehabilitation was no longer feasible. For these patients end-of-life care communication and advance care planning (e.g. do not attempt cardiopulmonary resuscitation, no more admissions to the hospital) had been performed and death was expected. Overall, 91% (n=53) of the patients were discharged back home after a median LOA of 35 days (IQR 21-61). Four patients were discharged to a residential care facility and one patient was discharged to a nursing home (Figure 1).

Figure 1: Flow chart of patients

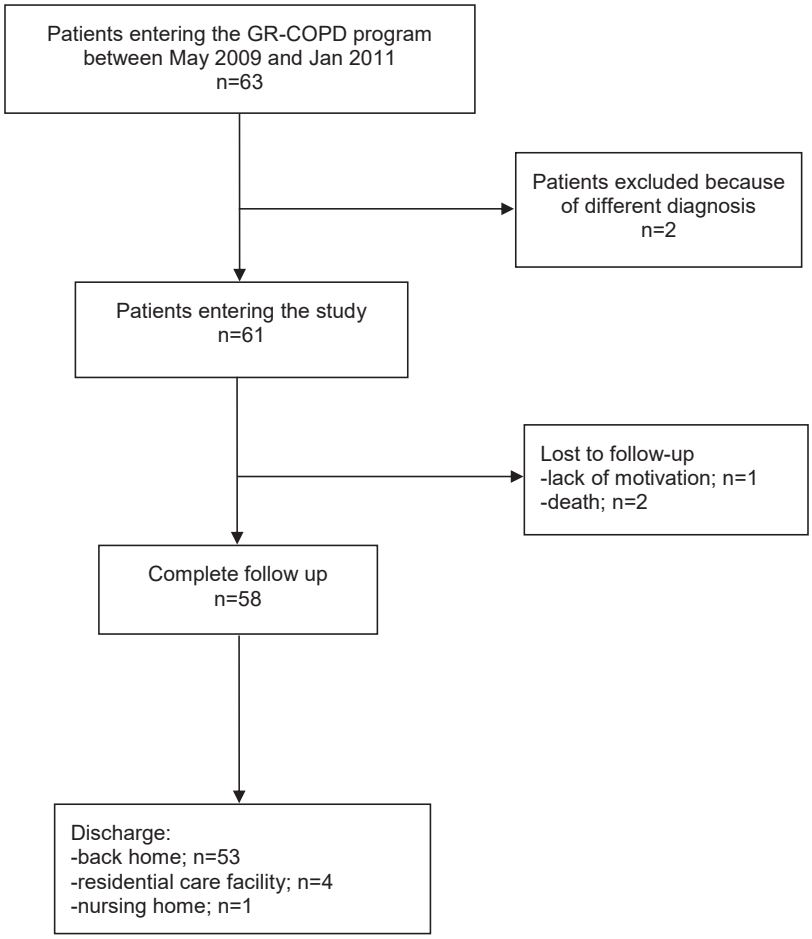


Table 1 presents the patient and disease characteristics on admission to the GR-COPD program (T0). All patients had advanced COPD (GOLD stage 3 (n=29) or GOLD stage 4 (n=32)), with a mean FEV_1%pred of 32.9 (±10.8). Of these, 17 (28%) patients were on LTOT. Comorbidity was prevalent, as 41% of the patients had a CIRS score ≥10, indicating severe impairment due to comorbidity. Organ and disease systems (except respiratory) showing the highest mean scores were: cardiac (0.97, 35% ≥ 2), musculoskeletal and integumentary (0.85, 33% ≥ 2) and endocrine-metabolic (0.75, 31% ≥ 2).

Table 1. Patient and disease characteristics on admission (baseline/T0) to the GR-COPD program.*

Number of patients	61
Age in years (SD)	68.9 (9.9)
Sex: woman, n (%)	30 (49)
Living alone, n (%)	28 (46)
LOA-H in days (IQR)	8 (7-11)
LOA-SNF in days (IQR)	35 (21-61)
GOLD 3, n (%)	29 (48)
GOLD 4, n (%)	32 (52)
FEV_1%pred (SD)	32.9 (10.8)
LTOT, n (%)	17 (28)
Comorbidity, CIRS (total score) (SD)	9.6 (4.3)
Smoker, n (%)	10 (16.5)

**Categorical variables are described as frequencies, while continuous variables are tested for normality and are presented as mean and SD or median and IQR in case of skewed data. Abbreviations: GR-COPD: geriatric rehabilitation program for patients with advanced chronic obstructive pulmonary disease; LOA-H: length of admission during hospital stay; LOA-SNF: length of admission during rehabilitation; IQR: interquartile range; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1%pred: forced expiratory volume in 1 s as percentage of predicted; LTOT: long-term oxygen therapy; CIRS: Cumulative Illness Rating Scale.*

Measurements on admission

Table 2 presents the outcomes of all measurements on admission (T0) to and discharge from the GR-COPD program. Functional capacity was impaired; on admission the BI and the 6MWT showed care dependency and limited exercise capacity. Peripheral muscle strength showed that 25 patients (41%) had a HF below the normative value. Although the mean BMI was within normal range, 20 patients (33%) had a BMI < 21 kg/m^2 indicating underweight. Depletion of the FFMI was present in 44% (n=27) of all patients. HADS scores showed that 47% of the patients had a higher risk (score of ≥ 8) for anxiety and 43% for depression. The mean CCQ score was 3.5 (±0.9), indicating severely limited health status.

Course of functional capacity during the GR-COPD program

There was a significant and clinically relevant improvement of functional capacity during the GR-COPD program (Table 2, Figure 2). The median BI improved from 17 (IQR 15-18) to 20 (IQR 17-20), and the mean 6MWT from 208 m (±119) to 274 m (±122) at discharge. In 41 patients the BI improved 2 or more points (>MCID), in 2 patients the BI on discharge was lower than on admission, and in 9 patients the BI did not change during the program. In 71.7% of the patients the 6MWT improved

Table 2. Outcomes of measurements on admission (T0) to and discharge from (T1) the GR-COPD program.

Measurement	T0	T1	p
Functional capacity			
BI (IQR)	17 (15-18)	20 (17-20)	<0.001[b]
6MWT (m) (SD)	208 (119)	274 (122)	<0.001[a]
HF (kgf) (SD)	52.0 (17.0)	55.6 (17.5)	<0.001[a]
HF < norm value, n (%)	25 (41)	18 (30)	0.024[c]
Nutritional status			
BMI (kg/m^2) (SD)	23.3 (4.7)	23.8 (4.0)	0.051[a]
BMI < 21kg/m^2, n (%)	20 (33)	12 (20)	0.007[c]
FFMI (kg/m^2) (SD)	15.8 (2.3)	-	-
Psychosocial functioning			
HADS_Anxiety	7.5 (4.2)	-	-
HADS_Depression	7.4 (4.6)	-	-
Health status			
CCQ (SD)	3.5 (0.9)	2.2 (1.0)	<0.001[a]

Categorical variables are described as frequencies, while continuous variables are tested for normality and are presented as mean and SD or median and IQR. Continuous variables were compared between T0 and T1 using a paired samples t-test[a] or Mann–Whitney test[b], as appropriate. Categorical variables were compared between T0 and T1 using chi^2-tests[c]. Abbreviations: GR-COPD: geriatric rehabilitation program for patients with advanced chronic obstructive pulmonary disease; BI: Barthel index; 6MWT: 6-minute walking test; HF: handgrip force; BMI: body mass index; FFMI: fat-free mass index; HADS: Hospital Anxiety and Depression Scale; CCQ: Clinical COPD Questionnaire.

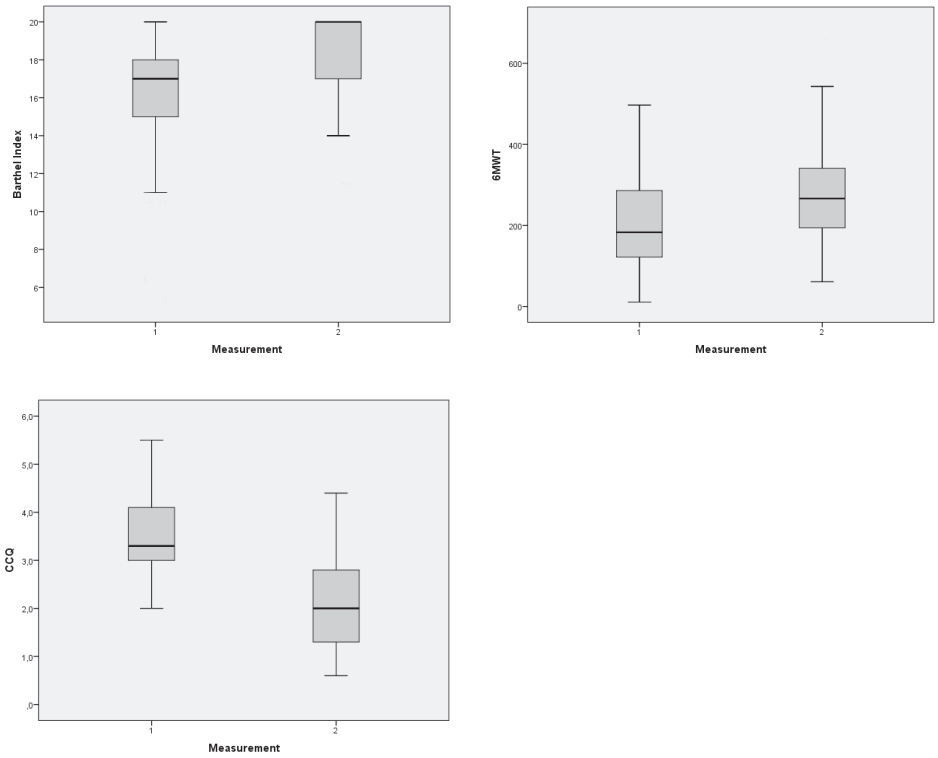
≥ 26 m (>MCID). In 2 patients the 6MWT did not change and in 6 patients the 6MWT decreased. The nutritional status measured by the mean BMI showed no significant improvement. However, the number of patients with underweight (BMI <21 kg/m^2) decreased from 20 to 12 (p=0.007). Improvement in health status was also significant and clinically relevant: the mean score of the CCQ improved from 3.5 (±0.9) on admission to 2.2 (±1.0) at discharge.

Discussion

Main findings

The main finding of this study is that, in patients with advanced COPD who suffered a recent exacerbation, comorbidity is frequent, functional capacity is impaired, and health status is severely limited. Furthermore, nutritional status is often impaired and many patients are at risk for an anxiety or depressive disorder. Neverthe-

Figure 2. Course of functional capacity and health status from admission (T0) to discharge (T1).



Abbreviations: 6MWT: six-minute walking test; CCQ: Clinical COPD questionnaire;

less, during the GR-COPD program, functional capacity and health status showed substantial and clinically relevant improvement. This implies that, although these patients are severely limited in training capacity, a postacute GR program is feasible and is likely to offer substantial benefits.

Strength and limitations

To the best of our knowledge, this is the first study focusing on feasibility, patient characteristics and course of functional capacity in patients with advanced COPD, admitted to a postacute GR program. The current study was not designed as an intervention trial but as a naturalistic prospective cohort study. Therefore, a control group was not part of this study and the current study can also be seen as a pilot study. Further research is essential and should focus on designing a controlled intervention trial to investigate the efficacy of the program. Other limitations are possible population bias due to criteria used to select patients for the program and the fact that we were unable to collect information on patients that were selected

for the program but refused to participate. Since these latter patients were discharged back home from the hospital, health status and functional capacity of our population is probably worse than that of the initial population that was indicated for the program in the hospital. This could bias the generalizability of our results. We used the BI to measure functional capacity. However, the BI might not be the most suitable instrument to measure functional capacity and impairment in patients with COPD due to the ceiling effect and insensitivity to change at the upper level of the scale.[27] Nevertheless, the BI is a widely used instrument and recent literature shows that it can be used in patients with COPD.[28] Our results also show the ceiling effect of the BI, but improvement was still clinically relevant.

Few data are available on GR programs specifically designed for patients with advanced COPD. A recent systematic review on the efficacy of geriatric rehabilitation failed to identify one disease-specific program for geriatric patients that has been well evaluated, other than orthopedic and general geriatric rehabilitation.[1] Studies on the effect of PR in elderly patients with COPD are scarce, but show positive outcomes of PR programs for relatively older COPD patients.[29,30] However, compared with our population, these studies included only stable COPD patients with less severe airflow obstruction and functional impairment. Furthermore, excluded from these latter studies were patients with comorbid diseases that are likely to limit exercise capacity. Studies on the effect of postacute PR programs in elderly COPD patients are also scarce. Puhan et al performed a systematic review to assess the effect of postacute PR on future hospital admissions, mortality, HRQoL and exercise capacity, in patients with COPD after a recent exacerbation.[8] The authors concluded that postacute PR is a highly effective and safe intervention to reduce hospital admissions and mortality and to improve HRQoL. Of the nine studies that met their eligibility criteria, five investigated the effect of an inpatient PR program that followed immediately after hospital admission.[31-35] Of these studies, one was conducted at an intensive care unit[31] and one study included patients with less severe airflow limitation compared with our population.[32] Three small studies reported positive effects on exercise capacity,[33] health-care utilization,[34] and HRQoL,[35] of a postacute PR program in populations who were more similar to ours with regard to age, lung function and exercise capacity. However, in those studies comorbidity was not always measured,[35] or patients with significant comorbidities were excluded from the PR program.[33] Although there are differences between our population and the populations described in studies on the effect of postacute PR, these data are in line with our results, indicating that postacute rehabilitation in patients with advanced COPD is feasible, safe and can probably offer substantial benefits.

A notable finding of the present study is that the mean age of the patients that entered the GR-COPD program was 68.9 years, which is relatively young considering that this is a GR program. However, indication for the GR-COPD program was based on disease severity and the presence of impaired functional capacity and health status with insufficient recovery during hospital stay. Age was not an inclusion or exclusion criterion. This suggests that, in patients with COPD, advanced disease with limited functional capacity and health status can be present at a relatively young age. Nevertheless, 54% of the patients were aged ≥ 70 years and almost 20% of our population were aged ≥80 years.

Implications for future research

Although our results suggest that the GR-COPD program is effective in this specific group of patients, our study design did not include a control group and a randomized controlled trial is compulsory to confirm these findings. As literature on this topic is scarce, further research is essential. Studies should focus on defining appropriate outcome measurements to identity which patient outcomes can be achieved and sustained, and identify patient characteristics that can predict which patients with advanced COPD are most likely to benefit from an post-acute GR program.

Conclusions

Patients with advanced COPD admitted to hospital for an acute exacerbation suffer from frequent comorbidities, severely impaired functional capacity and poor health status. Development and implementation of a postacute GR program for this group of patients is feasible and can probably offer substantial improvements.

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4

Health status measured by the Clinical COPD Questionnaire (CCQ) improves following post-acute pulmonary rehabilitation in patients with advanced COPD: a prospective observational study

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Abstract

Aims: To evaluate outcomes of the clinical chronic obstructive pulmonary disease (COPD) questionnaire (CCQ) in patients with advanced COPD admitted for a post-acute pulmonary rehabilitation (PR) program and to relate (change in) health status to lung function, degree of dyspnoea and (change in) functional capacity. *Methods*: This is a prospective observational study in patients with advanced COPD admitted for a post-acute PR program in a skilled nursing facility. Health status (CCQ) and functional capacity were measured before and after rehabilitation. *Results*: Health status measured by the CCQ was severely impaired and showed significant and clinically relevant improvement during the post-acute PR program. Moderate to strong correlations were found between CCQ scores and functional capacity on admission and at discharge. Moderate correlations were found between improvement in CCQ scores and improvement in functional capacity. No correlation was found between CCQ scores and lung function (forced expiratory volume in 1 s % predicted). *Conclusions*: Health status measured by the CCQ improves following a post-acute PR program in patients with advanced COPD and correlates with improvement in functional capacity. These results suggest that the CCQ is sensitive to change in response to PR in this specific group of patients.

Introduction

In chronic obstructive pulmonary disease (COPD), health-related quality of life (HRQoL) is increasingly recognised as an important measurement that reflects the patient's perspective of the impact of the disease on symptom burden, functional capacity and psychosocial functioning.[1,2] Therefore, more traditional parameters of disease severity (such as lung function) should be supplemented with measurements of HRQoL or health status. However, instruments to assess HRQoL or health status are often time-consuming and/or relatively difficult for the patients to comprehend. Furthermore, although instruments to measure HRQoL are widely used as important outcome measurements in research, their use in daily practice (especially in primary care) is limited. In 2003 van der Molen et al.[3] developed and validated the Clinical COPD Questionnaire (CCQ). The CCQ is a simple and reliable 10-item tool that focuses not only on the clinical status of the airways, but also on functional limitations and psychosocial dysfunction. The CCQ consists of three separate domains (i.e., symptoms, functional state and mental state) and was originally developed to measure the clinical health status in patients with COPD. Treatment in clinical practice can be aimed at these subdomains, which elaborates on tailor-made medicine in patients with COPD. The CCQ can also be used to evaluate the adequacy of clinical management[4] and to assess functional performance.[5] In fact, the functional state domain of the CCQ is reported to be the best patient-reported outcome tool for assessing functional performance in patients with COPD in primary care.[6] Furthermore, the CCQ can be used to measure the effect of integrated disease management interventions in primary care[6] and to predict exacerbations[7] and mortality[2] in patients with mild to moderate COPD. However, little is known about the use of the CCQ in patients with advanced COPD, or its use as a primary outcome measure in pulmonary rehabilitation (PR). Therefore, the aim of the present study was to evaluate outcomes of the CCQ in patients with advanced COPD admitted for post-acute PR and to correlate (improvement in) health status measured by the CCQ to lung function, degree of dyspnoea and (improvement in) functional capacity.

Materials and methods

Design and setting

This is a prospective observational study designed to evaluate outcomes of the CCQ in patients with advanced COPD and to relate (improvement in) health status to lung function, degree of dyspnoea and (improvement in) functional capacity. The

study was conducted at a skilled nursing facility (SNF) that offers geriatric rehabilitation for patients with advanced COPD. Data were collected from the patients' files by the patients' physicians and transferred to an anonymous data file (SPPS 20). Given the fact that this observational study measured a form of structured usual care, no written informed consent was required.
Baseline measurements (T0) were collected and performed within 3 days after admission to the SNF; these consisted of patient and disease characteristics, health status (CCQ), degree of dyspnoea (modified Medical Research Council (mMRC) scale) and functional capacity (Barthel Index (BI) and the Six-Minute Walking Test (6MWT)). At discharge from the SNF (T1), health status and functional capacity were measured again. Data were collected from May 2009 until January 2011.

Participants

Patients with severe (Global Initiative for Chronic Obstructive Lung Disease (GOLD)[8] stage 3) to very severe (GOLD stage 4) COPD, admitted to the hospital for an acute exacerbation, were indicated for the PR programme by a pulmonologist. PR was considered appropriate when patients suffered from high symptom burden and/or a substantial decline in health status and functional capacity without sufficient recovery during hospital stay. Furthermore, a multidisciplinary approach was required to achieve improvement in health status instead of physical therapy alone. Patients who lacked motivation or patients with prominent psychiatric or cognitive dysfunction interfering with PR were excluded from the programme. All patients admitted to the PR programme were eligible to participate in this study.

Pulmonary rehabilitation programme

The PR programme was offered at an SNF that offers geriatric rehabilitation. Geriatric rehabilitation consists of post-acute restorative inpatient treatment with a multidisciplinary patient-centred approach in a therapeutic environment.[9] Geriatric rehabilitation does not differ from rehabilitation medicine in its approach. However, patients admitted to geriatric rehabilitation programmes do have different characteristics: higher age, substantial comorbidity and limited functional and training capacity.[10] The SNF at which the present study was conducted has one ward with a multidisciplinary team that is specialised in post-acute care and rehabilitation for patients with advanced COPD.[11] The PR programme contains several modules on different aspects of rehabilitation. Goal setting and duration of the programme is tailored to the individual patient, and the programme is evaluated weekly and adjusted (as needed) by the multidisciplinary team. All patients follow a standardised weekly programme that contains a minimum of five 40-min physiotherapy sessions, occupational therapy once or twice a week, analysis and evaluation of nutritional

status every week and weekly group sessions (education of patients and relatives, and peer support contact). Assignment to therapies is stringent. A detailed description of the PR programme was recently published.[11]

Health status and degree of dyspnoea

Health status was measured using the Dutch version of the CCQ.[3] The CCQ is a validated and reliable 10-item, self-administered questionnaire. The CCQ consists of three subdomains: symptoms, functional state and mental state. Items are scored on a Likert scale (range 0–60). The final score is the sum of all items divided by 10; separate scores for all three domains can be calculated. Higher scores indicate a worse health status. The minimal clinically important difference (MCID) of the CCQ total score is − 0.4.[12] Degree of dyspnoea was measured using the mMRC dyspnoea scale.[7] The mMRC is an ordinal four-point scale (grades 0–4) based on degrees of various physical activities that precipitate dyspnoea. Grade 4 represents the most severe category.

Functional capacity

Functional capacity was measured by the modified BI and the 6MWT. The BI measures activities of daily living and is a valid, reliable and widely used instrument to assess activities of daily living improvement during rehabilitation programmes.[13] The total score ranges from 0 to 20, with 20 representing complete functional independence. The MCID for the BI is not well established for COPD patients. In stroke patients the MCID of the BI was calculated at +1.85.[14] The BI was assessed by a specialised nurse of the SNF.

The 6MWT is a practical, easy-to-perform and widely used instrument for measuring exercise capacity in patients with COPD. The 6MWT is strongly predictive of survival in patients with COPD and an important outcome measure for PR.[15,16] The MCID for the 6MWT in patients with severe COPD is +26 (±2) m.[17] The 6MWT was assessed by a physiotherapist of the multidisciplinary team of the SNF in a standardised setting in accordance with international guidelines.[15]

Statistical analysis

All data were processed using SPSS (IBM SPSS Statistics for Windows, version 20.0, IBM, Armonk, NY, USA). Descriptive analyses were used for measurements on admission (T0) and at discharge (T1). To compare the mean outcome measurements on admission (T0) and discharge (T1), the paired sample *t*-test was used. In case of skewed data (BI), the nonparametric Wilcoxon test was used. To investigate potential regression to the mean, a linear regression analysis was performed for change (T1 − T0) against baseline measurements (T0). Pearson's correlation

coefficient was calculated to determine the strength of linear correlations between pairs of variables of interest. In case of skewed data or measurements at interval level, Spearman's correlation coefficient was calculated. We defined statistical significance at P≤0.05 (two-sided level of significance).

Results

Study population

A total of 63 patients entered the programme during the specified period and were eligible to participate in this study. Of them, two were excluded because of a different diagnosis (one for asthma and one for small airway disease), two (5%) died during the rehabilitation programme and one dropped out because of lack of motivation. Patient and disease characteristics are presented in Table 1. Median length of admission to the SNF was 35 (21-61) days. The study population consisted of 30 women and 31 men with a mean age of 68.9 (±9.9) years. All patients had advanced COPD (GOLD stage 3 or 4) with a mean forced expiratory volume in 1 s (FEV_1) % predicted of 32.9 (±10.8); in addition, 17 patients (28%) were on long-term oxygen therapy.

Table 1. Patient and disease characteristics on admission (baseline/T0)

No. of patients	61
Age in years (SD)	68.9 (9.9)
Sex: woman, n (%)	30 (49)
Living alone, n (%)	28 (46)
LOA-H in days (IQR)	8 (7-11)
LOA-SNF in days (IQR)	35 (21-61)
GOLD 3, n (%)	29 (48)
GOLD 4, n (%)	32 (52)
FEV_1 % of predicted (SD)	32.9 (10.8)
LTOT, n (%)	17 (28)
Smoker, n (%)	10 (16.5)

Categorical variables are described as frequencies, while continuous variables were tested for normality and are presented as mean (SD) or median (IQR) in case of skewed data.
Abbreviations: FEV_1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IQR: interquartile range; LOA-H: length of admission during hospital stay; LOA-SNF: length of admission during rehabilitation; LTOT: long-term oxygen therapy.

Health status, degree of dyspnoea and functional capacity on admission

On admission, the mean CCQ score was 3.5 (±0.9), indicating severely limited health status, and the mean score on the mMRC was 3.8 (±1.1). Functional capacity was limited, as the median BI score (17 (interquartile range 15–18)) indicated care dependency and the mean 6MWT (208 (±119)m) indicated limited exercise capacity.

Course of health status and functional capacity during the PR programme

During the PR programme there was a significant and clinically relevant improvement in health status (CCQ) and functional capacity (BI and 6MWT) (Table 2). The mean CCQ improved from 3.5 (±0.9, range 1.3–5.8) on admission to 2.2 (±1.0, range 0.6–4.4) at discharge. All three subdomains of the CCQ showed significant improvement: of all patients, 86.8% showed an improvement on the CCQ equal to the MCID or more; in two patients the CCQ score did not change; and in three patients the score increased, indicating a deterioration of health status during the programme.

Table 2. Outcomes of measurements on admission (T0) and discharge (T1)

	T0		T1		p
CCQ (SD)	60	3.5 (0.9)	53	2.2 (1.0)	<0.001[a]
*symptoms	60	3.7 (1.1)	54	2.4 (1.1)	<0.001[a]
*functional state	60	3.9 (1.2)	53	2.6 (1.4)	<0.001[a]
*mental state	60	2.3 (1.6)	53	1.3 (1.4)	<0.001[a]
Barthel Index (IQR)	61	17 (15-18)	58	20 (17-20)	<0.001[b]
6MWT, meters (SD)	58	208 (119)	54	274 (122)	<0.001[a]

Variables were tested for normality and are presented as mean (SD) or median (IQR) in case of skewed data.

Abbreviations: 6MWT: Six-Minute Walking Test; IQR: interquartile range.

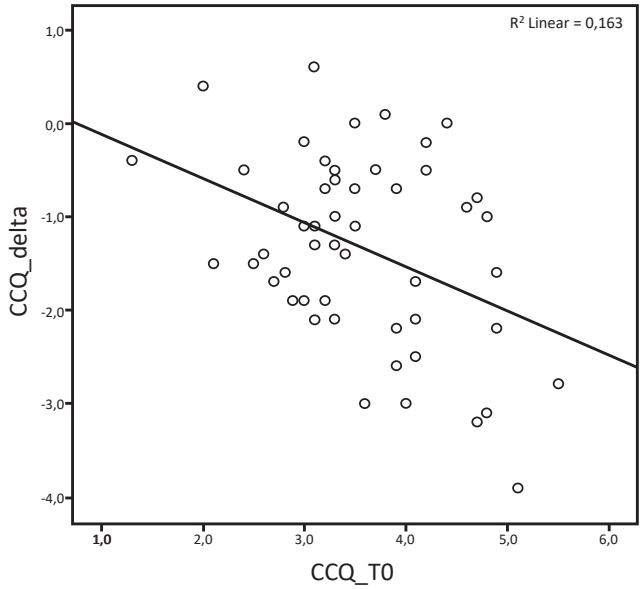
[a]*Variables were compared between T0 and T1 using a paired sample t-test, as appropriate.*

[b]*Variables were compared between T0 and T1 using a paired sample Wilcoxon test, as appropriate.*

On admission the median BI score was 17 (range 5–20), and 20 (range 11–20) at discharge. In 41 patients the BI improved two points or more, in 2 patients the BI at discharge was lower than on admission and in 9 patients the BI did not change during the programme. However, all these latter patients had a maximum score (19 or 20) on admission. The mean 6MWT improved from 208m (range 36–568 m) on admission to 274m (range 61–634 m) at discharge. In 71.7% of the patients the 6MWT improved >26 m. In two patients the 6MWT did not change and in six patients the 6MWT decreased.

To investigate potential for regression to the mean, a linear regression analysis was performed for change (T1 − T0) against baseline measurements (T0). Figure 1 shows the relation between improvement in CCQ (CCQ-delta) and CCQ at baseline (CCQ-T0). Results from the linear regression model show a Y-intercept (b0) of 0.36 and a gradient of the regression line (b1), representing the change in outcome variable (CCQ-delta) associated with one-unit change in the predictor (CCQ-T0) of − 0.473.

Figure 1. Scatterplot showing the relation between improvement in CCQ (CCQ-delta) and CCQ at baseline (CCQ-T0) Y-intercept (B_0) = 0.36°; gradient of regression line (b_1) representing the change in outcome variable (CCQ-delta) associated with one unit change in the predictor (CCQ-T0)= -0.473.



Abbreviations: CCQ: Clinical COPD questionnaire;

Relationship between health status, lung function, functional capacity and degree of dyspnoea on admission and discharge

To determine the correlation between health status as measured by the CCQ and lung function (FEV_1%pred), functional capacity (6MWT and BI) and degree of dyspnoea (mMRC) on admission and at discharge, we calculated the correlation coefficients between these variables (Table 3). On admission, there was a moderate to strong correlation between CCQ (CCQ total score and CCQ function domain score) and functional capacity measured by the 6MWT (CCQ total score: r = − 0.400, P = 0.002, CCQ function score: − 0.431, P = 0.001) and the BI (CCQ total score: r

Table 3. Correlations of CCQ score (total and subdomains) on admission (T0), discharge (T1) and change in CCQ scores (T1-T0) with measurements of functional capacity, degree of dyspnoea and lung function.

T		BI[b]	6MWT[a]	mMRC[b]	FEV_1[a]
T0					
	CCQ-total				
	r	-0.481**	-0.400**	0.392**	-0.126
	P	<0.001	0.002	0.003	0.343
	N	60	57	55	59
	CCQ-symptoms				
	r	-0.209	-0.167	0.117	-0.072
	P	0.126	0.235	0.414	0.605
	N	55	52	51	54
	CCQ-function				
	r	-0.573**	-0.431**	0.437**	-0.183
	P	<0.001	0.001	0.001	0.186
	N	55	52	52	54
	CCQ-mental				
	r	-0.192	-0.239	0.183	-0.113
	P	0.156	0.084	0.193	0.410
	N	56	53	52	55
T1					
	CCQ-total				
	r	-0.572**	-0.539**		
	P	<0.001	<0.001		
	N	53	51		
	CCQ-symptoms				
	r	-0.436**	-0.424**		
	P	0.002	0.003		
	N	48	47		
	CCQ-function				
	r	-0.579**	-0.503**		
	P	<0.001	<0.001		
	N	47	46		
	CCQ-mental				
	r	-0.197	-0.297*		
	P	0.179	0.043		
	N	48	47		
T1-T0					
	CCQ-total				
	r	-0.099	-0.432**	0.058	-0.223
	P	0.481	0.002	0.694	0.113
	N	53	50	48	52
	CCQ-symptoms				
	r	-0.110	-0.449**	0.062	-0.151
	P	0.468	0.002	0.696	0.321
	N	46	44	42	45
	CCQ-function				
	r	-0.201	-0.313*	0.051	-0.304*
	P	0.186	0.041	0.748	0.045
	N	45	43	42	44
	CCQ-mental				
	r	-0.067	-0.268	0.007	-0.069
	P	0.568	0.78	0.963	0.650
	N	46	44	42	45

Abbreviations: 6MWT: Six-Minute Walking Test; BI: Barthel Index; FEV_1: forced expiratory volume in 1 s; mMRC: modified Medical Research Council.

*[a]Spearman's correlation coefficient was calculated for non-normally distributed (BI) and interval (mMRC) measurements. [b]Pearson's correlation coefficient was calculated for normally distributed measurements (6MWT, FEV_1%pred). **Correlation is significant at the 0.01 level (two-tailed). *Correlation is significant at the 0.05 level (two-tailed).*

= − 0.481, P<0.001, CCQ function score: − 0.573, P<0.001). No correlation was found between the CCQ on admission (CCQ total score and CCQ separate domain scores) and lung function measured by the FEV_1% of predicted. On admission, there was a moderate correlation between the mMRC dyspnoea scale and the CCQ total score and the CCQ function domain score. We found no significant correlation between the mMRC dyspnoea scale and the symptom domain of the CCQ. At discharge, we found a strong correlation between the CCQ total score and the CCQ function domain score and functional capacity measured by the 6MWT (CCQ total score: r = − 0.572, P<0.001) and the BI (CCQ total score: r = − 0.539, P<0.001). To determine whether patients with an improvement in CCQ of more than the MCID are the same as those with clinically relevant functional improvements, we calculated the correlation coefficient between these variables. There was a moderate correlation between improvement in health status (CCQ-total score) and improvement in functional capacity (6MWT): r = − 0.432, P = 0.002. We found no significant correlation between improvement in CCQ and improvement in BI or between improvement in 6MWT and improvement in BI. Of the subjects with an improvement in the CCQ score equal to or greater than the MCID, 67.7 and 73.9% also showed a clinically relevant improvement on the 6MWT and the BI, respectively. Overall, 45.3% of the subjects showed clinically relevant improvements on all three outcome measurements (CCQ, 6MWT and BI). We found no correlation between baseline lung function (FEV_1% of predicted) and improvement in health status or functional capacity.

Discussion

Main findings

The first main finding of this study is that health status measured by the CCQ is severely impaired in this group of patients. Second, health status measured by the CCQ showed substantial and clinically relevant improvement during the PR programme; this improvement correlates well with improvement in functional capacity, indicating that the CCQ is sensitive to change in response to PR.

Strengths and limitations of this study

This is the first study that describes the course of health status as measured by the CCQ in patients with advanced COPD during a post-acute PR programme, with follow-up of almost all patients and few missing data at follow-up. However, this study warrants some limitations. Our population might be biased because we did not collect information on patients who were selected for the PR programme but were

not motivated to participate. Patients who refused to participate were discharged from the hospital. The health status and functional capacity of our population may be even worse than that of the initial population that was indicated for PR in the hospital, because most patients who refused to participate were discharged home. Furthermore, part of the improvement in health status measured by the CCQ might be caused by the 'in care effect' of patients participating in a study. PR is expected to improve functional capacity, whereas improvement in the CCQ might partly be caused by participation in a study like the present one. Correlation between these two outcome measurements might therefore be overestimated. However, because of the observational design of the study and the fact that we solely measured a form of structured usual care, the 'in care effect' cannot be ruled out completely, but probably has limited influence on our results.

As the current study is an analysis of change between baseline and follow-up, a regression to the mean effect should be considered as a possible cause of observed change. The results of the linear regression analysis show that, when adjusted for baseline, improvement in CCQ reduces from − 1.3 to − 0.5. This means that even after adjusting for regression to the mean there continues to be a significant and clinically relevant change.

To evaluate the use of the CCQ in this group of patients, comparison of the CCQ with another HRQoL instrument that is regularly used in this group of patients, namely, the Chronic Respiratory Questionnaire Self-Administered Standardized Format (CRQ-SAS),[18] was initially included in the design of the study. However, during our study, compliance with the CRQ-SAS was very low, leading to very high rates of missing data (50%), and we were therefore unable to present reliable results from the CRQ-SAS.

Nevertheless, this is still an interesting result, as it also confirms that HRQoL instruments such as the CRQ are often time-consuming and relatively difficult for patients to comprehend, leading to limited use, and usefulness, in daily practice. Compliance with the CCQ was, however, very good, leading tovery few missing data (<2% at baseline; 8% at follow-up).

The last limitation is the fact that we did not have a control group, and although our results suggest that the CCQ is a responsive instrument for measuring change in health status following a post-acute PR programme in patients with advanced COPD, a randomised controlled trial would serve well to further confirm these findings.

Interpretation of findings in relation to previously published work

Literature on health status as measured by the CCQ in patients with advanced COPD is scarce. The CCQ was originally developed and validated by van der

Molen et al.[3] and has since been validated for the Italian[19] and Greek language[20] in patients with stable COPD. Compared with our results, data from these latter studies show lower CCQ scores (total scores and separate domain scores). This can be explained by the fact that our population suffered from a recent exacerbation and that exacerbations have a negative effect on health status. Recently, Kocks et al.[21] reported data from two randomised controlled COPD exacerbation trials on the day-to-day course of patient-reported health status (as measured with the CCQ) during exacerbations. They reported results from 210 COPD patients admitted to the hospital for an acute exacerbation (mean age 70.6 years, mean FEV_1: 37% of predicted); the CCQ total score on admission to the hospital was 3.3 (±0.93). Although this score is similar to our results, the time at which the CCQ score was measured is different, as we measured the CCQ on admission to the SNF. In the study by Kocks et al., the CCQ total score improved rapidly during hospital stay, with a mean score of 2.3 on day 7. These results seem to confirm that our population indeed consisted of those patients who failed to recover during hospital stay.

Our results show a substantial and clinically relevant improvement in health status during the PR programme. This suggests that the CCQ is sensitive to change in response to PR in this group of patients. Literature on the responsiveness of the CCQ to interventions such as PR, or other forms of integrated care, is also scarce. The Picasso Bocholtz study[6] evaluated the effect of Integrated Disease Management on health status as measured by the CCQ in 106 primary-care patients with mild to moderate COPD (mean age 64 years, mean FEV_1 63% of predicted). At the start of the study, the mean CCQ total score was 1.5, with an overall improvement of − 0.4 ($P = 0.001$) during follow-up. In the study by Damato et al.,[19] the CCQ showed sensitiveness to change in 46 patients undergoing an inpatient PR programme; the CCQ total score improved from 2.0 at baseline to 1.3 after PR ($P<0.001$). Our data are in line with these studies, indicating that the CCQ is sensitive to change following interventions such as PR.

We found no correlation between CCQ total score at baseline and lung function (FEV_1% of predicted). This is in line with a growing body of evidence showing that traditional measurements of disease severity (such as lung function) do not correlate well with HRQoL or health status.[1,2] However, our results differ from those of van der Molen et al.[3] and Damato et al.[19] In both latter studies a significant correlation was found between the mean FEV_1% of predicted and the mean CCQ total score (van der Molen et al.: $r = − 0.38$, $P<0.01$; Damato et al.: $r = − 0.57$, $P<0.01$). These correlation coefficients account for the total groups, including healthy smokers and subjects at risk. In COPD patients (GOLD stage 1–4), van der Molen et al. reported a correlation of $r = − 0.49$ ($P<0.001$). An explanation for these conflicting results can be that all our patients suffered from advanced COPD

and thus differed substantially from those in the other two studies. With disease progression, health status deteriorates and is probably relatively less influenced by the degree of airflow limitation. During the PR programme, we found no correlation between baseline lung function (FEV_1% of predicted) and improvement in health status or functional capacity. This suggests that disease severity, as measured by the degree of airflow limitation, does not seem to predict which patients benefit most from the PR programme.

Implications for future research, policy and practice

In the present study, we evaluated the use of the CCQ in patients with advanced COPD admitted for post-acute PR. Considering our results, we recommend that the CCQ should be used as a (primary) outcome measure in an experimental study design to evaluate the effect of post-acute (inpatient/outpatient) PR on health status in patients with advanced COPD. Our study also confirms that the CCQ is a practical and easy-to-use instrument for assessing health status, not only in research but also in daily practice. Our study was conducted with patients who were recruited after hospital admission for an acute exacerbation and admitted for inpatient PR. Thus, our patients were not treated in primary care during this study. However, in primary care, patients with advanced COPD are a growing group, with a huge burden of disease and in great need of better care. Therefore, research should also focus on the course of health status measured by the CCQ in patients with advanced COPD in primary care and the clinical use of the CCQ in elaborating tailor-made medicine for this specific group of patients.

Conclusions

In patients with advanced COPD, health status measured by the CCQ improves after a post-acute PR programme. Moderate-to strong correlations were found between the CCQ scores and functional capacity, showing that the CCQ correlates well with other important outcome measurements of PR. These results suggest that the CCQ is sensitive to change in response to PR in this group of patients.

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A prospective cohort study on the effects of geriatric rehabilitation following acute exacerbations of COPD

5

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Abstract

Objectives: Older patients with COPD, hospitalized for an acute exacerbation, often do not receive recommended postacute pulmonary rehabilitation. This underuse might be related to the impaired clinical and functional status of these patients, who are more likely to present with frailty, comorbidities, and disability. Having developed and implemented a geriatric rehabilitation program for these patients (GR_COPD), the primary aim of this study was to investigate the effectiveness of this program. *Design and intervention*: A prospective cohort study with a three-month follow-up period. Patients who declined the GR_COPD program were considered as controls. *Setting and participants*: The study was conducted at the pulmonary department of two hospitals. Patients were eligible when hospitalized due to an acute exacerbation of COPD and indicated for the GR_COPD program based on standardized criteria. *Methods*: Primary outcome was defined as change in disease-specific health status measured with the clinical COPD questionnaire (CCQ), secondary outcome as the exacerbation rate ratio during follow-up. To balance potential confounders between the intervention and control group, propensity score-based weighted linear regression analyses were performed. *Results*: Of the 158 included patients [78 (49.4%) male, mean age 70.8(±8.1) years, mean forced expiratory volume in 1 s: 35.5 (±12.8) as % of predicted], 78 received the GR_COPD program. The results of the CCQ showed a significant and clinically relevant treatment effect of -0.56 points (CI -0.89 to -0.23; p=0.001). Patients in the control group had 2.7 times more exacerbations compared with the intervention group [CI 2.13 to 3.58; p<0.001]. *Conclusion and implications:* This study shows a clinically relevant effect of the GR_COPD program on disease-specific health status and exacerbation rate. Implementation of the program for older patients with severe COPD hospitalized for an acute exacerbation is recommended.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable, treatable, but often progressive chronic disease that is characterized by persistent airflow limitation and a chronic inflammation of the airways.[1] COPD is an increasing problem as it is becoming the third leading cause of morbidity and mortality worldwide.[2] This trend is especially true in older adults, since prevalence and disease severity of COPD are both strongly related to age.[2] Acute exacerbations of COPD represent a major health care burden. They are the most frequent reason for hospital admissions and death and negatively influence quality of life and prognosis in patients with COPD.[3-6]

Pulmonary rehabilitation in the early postacute period of an exacerbation (postacute PR) is an effective intervention to counteract deteriorating health status caused by acute hospital admission.[3] However, referral, motivation and adherence to postacute PR are difficult and it remains unclear how postacute PR can best be organized for specific groups of patients.[3,7] For example, aging populations change the demographics and characteristics of hospitalized patients with COPD, i.e. multimorbidity and frailty often interfere with postacute PR.[8] Secondly, older patients with COPD are often (temporarily) care-dependent after hospital admission. This care-dependency requires a specific setting for postacute PR and a fluid transition from hospital to rehabilitation setting. Lastly, many older patients with COPD require palliative care and advance care planning.[9] However, palliative care is seldom offered to patients with COPD, and integration of palliative care aspects into rehabilitation is still not optimal.[10]

Geriatric rehabilitation is an interesting option for these COPD patients and is defined as "*evaluative, diagnostic and therapeutic interventions whose purpose is to restore functional ability or enhance residual functional capability in older people with disabling impairments*".[11] Furthermore, integration of palliative care methods into geriatric rehabilitation programs is already considered standard care.[12,13] Geriatric rehabilitation can be provided in hospitals, intermediate care facilities, or at skilled nursing facilities. These latter facilities are usually situated within nursing homes, and organized as structured care pathways in collaboration with several departments of adjacent hospital(s).

The systematic review of Bachmann et al. showed that geriatric rehabilitation can improve outcomes related to function, admission to nursing homes, and mortality.[13] However, their review only included studies on general and orthopedic geriatric rehabilitation and lacked studies on the effectiveness of programs in other clinical specialties (e.g. pulmonary, cardiac or stroke) specifically designed for geriatric

patients. This lack of evidence indicates the need for other types of geriatric rehabilitation programs.[13]

In 2009 we developed and implemented a postacute geriatric rehabilitation program for older patients with COPD, called the GR_COPD program. Published clinical data and preliminary evaluation of patients' responses showed that the program was feasible and likely to offer substantial improvements in health- and functional status.[12,14] However, since the feasibility study was not a regular effectiveness trial and lacked a control group, the efficacy of the program could not be determined.

Therefore, the GR_COPD study was conducted with the aim to investigate effectiveness of the GR_COPD program on health status (primary outcome) and exacerbation rate and functional status (secondary outcomes); the results of the latter study are presented here.

Methods

Design

This was a prospective cohort study conducted in the pulmonary department of two hospitals. Data were collected during hospital stay (i.e. at start of the study; T0) and during a hospital visit at 3-month follow-up (T1). Patients were included between January 2015 and January 2018. The Medical Ethics committee of Leiden University Medical Centre approved the study (P14.248), which was registered in the Netherlands National Trial Register (NTR6261).

Study population

All patients admitted to hospital with an acute exacerbation COPD, according to the Global Initiative for chronic Obstructive Lung disease (GOLD) standards, were eligible for this study.[1] Patients also needed an indication for rehabilitation based on standard inclusion/exclusion criteria (Box 1). When diagnosis and indication for rehabilitation were present, patients were invited to participate and the motivation for the GR_COPD program was assessed. All participants signed a written informed consent.

Randomization for the GR_COPD program was considered unethical as rehabilitation after an acute exacerbation has proven benefits and the program was already implemented in practice. Therefore, all patients included in the study were offered the GR_COPD program; however, those patients who declined the program were considered as controls. Treatment and control participants were recruited in both hospitals.

Box 1. Criteria for the GR_COPD program.

Major inclusion criteria:
1. Decline of functional status (ADL)
2. Health status is severely impaired, as measured by CCQ, score ≥ 2.0
3. Frequent exacerbations; ≥ 2 in the last 6 months (excluding the present exacerbation)

Minor inclusion criteria:
1. Hypoxemia (excluding pre-existent chronic respiratory failure)
2. Impaired nutritional status: BMI < 21 kg/m^2 and/or FFMi depletion
3. Patients at risk for clinically relevant anxiety disorder or depression; HADS ≥ 8 on either subscale

Indication for the GR_COPD program: 2 major OR 1 major AND 2 minor criteria
Exclusion criteria:
1. Conditions interfering with rehabilitation, such as end-stage of disease
2. Major psychiatric or cognitive disease

Abbreviations: ADL: activities of daily living; CCQ: Clinical COPD questionnaire; BMI: body mass index; FFMI: fat-free mass index; HADS: Hospital anxiety and depression scale.

GR_COPD program

The complete GR_COPD program has been described in detail elsewhere and is available in appendix 1; briefly, it consisted of a six-week inpatient multidisciplinary rehabilitation program delivered immediately after hospital admission.[12] The program is organized as an integrated care pathway and contains multiple standard modules, e.g. daily physiotherapy sessions, occupational therapy, and an extensive self-management education program. Patients followed a standardized daily program, individually tailored to the patient's needs and possibilities, based on a comprehensive assessment.

Measurements

The following information was collected: age, sex, spirometry (according to the GOLD guidelines),[15] co-morbidity [Charlson Comorbidity Index (CCI); with a total score of ≥2 (excluding COPD) indicating major co-morbidity],[16] smoking status (current smoker/non-smoker) and the use of oxygen therapy (yes/no). Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS); a score of ≥8 on either subscale indicates a high risk for the presence of an anxiety disorder or depression.[17] Nutritional status was measured

by calculating body mass index (BMI; kg/m^2); and was divided into underweight (<21 kg/m^2), normal weight (21-30 kg/m^2), and obesity (>30 kg/m^2).[18]

Primary outcome

The primary outcome was defined as change in disease-specific health status as measured with the clinical COPD questionnaire (CCQ).[19] The CCQ is a validated, reliable, 10-item self-administered questionnaire (appendix 2). Items are scored on a scale ranging from 0-6; the final score is the sum of all items divided by 10, resulting in a total-score ranging from 0-6. The CCQ is sensitive to change in response to rehabilitation in these patients and the minimal clinical important difference (MCID) of the CCQ total score is ±0.4.[20-22]

Secondary outcomes

Exacerbation rate and change in functional status were defined as secondary outcomes. Exacerbation rate during follow-up was assessed using a standard question: “How many acute exacerbations (periods of acute worsening of respiratory symptoms that resulted in additional therapy [corticosteroids and/or antibiotics) and/or hospital admission] did you have in the previous three months?” In case of missing data, information was retrieved from the patient’s file.

Functional status was measured with the Barthel index (BI) for activities of daily living (ADL); the BI is a valid, reliable instrument to assess ADL during rehabilitation with a MCID of ± 1.85.[23,24] Total score ranges from 0-20, with 20 representing complete functional independence, 15-19 mild, 10-14 moderate and <10 severe care dependency, respectively.[24] Exercise capacity was measured with the six-minute walking test (6MWT), assessed according to the ERS guidelines.[25] The 6MWT is a widely used instrument to measure exercise capacity in patients with COPD with a MCID of ±30 meter.[26] Scores are measured in number of meters walked in six minutes and range from zero to the maximum amount. A score of zero indicates that the patient is unable to walk or perform the test.

Effect evaluation

General statistical analysis

All data were processed using the SPSS, version 23. Descriptive analyses were used for baseline patient and disease characteristics (at T0). Categorical variables are described as frequencies; continuous variables were tested for normality and are presented as mean and standard deviation (SD), or median and interquartile range (IQR) in case of skewed data.

Propensity score

To balance potential confounders between the intervention (GR_COPD) group and the controls, the propensity score (PS) was estimated and PS analyses was performed. PS estimation and analysis were based on recently published recommendations that were obtained from a research method symposium of the American Geriatrics Society.[27] To estimate the PS, potential confounders were identified based on published data and included the following variables: age, sex, marital status, lung function, oxygen therapy, exacerbation rate, co-morbidity score, smoking status, ADL status, BMI, HADS and hospital location. These variables were determined prior to data lock and specified in the Dutch Trial Register (NTR6261). All variables included in the PS were measured before treatment initiation. Continuous variables were transformed into categorical variables (when appropriate) according to literature.[16-18] Then, the PS (probability of receiving rehabilitation) was estimated for all individuals included in the dataset using a logistic model encompassing 27 parameters. The PS model was then evaluated using the standardized mean difference (SMD) to assess the balance in potential confounders between the two groups. An SMD of <0.1 was considered acceptable.[28,29] Overlap in the distribution of the PS between the two groups was examined using a graphical presentation.

The primary outcome measure was the mean change in health status as measured by the CCQ_delta during follow-up (CCQ at T1 minus CCQ at T0) adjusted for the CCQ score at T0. The adjusted treatment effect (ATE) was estimated with a weighted linear regression, using PS-based weights defined as the inverse of the probability of receiving the treatment that the patients actually received. Thus, the weight (w) to estimate ATE is w=1/PS for the intervention group and w=1/(1-PS) for the control patients. The CCQ score at T0 was added to the model as a second covariate.

Secondary outcomes (analyzed in a similar way) were mean change in ADL status and functional exercise capacity (also controlled for baseline values). Poisson regression analysis was used for the exacerbation rate during follow-up as a dependent variable (since exacerbation rate is a count outcome). Data were visually assessed for the required model assumptions. The following sensitivity analyses were made: we calculated the PS and weight (w) for the dataset with complete CCQ results at T1 that were used for the primary analysis (n=125) and explored the influence of extreme weights by truncation using maximum weights of five and ten.

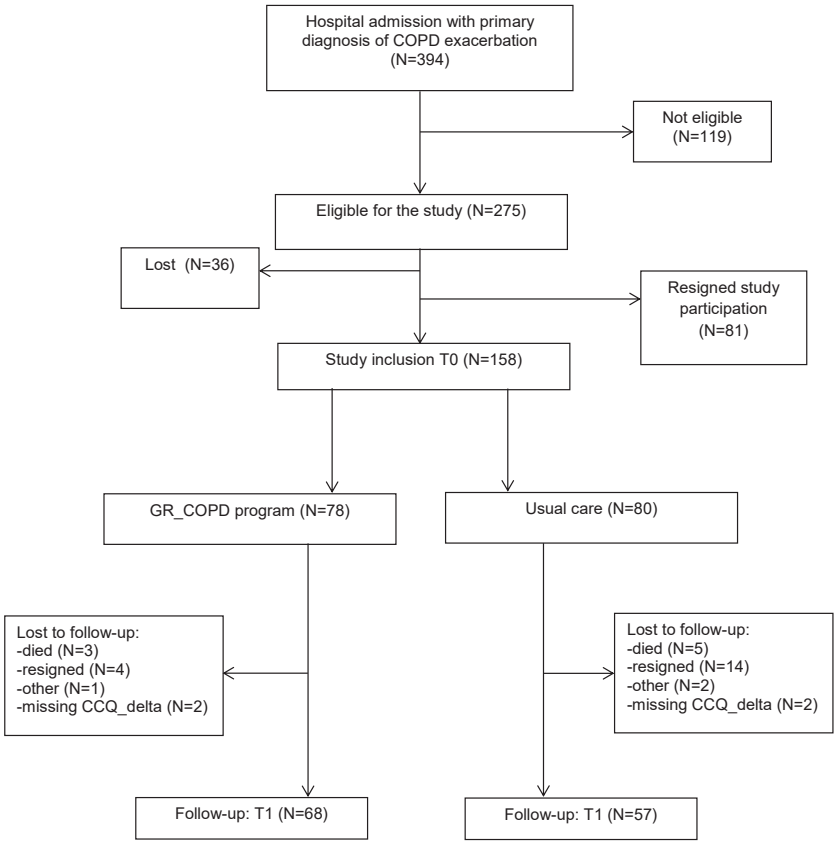
Results

General results

During the inclusion period, 394 patients were hospitalized for an acute exacerbation (Figure 1); of these, 275 met the inclusion criteria and were eligible for this study. Of this latter group, 81 refused participation and 36 patients could not be included due to other reasons (i.e. most were already discharged).

Finally, 158 patients were included: 78 (49.4%) male, mean age 70.8 (±8.1) years, and mean forced expiratory volume in 1 s (FEV_1) as % of predicted value: 35.5 (±12.8). Of these, 78 patients received the GR_COPD program and the remaining 80 patients served as controls.

Figure 1. Flow chart of the GR_COPD study.



Abbreviations: COPD: chronic obstructive pulmonary disease; CCQ: Clinical COPD questionnaire;

No differences in age, sex, CCQ and HADS scores were found between the included patients and those that declined participation or were lost before they could be included. Table 1 presents baseline data on the participants before and after weighting. Before weighting, patients in the intervention group had worse lung function and a higher percentage of current smokers, higher HADS and lower co-morbidity scores, compared with the controls. After PS weighting, the FEV_1 % predicted was still higher in the controls; however, when classified into GOLD stages no differences were found, indicating sufficient balance in lung function as a potential confounder between the two groups. Although the percentage of current smokers was lower in the controls after PS weighting (SMD 0.10), we considered this difference acceptable, also taking into account the expected negative influence of smoking on outcome measures.

During follow-up, eight patients died, 18 resigned from the study and three were lost for other reasons. In four other patients, the primary outcome measure (CCQ_delta) was missing. Patients that dropped out of the study [n=21; 9 (43%) male] were slightly older [73.3 (± 6.8) years] with slightly better lung function [FEV_1 38.2 (±13.5) % predicted] at baseline compared to participants that completed follow-up. No other differences at baseline were found. Eight patients died during follow-up [sex: 75% male; mean age 75.5 (±7.9); mean FEV_1 32.5 (±14.5) % predicted; mean CCQ_T0: 3.7 (±1.1)].

Estimation of treatment effect

Table 2 shows the treatment effect for the primary and secondary outcome measures. During follow-up, the intervention group improved (on average) 1.42 CCQ points compared with 0.75 points in the controls (unadjusted values); this difference represents a significant and clinically relevant adjusted treatment effect of -0.56 points (p=0.001). Effect analysis of the exacerbation rate during follow-up, showed that the control group 2.7 times more frequently had an acute exacerbation compared with the intervention group [rate ratio 2.7 (CI 2.13 to 3.58); p<0.001]. Regarding functional status, the BI showed a clinically relevant improvement in the intervention group; however, when adjusted for baseline data, the difference between the two groups was no longer significant (p=0.56). The 6MWT showed a clinically relevant improvement in both groups, with no significant differences between the groups on the 6MWT_delta [adjusted treatment effect +89 (±99) vs +50 (±114); p=0.76].

Sensitivity analysis

A secondary PS and weight (*w*) was calculated for the dataset including only those participants with complete CCQ results at T1 (n=125) and the primary analysis

Table 1. Baseline data (T0); patients and disease characteristics, stratified between intervention (GR-COPD) group and control group, before and after weighting using propensity score based weights.

		Before PS weighting			After PS weighting		
	Total group N=158	GR-COPD N=78	control N=80	SMD	GR-COPD	control	SMD
Age, years; mean (SD)	70.8 (8.1)	70.2 (8.5)	71.3 (7.6)	-0.14	71.3 (8.9)	71.6 (7.4)	-0.03
Sex, male; n (%)	78 (49.4)	33 (42.3)	45 (56.2)	-0.28	66 (44.6)	70 (42.4)	0.04
Living alone; n (%)	65 (41.1)	33 (42.3)	32 (40.0)	0.05	64 (43.2)	75 (45.5)	-0.05
FEV_1%p; mean (SD)	35.5 (12.8)	33.6 (13.4)	37.4 (12.1)	0.29	32.9 (13.2)	35.0 (12.0)	0.17
GOLD stage; n (%)				0.47			0.07
2	33 (20.9)	12 (15.3)	21 (26.3)		24 (16.2)	29 (17.6)	
3	80 (50.6)	36 (46.2)	44 (55.0)		78 (52.7)	81 (49.1)	
4	45 (28.5)	30 (38.5)	15 (18.7)		46 (31.1)	55 (33.3)	
Oxygen therapy; n (%)	44 (27.8)	25 (32.0)	19 (23.7)	0.19	49 (33.1)	60 (36.1)	-0.06
AE ≥2; n (%)		39 (50.0)	34 (42.5)	0.15	66 (39.6)	62 (42.3)	0.09
CCI ≥2; n (%)	93 (58.9)	42 (53.8)	51 (63.8)	-0.20	86 (58.1)	91 (55.2)	0.06
Current smoker; n (%)	50 (31.6)	33 (42.3)	17 (21.2)	0.46	52 (35.1)	50 (30.3)	0.10
HADS-A; mean (SD)	7.7 (4.6)	8.3 (4.7)	7.2 (4.5)	0.23	7.8 (4.5)	7.7 (4.1)	0.04
HADS-D; mean (SD)	7.4 (4.2)	8.1 (4.2)	6.8 (4.2)	0.30	7.4 (4.0)	7.1 (3.8)	0.08
BMI; mean (SD)	24.9 (5.6)	24.4 (5.0)	25.4 (6.0)	-0.18	24.6 (5.4)	24.9 (5.5)	-0.05
BMI categories; n (%)				0.20			0.08
underweight	37 (23.4)	17 (21.8)	20 (25.0)		36 (24.2)	37 (22.1)	
normal	94 (59.5)	50 (66.7)	44 (55.0)		89 (59.7)	105 (63.6)	
obesity	27 (17.1)	11 (14.1)	16 (20.0)		24 (16.1)	23 (13.9)	
Location, Deventer; n (%)	83 (52.5)	56 (71.8)	27 (33.7)	0.82	82 (55.0)	90 (54.2)	0.02

All the above variables were included in the PS model.

Abbreviations: PS: propensity score; SMD: standardized mean difference; FEV_1%p: forced expiratory volume in one second as percent of predicted value; GOLD: global initiative for chronic obstructive lung disease; AE: exacerbation rate during six months prior to hospital admission; CCI: Charlson co-morbidity index; HADS: hospital anxiety (A) and depression (D) scale; BMI: body mass index.

Table 2. Results of primary and secondary effect analysis.

Variable	N	T0		*T1*		*Unadjusted change score*		Adjusted between-group differences (95% CI)*	*p-value*
		GR-COPD	control	GR-COPD	*control*	*GR-COPD*	*control*		
CCQ, mean (SD)	125	3.8 (1.1)	3.6 (0.9)	*2.3 (1.0)*	*2.8 (1.0)*	*-1.42 (1.1)*	-0.75 (1.1)	-0.56 (-0.89 to -0.23)	0.001
BI, median (IQR)	116	17 (15-19)	19 (17-20)	*19 (17-20)*	*19 (17-20)*	*1.3 (3.1)*	0.1 (2.6)	0.26 (-0.63 to 1.15)	0.562
6MWT, mean (SD)	95	190 (105)	234 (115)	*280 (116)*	*284 (132)*	*89 (99)*	50 (114)	6.09 (-33.4 to 45.6)	0.760
				T1				RR**	
Exacerbation rate, mean (SD)	129	-	-	*0.63 (0.9)*	*1.56 (1.2)*			2.77 (2.13 to 3.58)	<0.001

*Average treatment effect (delta_CCQ/BI/6MWD) was estimated using weighted linear regression using propensity score based weights, adjusted for T0 scores.

**Poisson regression analysis, presenting rate ratio as effect measure.

Abbreviations: CCQ: clinical COPD questionnaire; BI: Barthel Index; 6MWT: six-minute walking test;

(change in CCQ) was repeated using weighted linear regression. Results showed a very similar adjusted treatment effect (beta -0.53; CI -0.85 to -0.20; p=0.002). Also, only small differences were found in treatment effect when truncating maximum weights to five (beta -0.53; CI -0.86 to -0.20; p=0.002) and to ten (beta 0.56; CI -0.89 to -0.23; p=0.001).

Discussion

The main finding of this study is a significant and clinically relevant effect of the GR_COPD program on health status and on exacerbation rate during follow-up.
These are the first reported data on the effects of geriatric rehabilitation for patients with severe COPD. When comparing these data with the results of our feasibility study, several similarities emerge.[14] First, patients' characteristics, such as age [68.9 (±9.9) years], sex (51% male), marital status (46% living alone) and lung function [FEV_1 32.9 (±10.8) % predicted] are similar. More interestingly, the present results confirm the outcomes of our feasibility study on the preliminary evaluation of patients' response to the program [mean CCQ score improved from 3.5 (±0.9) to 2.2 (±1.0)], showing that these results are robust and reproducible.
Our data are in with line others who reported positive effects of rehabilitation in the early postacute phase of an exacerbation.[3] The systematic review of Puhan et al that investigated the effect of short-term hospital based and outpatient or home-based programs, described only one study with an extensive postacute PR program similar to our program.[3,30] In this latter study, 46 patients [mean age 64.0 (±1.9)(intervention); 68.0 (±2.2)(controls); mean FEV_1, 36 (±7) % predicted] hospitalized for an exacerbation received either usual care or a 10-day hospital based training, followed by a 6-month program of supervised walking training at home and education.[31] The authors reported sustained improvements in quality of life and exercise capacity, but no data on co-morbidity and functional status were presented, making comparison to our data difficult. One study in the review of Puhan et al also reported on exacerbation rate as outcome and showed a trend in a reduction of exacerbation rate in the intervention group; however, only 26 patients were included and the effect was not significant (p=0.06).[32] Furthermore, the intervention consisted of a home-based program and patients were slightly younger [mean age 67 y (±9.7) (intervention); 65.0 y (±11.0) (controls)] with less severe airflow obstruction [mean FEV_1, 38 (±12) and 42(±12) % predicted, intervention and controls respectively] compared with our population. Thus, although the usefulness of this comparison is debatable, the effect we found on exacerbation rate seems relatively large. Hypothetically, this might also be an effect of the inpatient setting,

as the GR_COPD program offered a relatively safe and proactive environment with 24/7 medical care for (on average) the first six weeks follow-up. In conclusion, although our novel results are broadly in line with others, due to the heterogeneity in patient characteristics, setting and intervention, comparison is somewhat limited.

Strengths and limitations

Our study design encompasses both strengths and limitations. Conducting trials on the effects of postacute PR is challenging.[3] For example, recruitment of patients is problematic and randomization is considered unethical given the poor health status of most of these patients and the proven benefits.[3] As these difficulties probably apply even more to geriatric patients, more observational studies are required as they are an important source of data when evaluating treatment benefits and harms in older adults.[3,27] Because lack of comparability in outcome risk factors between the treatment and control group could lead to confounding, we chose to use the recommended PS weighting techniques.[27] Nevertheless, confounding is still possible and cannot be fully excluded. Because this was a prospective observational cohort-study and lenient exclusion criteria were applied, generalizability within this group and setting is high. However, selection bias is possible due to the criteria applied and because 36 eligible patients were not included since they were already discharged. Moreover, patients willing to participate might have been a selective group, even though no differences were found in demographics, CCQ and HADS scores between included and not included patients.

There was no effect of the GR_COPD program on functional status. Although the BI improved in the intervention group, this effect was not significant when controlling for baseline data. This lack of treatment effect is probably partly due to the ceiling effect of the BI, i.e. at baseline 47 (29.8%) patients already had the maximum score of 20. This questions the validity of the BI as a suitable outcome measure in this specific group of patients and setting. Also, no treatment effect was found on the 6MWT, which is unexpected considering earlier studies on postacute PR on exercise capacity. Explanations for this finding could be the wide range of the 6MWT in both our groups, the amount of missing data (40%) leading to limited power, and/or more room for improvement in the treatment group considering their lower baseline values. Furthermore, in our patients, baseline 6MWT values were relatively low compared with others.[30,33,34] These results reflect the poor functional status of our patients, and also question the relevance of the 6MWT as an outcome measure in these patients.

Conclusion and implication

This study shows beneficial effects of the GR_COPD program on disease-specific health status and exacerbation rate. The results indicate that geriatric rehabilitation for older patients with severe COPD hospitalized for an acute exacerbation is effective and could be implemented in clinical practice. Future research may establish whether these results can be maintained for a longer period and whether more suitable and relevant outcome measurements on functional status are required for this specific group of older patients.

Appendix 1 Chapter 5: The GR_COPD program

The GR_COPD program was developed as a structured-care pathway. The program offers multidisciplinary patient-centred rehabilitation that also integrates palliative care aspects, to older patients with COPD who have been hospitalised for an acute exacerbation. The program aims to counteract or stabilise the gradual decline in health status, achieve sustainable improvements in functional status, quality of life and self-management, and prevent hospital readmissions. The multidisciplinary team that offers the GR_COPD program consists of an elderly care physician, a skilled nurse, a physiotherapist, a psychologist, an occupational therapist, a speech and language pathologist, a dietician, and a social worker. The GR-COPD program contains several modules concerning different aspects of rehabilitation and palliative care, categorized into three domains: i) body structure and function, ii) functional status and iii) self-management. These three domains encompass several standard treatment modules, all targeted at improving disease-specific health status as the ultimate goal of the program.

Improvement in body structure and function is achieved through treatment modules that focus on a) optimizing pharmacological treatment, inhalation techniques and oxygen use, b) prevention and treatment of co-morbidities, c) optimizing nutritional status and/or treatment of undernourishment, and d) improving symptom burden.

To improve functional status, patients receive endurance and strength training, inspiratory muscle training, relaxation techniques, breathing regulation skills, mucus evacuation techniques and occupational therapy. If endurance and strength training is not feasible, due to limited training capacity, rehabilitation is aimed at decreasing care dependency, home adaptation, medical aids and providing professional support at home.

Improvement of self-management, as the third domain of the GR_COPD program, is pursued by the following treatment modules: education on COPD, peer-group support, smoking cessation support, training of energy saving techniques, general advice concerning healthy aging (e.g. nutrition, exercise), and assessment of compliance and coping responses (e.g. patients compliance with care recommendations, adaptive coping responses). Furthermore, the needs of informal/family caregivers are addressed and advance care planning is discussed.

The treatment program (including goal setting) is tailored to the individual patient, based on a comprehensive assessment (GA) that is conducted within the first week after admission. The program is weekly evaluated and adjusted (as needed) by the multidisciplinary team and the pulmonologist, who makes monthly visits to all patients. All patients follow a standardized 4-6 weeks program and assignment to therapies is stringent. The program contains a minimum of six 40-min physiotherapy

sessions per week, usually three endurance- and three strength training sessions. Group sessions are combined with individual training. Furthermore, training of breathing-, huffing- and relaxation techniques is offered once a week. Occupational therapy is given once or twice a week in 30- to 45-min sessions and analysis and evaluation of nutritional status is done by the dietician every week. Patients participate in weekly group sessions, which are supervised by the psychologist, and are aimed at education of patients and relatives on self-management strategies and peer support contact.

Appendix 2 Chapter 5

Clinical COPD Questionnaire Please circle the number of the response that best describes how you have been feeling during the **past week** (only **one** response for each question)							
On average, **during the past week**, how often did you feel:	never	hardly ever	a few times	several times	many times	a great many times	almost all the time
1. Short of breath **at rest**?	0	1	2	3	4	5	6
2. Short of breath **doing physical activities**?	0	1	2	3	4	5	6
3. **Concerned** about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4. **Depressed (down)** because of your breathing problems?	0	1	2	3	4	5	6
In general, **during the past week**, how must of the time:	0	1	2	3	4	5	6
5. Did you **cough**?	0	1	2	3	4	5	6
6. Did you **produce phlegm**?	0	1	2	3	4	5	6
On average, **during the past week**, how limited were you in these activities **because of your breathing problems**:	not limited at all	very slightly limited	slightly limited	moderately limited	very limited	extremely limited	totally limited or unable to do
7. Strenuous physical activities (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8. Moderate physical activities (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9. Daily activities at home (such as dressing, washing yourself)?	0	1	2	3	4	5	6
10. Social activities (such as talking, being with children, visiting friends/relatives)?	0	1	2	3	4	5	6

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Pain in patients with COPD: a systematic review and meta-analysis

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Abstract

Objectives: To systematically investigate the prevalence of pain, factors related with pain and pain management interventions in patients with chronic obstructive pulmonary disease (COPD). *Design*: Systematic review and meta-analysis. Data sources and study eligibility criteria: PubMed (MEDLINE), EMBASE, CINAHL and PsychINFO from 1966 to December 2013. Studies were included if they presented clinical data on pain or symptom burden in patients with COPD, or pain as a domain of quality of life (QoL). All types of study designs were included. *Results*: Of the 1571 articles that were identified, 39 met the inclusion criteria and were included in this review. Fourteen studies focused on pain and symptom burden (including pain) in patients with COPD and 25 studies focused on QoL using a questionnaire that included a separate pain domain. Reported pain prevalence in high-quality studies ranged from 32 to 60%. Included studies report that pain is more prevalent in patients with COPD compared to participants from the general population. Co-morbidity, nutritional status, QoL and several symptoms were related to pain. None of the included studies reported a significant relationship between lung function and pain prevalence or severity. However, studies investigating pain in patients with moderate COPD reported higher pain prevalence compared to studies in patients with severe of very severe COPD. *Conclusions*: Although literature on this topic is limited and shows substantial heterogeneity, pain seems to be a significant problem in patients with COPD and is related to several other symptoms, comorbidity and QoL. Data synthesis suggests that pain is more prevalent in patients with moderate COPD compared to patients with severe or very severe COPD. Further research is needed and should focus on determining a more accurate pain prevalence, investigating the relationship between pain prevalence, disease severity and comorbidity and explore implementation and efficacy of pain management interventions in patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic, usually progressive airway disease. Both the prevalence and disease severity of COPD are strongly related to age and worldwide, the rate of related morbidity and mortality is rising.[1] COPD represents a major burden for individual patients, healthcare systems and societies in terms of healthcare costs.[2] As the disease progresses, health status becomes increasingly impaired. Especially in advanced COPD, patients suffer from high symptom burden, impaired functional capacity and poor quality of life (QoL).[3,4] Well-known symptoms in COPD are dyspnoea, cough and wheezing, whereas other symptoms such as fatigue, nausea and insomnia are also frequently reported.[5] Recent literature indicates that pain is also a significant symptom in patients with COPD. Two systematic reviews on patients with end-stage COPD[6,7] reported prevalences of pain of 21–77%. Both these reviews reported only on studies including patients with advanced or terminal disease or studies on palliative care in patients with very severe COPD. Less is known about pain in patients with mild-to-moderate disease. In a cross-sectional study on pain in patients with moderate-to severe COPD, HajGhanbari et al[8] reported that pain is more prevalent among individuals with COPD compared with healthy adults. Bentsen et al[9] found similar results, reporting pain in 45% of the patients with moderate COPD compared with 34% in the general population. Other questions remain about pain in COPD. For example, the relationship with disease severity and comorbidity remains unclear and information on the causes and characteristics of pain, and how pain influences functional capacity and QoL, is scarce.[8,9] There are several factors related to COPD that may contribute to a higher pain prevalence in patients with COPD. The systemic inflammatory process, which activates cytokines, may generate chronic and neuropathic pain. Musculoskeletal disorders and comorbidities (including mechanical limitations of chest wall movement due to hyperinflation and osteoporosis) are also considered possible causes of pain in patients with COPD and inactivity may aggravate common age-related comorbidities such as osteoarthritis and low back pain.[8] Improving knowledge on aetiology, characteristics, correlations and impact of pain is important and necessary to improve pain recognition and pain treatment in patients with COPD. It is likely that adequate pain recognition and treatment is important in improving QoL, exercise tolerance and lifelong adherence to physical activity in patients with COPD. Thus, pain seems to be a relevant but poorly understood problem in patients with COPD. Therefore, the aim of this review is to systematically describe and investigate pain in patients with COPD. More specifically, to examine the prevalence of pain and factors related with pain and to identify interventions that may reduce pain in patients with COPD.

Methods

Electronic searches

We conducted a systematic search using MEDLINE/PubMed (from 1966 to December 2013), EMBASE (from 1980 to December 2013), CINAHL (from 1981 to December 2013) and PsychINFO (from 1980 to December 2013) using the following groups of keywords:

1. Pain, pains, Pain Measurement, Analgesics, analgesic (PubMed), pain, pain assessment, analgesia, analgesic (EMBASE), Pain, analgesia, analgesic (CINAHL), Pain, Aphagia, Back Pain, Chronic Pain, Headache, Myofascial Pain, Neuralgia, Neuropathic Pain, Somatoform Pain Disorder, Analgesia, analgesic (PsychINFO).
2. Pulmonary Disease, Chronic Obstructive, COPD, Lung Diseases, Obstructive, chronic bronchitis, chronic obstructive airway disease, chronic airway obstruction, chronic airway obstructions, COAD, chronic airflow obstruction, chronic airflow obstructions, Pulmonary Emphysema.

Keywords were entered using controlled terms (eg, Medical Subject Headings in Medline) and as free-text word. Within each group the keywords were combined using 'OR' and the two groups were combined using 'AND' (supplementary file). No language or other restrictions were applied. Reference lists from included studies and reviews were searched by hand to identify additional articles. All articles that were identified by the electronic search were put into a reference database (Reference Manager V.12.0).

Selection of studies

Articles that reported original data on pain in patients with COPD, or assessed pain as a domain of QoL in patients with COPD, were considered eligible. We included all types of study designs (cross-sectional, longitudinal, prospective/retrospective, qualitative/quantitative design). Articles without an (English) abstract, reviews, editorials, conference abstracts and case reports were excluded. Two members of the review team (EFvDvI and KG) independently assessed the titles and abstracts of all potentially relevant publications that were identified from the search. Decisions of the two reviewers about inclusion/exclusion were compared and, in case of disagreement, were resolved by asking a third reviewer (DJAJ) to achieve consensus. Subsequently, the same two reviewers evaluated the full text of all potentially eligible articles. Decisions about inclusion and exclusion were again compared and, in case of disagreement, resolved by asking the third reviewer in order to achieve consensus.

Data extraction and quality assessment

Details on study design, patients, setting and outcome were recorded by two independent reviewers (EFvDvI and KG). For each study the following items were recorded: author, journal, year of publication, country of origin, design and aim of the study, setting, inclusion and exclusion criteria, response rate, number of patients, patient characteristics [age, forced expiratory volume in 1 s as % of predicted value (FEV_1% predicted), Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade, and gender], pain and QoL instrument used, reported pain prevalence or mean score on the pain domain of the QoL instrument, correlations, limitations and conclusions.

All included articles were ranked for quality according to the Mixed Method Appraisal Tool (MMAT).[10] The MMAT has recently been developed for the appraisal stage of systematic literature reviews that include quantitative, qualitative and mixed methods studies. The MMAT has proven to be an effective and practical quality assessment tool for mixed method review studies.[10] The MMAT consists of four criteria for the appraisal of quantitative (descriptive, randomised and non-randomised) and qualitative studies. Hence, each study design is judged within its methodological domain (Table 1). The MMAT scores range from 100% (all four criteria are met) to 25% (one criterion is met). In the present review, quality assessment scores were calculated for all included studies. Ranking according to the MMAT was conducted by two independent reviewers (EFvDvI and KG) and any disagreement in the MMAT scores was resolved by discussion or by asking a third reviewer (DJAJ) for advice to reach consensus.

Data synthesis and meta-analysis

A meta-analysis was performed concerning the Short-Form health survey (SF)-36_Bodily Pain data. The SF-36 is a widely used, self-administered, reliable and valid instrument to assess generic health-related QoL.[11] The SF-36 consists of 36 items divided into eight subdomains. The score of each subdomain ranges from 0 to 100, with 100 representing the best quality of life. The questionnaire contains two questions related to pain: the SF-36 bodily pain subdomain (SF-36_BP): 'How much bodily pain have you had during the past (4) week(s)?' [score from 0 (no pain) to 6 (very severe pain)] and 'During the past (4) week(s), how much did pain interfere with your normal work (including both work outside the home and housework)?' [score from 0 (not at all) to 5 (extremely)] We performed a meta-analysis with a Forest plot using a Microsoft Excel spreadsheets, as developed by Neyeloff et al.[12] They showed that this method produces a statistically adequate but graphically appealing forest plot summarising descriptive data. We assumed a random-effects model to calculate the mean score on the SF-36_BP item and a 95% CI. The

Table 1. Criteria Mixed Methods Appraisal Tool (MMAT), by Pluye et al.[10]

Types of mixed methods study components or primary studies	Methodological quality criteria (see tutorial for definitions and examples)	Responses Yes No Can't tell Comments
Screening questions (for all types)	Are there clear qualitative and quantitative research questions (or objectives*), or a clear mixed methods. question (or objectives*)? Do the collected data allow address the research. question (objective)? E.g., consider whether the follow-up period is long enough for the outcome to occur (for longitudinal studies or study components). ***Further appraisal may be not feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions.***	
1. Qualitative	1.1. Are the sources of qualitative data (archives, documents, informants, observations) relevant to address the research question (objective)? 1.2. Is the process for analyzing qualitative data relevant to address the research question (objective)? 1.3. Is appropriate consideration given to how findings relate to the context, e.g., the setting, in which the data were collected? 1.4. Is appropriate consideration given to how findings relate to researchers' influence, e.g., through their interactions with participants?	
2. Quantitative randomized controlled (trials)	2.1. Is there a clear description of the randomization (or an appropriate sequence generation)? 2.2. Is there a clear description of the allocation concealment (or blinding when applicable)? 2.3. Are there complete outcome data (80% or above)? 2.4. Is there low withdrawal/drop-out (below 20%)?	
3. Quantitative non-randomized	3.1. Are participants (organizations) recruited in a way that minimizes selection bias? 3.2. Are measurements appropriate (clear origin, or validity known, or standard instrument: and absence of contamination between groups when appropriate) regarding the exposure intervention and outcomes? 3.3. In the groups being compared (exposed vs. non-exposed: with intervention vs. without; cases vs. controls), are the participants comparable, or do researchers take into account (control for) the difference between these groups? 3.4. Are there complete outcome data (80% or above), and, when applicable, an acceptable response rate (60% or above), or an acceptable follow-up rate for cohort studies (depending on the duration of follow-up)?	

Table 1. Criteria Mixed Methods Appraisal Tool (MMAT), by Pluye et al.[10] (*continued*)

Types of mixed methods study components or primary studies	Methodological quality criteria (see tutorial for definitions and examples)	Responses Yes No Can't tell Comments
4. Quantitative descriptive	4.l. Is the sampling strategy relevant to address the quantitative research question (quantitative aspect of the mixed methods question)? 4.2. Is the sample representative of the population understudy? 4.3. Are measurements appropriate (clear origin, or validity known, or standard instrument)? 4.4. Is there an acceptable response rate (60% or above)?	
5. Mixed methods	5.1. Is the mixed methods research design relevant to address the qualitative and quantitative research questions (or objectives), or the qualitative and quantitative aspects of the mixed methods question (or objective)? 5.2. Is the integration of qualitative and quantitative data (or results*) relevant to address the research question (objective)? 5.3. Is appropriate consideration given to the limitations associated with this integration, e.g., the divergence of qualitative and quantitative data (or results*) in a triangulation design? *Criteria for the qualitative component (1.1 to 1.4), and appropriate criteria for the quantitative component (2.1 to 2.4. or 3.1 to 3.4. or 4.1 to 4.4), must be also applied.*	

*These two items are not considered as double-barreled items since in mixed methods research, (1) there may be research questions (quantitative research) and or research objectives (qualitative research), and (2) data may be integrated, and/or qualitative findings and quantitative results can be integrated.

heterogeneity was assessed with the Q statistic and the I2 index. Meta-analyses and Forest plots using a Microsoft excel spreadsheet were conducted by step-by-step guide focusing on descriptive data analysis.[12] To determine the strength of the linear correlations between lung function (FEV_1% predicted) and pain prevalence and the SF-36_BP score, we calculated the correlation coefficient between these variables. In case of normally distributed data, Pearson correlation coefficient was calculated. In case of non-normally distributed data a non-parametric test (Spearman's test) was used. We defined statistical significance at $p \leq 0.05$ (two-sided level of significance). In studies that presented only the GOLD grade distribution the mean GOLD grade was calculated and converted into a mean FEV_1%-predicted.

Results

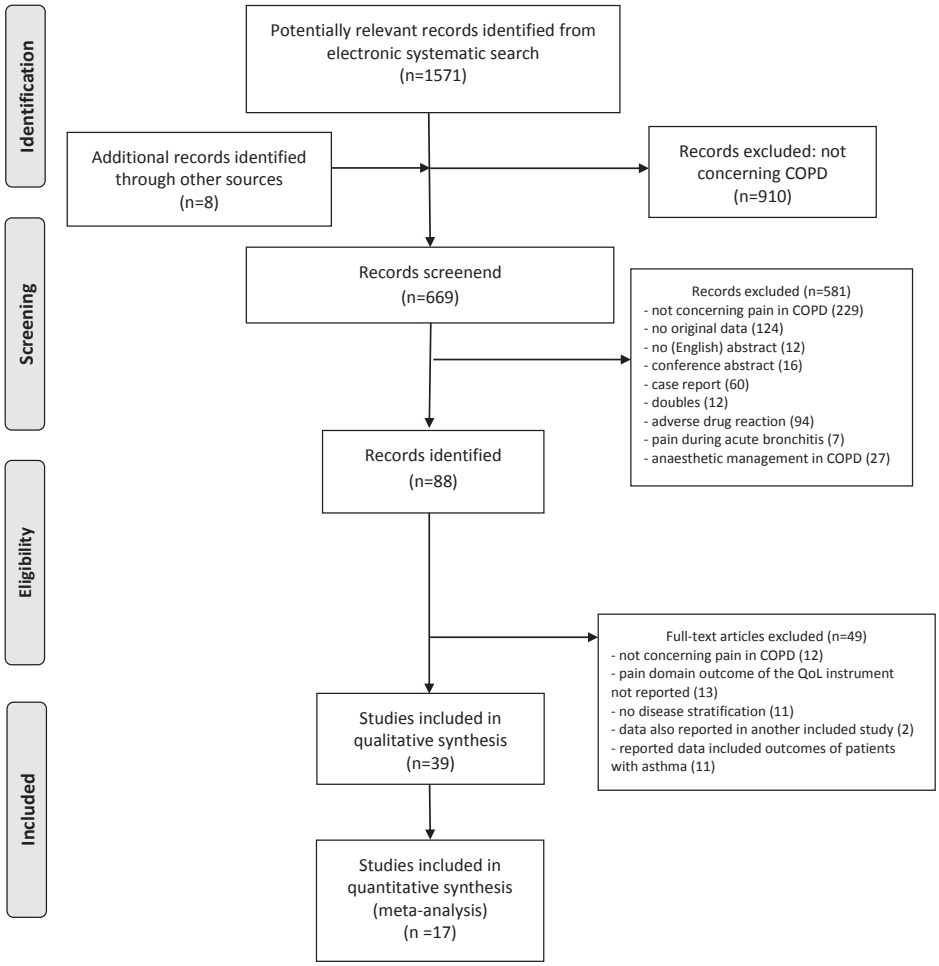
Study selection and characteristics

The electronic systematic search identified 1571 eligible citations (PubMed 1067, EMBASE 379, CINAHL 71, PsychINFO 54). Eight studies were identified using other sources. A total of 1491 citations were excluded based on title and abstract. In total, 88 articles were reviewed in detail. Reasons for exclusion are reported in the PRISMA flowchart (Figure 1). Thirty-nine studies met the inclusion criteria and were included in the review (Tables 2 and 3).

Fourteen studies focused on pain and symptom burden (including pain) in COPD[5,8,9,13-23] and 25 studies focused on QoL using a questionnaire that included a separate pain domain[4,24-47] (Table 2 and 3). The included studies were published between 1995 and 2013. All included studies on symptom burden in COPD were published in the past decade (2000–2013) and studies with a specific focus on pain in COPD were published in the last 5 years (Figure 2).

Of the 14 articles on pain and symptom burden in COPD, three reports from Bentsen et al[9,21,22] and two reports from Borge et al[18,20] were based on the same original research study. Ten studies were conducted at the outpatient pulmonary department of a hospital (secondary and tertiary care), one in primary care and three were population-based studies. Most studies on pain and symptom burden (n=10; 71%) had a cross-sectional design. The majority of the included studies on pain as a domain of QoL also used a cross-sectional design (n=17; 68%), seven studies used a prospective design [observational (n=3) and interventional (n=4)] and one study used a retrospective design. Almost all studies (n=21) on pain as a domain of QoL included patients with COPD recruited from an outpatient pulmonary department or hospital/intensive care unit setting (secondary and tertiary care).

Figure 1. Flow diagram of the inclusion of studies (according to the PRISMA guidelines).



Abbreviations: COPD: chronic obstructive pulmonary disease; PRISMA: preferred reporting items for systematic reviews and meta-analyses

Quality assessment

Of the 14 studies on pain and symptom burden in COPD, 10 had a MMAT score of 100%, three scored 75% and one study scored 50% (Table 2). Shortcomings in quality included insufficient response rate,[13,14,18,20] or insufficient comparability between participants.[13] Of the 25 studies on pain as a subdomain of QoL, 20 had a score of 75% (n=14) or 100% (n=6). The most frequent shortcoming in quality assessment was an insufficiently or not reported response rate (n=19; Table 3).

Table 2: Pain and symptom burden

Author	Aim	Setting & sample	N (COPD patients)	Mean age in years (SD)	FEV_1 % of predicted (SD)	GOLD-stage	Pain-, symptom-, QoL- instrument used	Outcome (pain prevalence)	MMAT score
Claessens et al.[13] (2000)* USA	To compare the course of illness and patterns of care for patients with non-small-cell lung carcinoma (NSCLC) and COPD	Secondary care Patients with severe COPD or stage II of IV NSCLC, recruited on admission to the hospital because of acute illness/exacerbation	1008	70 (-)	_	_	Screening question: *"How much of the time do you experience pain?". "How severe is the pain"*	21%	50% 3.1:+ 3.2:+ 3.3:- 3.4:-
Elkington et al.[14] (2005)*** UK	To assess the healthcare needs of COPD patients in the last year of life	Population based Informants of COPD or emphysema deaths were identified by the Office for National Statistics.	209	76.8(-)	_	_	VOICES	72%	75% 4.1:+ 4.2:+ 4.3:+ 4.4:-
Rashiq et al.[15] (2009)** Canada	To determine the associations of Chronic Non Cancer Pain (CNCP) with a wide range of factors in the biological, psychological and social domain	Population based Sample from data from the Canadian National Population Health Survey.	2289	_	_	_	Screening question: "*Are you usually free of pain and discomfort*?"	34.9%	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Blinderman et al.[16] (2009)* USA	To evaluate the pattern of symptom distress and investigate the relationships among symptoms and measures of comorbidity, physical and mental functioning and QoL in patients with advanced COPD.	Secondary care Patients identified by review medical records in outpatients pulmonary department	100	62.2(10.5)	24.4(3.9)	_	MSAS SIP MILQ	41%	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+

Table 2: Pain and symptom burden (*continued*)

Author	Aim	Setting & sample	N (COPD patients)	Mean age in years (SD)	FEV_1 % of predicted (SD)	GOLD-stage	Pain-, symptom-, QoL- instrument used	Outcome (pain prevalence)	MMAT score
Lohne et al.[17] (2010)**** Norway	To evaluate pain experiences of patients with COPD	Tertiary care Patients newly admitted to hospital(tertiary referral centre) for COPD assessment and lung transplantation assessment	16	57.9(4.1)	21.1(5.8)	_	Semi-structured interview BPI	38%	100% 1.1:+ 1.2:+ 1.3:+ 1.4:+
Borge et al.[18] (2010)** Norway	To explore the relationships between demographic and clinical variables and symptoms for patients with COPD	Secondary care Patients recruited from outpatient pulmonary department of a hospital	154	64.6(10.2)	59.1(22.6)	GOLD 1:18.2% GOLD 2:46.8% GOLD 3:25.3% GOLD 4:9.7%	BPI HADS LFS GSDS RQLQ	-	75% 4.1:+ 4.2:+ 4.3:+ 4.4:-
White et al.[19] (2011)** UK	To determine the palliative care needs in patients with advanced COPD	Primary care Patients in care of GP's with diagnosis of COPD, identified from medical records	145	71.6(9.7)	29.1 (9.5)	_	LLPS MRC HADS CCQ	40%	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+
Janssen et al.[5] (2011)** Netherlands	To assess severity of symptoms, presence of comorbidities, and current provision of health care in outpatients with advanced COPD or chronic heart failure (CHF)	Secondary care Patients recruited from outpatient pulmonary department of 1 academic and 5 general hospitals	105	66.3(9.2)	34.1(13.5)	GOLD 1: - GOLD 2: - GOLD 3:26.7% GOLD 4:73.3%	VAS	32.4%	100% 4.1:+ 4.2:+ 4.3:+ 4.4:+

Table 2: Pain and symptom burden (*continued*)

Author	Aim	Setting & sample	N (COPD patients)	Mean age in years (SD)	FEV_1 % of predicted (SD)	GOLD-stage	Pain-, symptom-, QoL- instrument used	Outcome (pain prevalence)	MMAT score
Bentsen et al.[9] (2011)** Norway	To evaluate the prevalence and characteristics of pain in patients with COPD compared to a sample from the Norwegian general population	Secondary care Patients: sample of patients with COPD who underwent outpatient PR program. Controls: age appropriate sample from Norwegian general population	100	65(9.2)	48.0 (16.0)	GOLD 1: - GOLD 2:53% GOLD 3:31% GOLD 4:16%	Screening question: "A*re you generally bothered with pain?*" NRS BPI	45%	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+
Borge et al.[20] (2011)** Norway	To explore the prevalence and intensity of pain, its location, how demographic and clinical variables may be related to pain and how pain is associated with QoL	Secondary care Patients recruited from outpatient pulmonary department	154	64.6(10.2)	59.1(22.6)	GOLD 1:18.2% GOLD 2:46.8% GOLD 3:25.3% GOLD 4:9.7%	BPI RQLQ QOLS	72.1%	75% 4.1:+ 4.2:+ 4.3:+ 4.4:-
Bentsen et al.[21] (2012)** Norway	To evaluate the differences in respiratory parameters between COPD patients who did and did not have pain	Secondary care Sample of patients with COPD who underwent PR program at the outpatient pulmonary department	100	65(9.2)	48.0 (16.0)	GOLD 1: - GOLD 2:53% GOLD 3:31% GOLD 4:16%	Screening question: "*Are you generally bothered with pain?*" SGRQ	-	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+
Hajghanbari et al.[8] (2012)** Canada	To determinate if pain is more common in COPD patients than in healthy people and if pain is related to physical activity, QoL and comorbidities	Secondary care Patients recruited from caseload of respirologists and PR programs. Controls recruited from local population	47	70 (6.7)	44.7 (19.2)	_	MPQ BPI TSK SF-36	50%	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+

Table 2: Pain and symptom burden (*continued*)

Author	Aim	Setting & sample	N (COPD patients)	Mean age in years (SD)	FEV_1 % of predicted (SD)	GOLD-stage	Pain-, symptom-, QoL- instrument used	Outcome (pain prevalence)	MMAT score
Bentsen et al.[22] (2013)** Norway	To examine the prevalence of multiple symptoms in patients with COPD and to examine the relationship between the patients outlook for the future and multiple symptoms	Secondary care Sample of patients with COPD who underwent PR program at the outpatient pulmonary department	100	66.1(8.3)	46(15)	GOLD 1: - GOLD 2 44% GOLD 3:43% GOLD 4:13%	Screening question: "Are you generally bothered with pain?" BPQ NRS	-	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+
Roberts et al.[23] (2013)** USA	To describe chronic pain prevalence among patients with COPD compared with similar patients with other chronic diseases in a managed care population in the USA.	Population based Cases and controls selected from members of a regional managed care plan	7952	69.3(-)	_	GOLD 1:21.5% GOLD 2:55.5% GOLD 3:19.5% GOLD 4:3.5%	Identification of pain was based on both pain diagnosis and management and was assessed using diagnosis and procedure codes from the managed care claims database and outpatient pharmacy information.	59.8%	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+

* Prospective cohort study; ** cross-sectional study; ***mixed method; **** retrospective post-bereavement study;

Abbreviations: VOICES: VOICES questionnaire; MSAS: Memorial Symptom Assessment Scale; SIP: Sickness Impact Profile; MILQ: Multidimensional Index of Life Quality; BPI: Brief Pain Inventory; HADS: Hospital Anxiety and Depression Scale; LFS: Lee Fatigue Scale; GSDS: General Sleep Disturbances Scale; RQLQ: Respiratory Quality of Life Questionnaire; LLPS: London and Leeds Pain Survey; MRC: Medical Respiratory Counsel dyspnoea scale; CCQ: Clinical COPD Questionnaire; VAS: Visual Analogue Scale; NRS: Numeric Rating Scale; QOLS: Quality Of Life Scale; SGRQ: St George Respiratory Questionnaire; MPQ: McGill Pain Questionnaire;: TSK: Tampa Scale for Kinesiophobia; SF-36: Short Form Health Survey-36; BPQ: Breathing Problems Questionnaire;
CHF: chronic heart failure; CNCP: Chronic Non Cancer Pain; MMAT: Mixed Method Appraisal Tool; NSCLC: non-small-cell lung carcinoma; QoL: Quality of Life

Table 3: Pain as a subdomain of Quality of Life (QoL)

Author	Aim	Setting & sample	N (COPD patients)	Mean age(SD) in years	FEV_1% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Mahler et al.[25] (1995)**** USA	To examine longitudinal changes in clinical parameters in patients with COPD	Secondary care Patients recruited from the outpatient pulmonary department of 3 hospitals	110	67(8)	44(17)	-	SF-20	38.9(32.9)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:-
Mahler et al.[24] (1995)* USA	To evaluate the SF-36 as an instrument for measuring HRQoL in patients with symptomatic COPD	Secondary care Patients with COPD and no significant comorbidity recruited from an outpatient pulmonary department	50	72(8)	48.2(21.9)	GOLD 1:18% GOLD 2: 20% GOLD 3&4: 62%	SF-36	70.5(24.2)	75% 4.1:+ 4.2:+ 4.3:+ 4.4 -
Hoang Thi et al.[26] (1997)**** France	To seek factors predicting HRQoL in severe COPD patients on LTOT	Primary care Patients on LTOT monitored at home by a region organization for medical assistance of COPD patients	61	66.0(6.4)	_	GOLD 1: - GOLD 2: - GOLD 3&4:100%	DHP	46.6(38.1)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:-
Monso et al.[27] (1998)* Spain	To identify physiological parameters related to QoL in severe COPD patients using LTOT	Secondary care Patients with COPD on LTOT recruited from outpatient pulmonary department of a university hospital	47	65.2(8.2)	31.8(11.9)	GOLD 1: - GOLD 2: - GOLD 3&4:100%	NHP	35.1(31.6)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:-
Schlenk et al.[28] (1998)* USA	To examine HRQoL as measured by the SF-36 across patient populations with chronic disorders and to compare QoL in these subjects with normative data on healthy persons	Primary care Sample comprised from 6 studies of persons with chronic disorders. Patients with COPD were recruited from a pilot study designed to determine the effect of home based PR on HRQoL	13	66.7(3.7)	_	_	SF-36	58.54(24.16)	25% 4.1: - 4.2: - 4.3: + 4.4: -

Table 3: Pain as a subdomain of Quality of Life (QoL) (*continued*)

Author	Aim	Setting & sample	N (COPD patients)	Mean age(SD) in years	FEV_1% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Hajiro et al.[29] (1999)* Japan	To compare categorizations of the level of dyspnoea with the staging of disease severity as defined by the FEV_1 in representing how HRQoL is distributed in patients with COPD	Secondary care Patients (100% male) with stable COPD recruited from outpatient pulmonary department of a university hospital	194	70(8)	41.5(15.6)	GOLD 1:29% GOLD 2:32% GOLD 3:39% GOLD 4: -	SF-36	65.5(21.3)	100% 4.1: + 4.2: + 4.3: + 4.4: -
Stavem et al.[30] (1999)* Norway	To assess relationships between health status and measures of dyspnoea, lung function and exercise capacity in patients with COPD	Secondary care Patients with COPD recruited from outpatient pulmonary department of a hospital	59	57(9)	54(17)	GOLD 1:42% GOLD 2:36% GOLD 3:22% GOLD 4: -	SF-36	64.0(27.6)	100% 4.1: + 4.2: + 4.3: + 4.4: +
Gore et al.[31] (2000)* UK	To examine if patients with severe COPD are relatively disadvantaged in terms of medical and social care compared to patients with inoperable lung cancer	Secondary care Patients attending for follow up at the outpatient pulmonary department of a hospital	50	70.5(5.5)	_	GOLD 1: - GOLD 2: - GOLD 3&4:100%	SF-36	- (only figures presented)	100% 4.1: + 4.2: + 4.3: + 4.4: +
Kaelin et al.[32] (2001)*** USA	To examine the efficacy of a program using symptom limited interval training combined with strength training on 6MWT, increases in exercise capacity and QoL	Secondary care Patients with primary diagnosis of COPD entering a PR program at an outpatient pulmonary department	50	68.4(6.9)	39.5(11.5)	_	HSQ	pre-PR: 65.9 (26.7) post-PR: 69.5 (21.6) NS	50% 4.1:+ 4.2:+ 4.3: - 4.4: -
Boueri et al.[33] (2001)*** USA	To evaluate the effects of a 3-week comprehensive PR program on QoL in patients with COPD	Tertiary care Patients with COPD, referred for PR at the outpatient pulmonary department of a pulmonary tertiary care centre	37	66(7.3)	29.6(10.9)	_	SF-36	pre-PR; 77.5(27.4) post-PR; 83.2(18.5) p=0.100	75% 4.1:+ 4.1:+ 4.3:+ 4.4: -

Table 3: Pain as a subdomain of Quality of Life (QoL) (*continued*)

Author	Aim	Setting & sample	N (COPD patients)	Mean age(SD) in years	FEV_1% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
de Torres et al.[34] (2002)*** USA	To investigate the capacity of several of the most frequently used outcome measurements to detect changes after PR in a population of patients with severe COPD who qualified for LVRS	Secondary care 7 hospitals participating in a trial comparing LVRS and standard medical treatment. Population consisted of the first 37 consecutive patients with severe COPD selected for LVRS.	37	63(6)	_	GOLD 1: - GOLD 2: - GOLD 3&4:100%	SF-36	pre-PR:87(18) post-PR:87(18) NS	50% 4.1:+ 4.2:+ 4.3: - 4.4: -
Ambrosino et al.[35] (2002)**** Italy	To evaluate the perceived health and cognitive status in survivors of COPD exacerbations requiring mechanical ventilation	Secondary care Patients (P): COPD patients at their first episode of acute on chronic respiratory failure requiring mechanical ventilation. Controls (C): stable COPD patients on LTOT (>6 months) with no previous ICU admission	97 P:63 C:34	 68(7) 67(7)	 30(16) 36(19)	GOLD 1: - GOLD 2: - GOLD 3&4: 100%	NHP	P:21.2(28.4) C:13.7(19.2) p=0.17	50% 3.1:+ 3.2:+ 3.3: - 3.4: -
Sant'Anna et al.[36] (2003)* Brazil	To assess HRQoL in low an income population of patients with hypoxemia and COPD receiving LTOT	Tertiary care Patients (P): patients with COPD and LTOT recruited from an outpatient pulmonary department of a tertiary care university hospital Controls (C): patients with COPD but no severe hypoxemia	69 P:36 C:33	 63.5(10.8) 63.1(9.2)	 32.1%(14.4) 35.7%(13.9)	_	SF-36	P:56.9(32.4) C:68.1(28.9) NS	75% 3.1:+ 3.2:+ 3.3: - 3.4:+

Table 3: Pain as a subdomain of Quality of Life (QoL) (*continued*)

Author	Aim	Setting & sample	N (COPD patients)	Mean age(SD) in years	FEV_1% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Van Manen et al.[37] (2003)* Netherlands	To determine the influence of COPD on HRQoL independent of comorbidity	Primary care Patients (P): patients with COPD and comorbidity Controls(C): patients with COPD and comorbidity	148 P:107 C:41	_	_	GOLD 1:24% GOLD 2:39% GOLD 3&4:37%	SF-36	P:83.6(23.2) C:88.8(18.5)	75% 3.1:+ 3.1:+ 3.3:+ 3.4: -
Sato et al.[38] (2004)*/*** Japan	To investigate the responsiveness of the SF-36 in patients with COPD and asthma	Secondary care Patients recruited from the outpatient pulmonary department of an universal hospital.	*Cross-sectional* Pre-treatment 152 In-treatment 123 *Longitudinal* 136	69.1(7.4) 70.1(7.3) 69.1(7.4)	44.9(17.3) 49.9(18.1) 44.9(17.3)	_	SF-36	*Cross-sectional* Pre-treatment 73.4(24.3) In-treatment: 80.3(22.8) p=0.02 *Longitudinal* 73.8(25.3)	75% 4.1:+ 4.2:+ 4.3:+ 4.4: -
Katsura et al.[39] (2005)* Japan	To evaluate the effects of body weight on both generic and disease specific HRQoL of patients with COPD	Secondary care Patients (88% male) with stable COPD recruited from outpatient pulmonary department	83	74.6(6.4)	53.9(22.2)	_	SF-36	- (only figures presented)	75% 4.1: + 4.2: + 4.3: + 4.4: -
Rutten-van Molken et al.[40] (2006)* Netherlands	To assess the discriminative properties of the EQ-5D with respect to COPD severity according to the GOLD criteria in a large multinational study	Secondary care Patients recruited form an outpatient pulmonary department	1235	64.5(8.4)	48.8(12.2)	GOLD 1:0.0% GOLD 2:50.7% GOLD 3:41.8% GOLD 4:7.4%	EQ-5D	- (only figures presented)	75% 4.1: + 4.2: + 4.3: + 4.4: -

Table 3: Pain as a subdomain of Quality of Life (QoL) (*continued*)

Author	Aim	Setting & sample	N (COPD patients)	Mean age(SD) in years	FEV_1% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Punekar et al.[41] (2007)* USA,5 EU countries	To assess and compare health status among COPD patients presenting for treatment in 6 countries and in 2 healthcare settings using a generic health status instrument	Population based, primary(PC) and secondary care(SC) Physicians were randomly selected. Patient selection: the first 6 consecutive patients diagnosed and treated for COPD presenting for consultation during the next 10 working days.	2703 PC: 1381 SC:1322	 66(10.8) 66(11.3)	_	PC GOLD 1:37% GOLD 2:31% GOLD 3:32% GOLD 4: - SC: GOLD 1:25% GOLD 2:36% GOLD 3:39% GOLD 4: -	EQ-5D	PC Any problems: 53% SC Any problems: 56%	100% 4.1: + 4.2: + 4.3: + 4.4: +
Bailey et al.[42] (2008)** USA	To examine the relationship between improvements in 6MWT and QoL in patients with COPD following a PR program	Secondary care Patients with COPD that completed an outpatient PR program.	139	68(11.8)	44.7(20.0)	_	SF-36	pre-PR; 63.1(22.4) post-PR; 70.1(62.5) p=0.212	75% 4.1:+ 4.2:+ 4.3:+ 4.4:-
Habraken et al.[43] (2009)* Netherlands	To compare self-reported HRQoL data of COPD patients with GOLD stage 4 and end-stage NSCLC patients	Secondary and tertiary care Patients identified from medical records of the outpatient pulmonary department of 4 hospitals and 1 tertiary pulmonary centre	82	69.5(6.7)	_	GOLD 1: - GOLD 2: - GOLD 3: - GOLD 4:100%	SF-36	62 (IQR 41-100)	75% 4.1: + 4.2: + 4.3: + 4.4: -
Kil et al.[44] (2010)* South Korea	To determine the prevalence of depression and examine its impact on HRQoL among older patients with COPD	Secondary care Patients recruited from the outpatient pulmonary department of an academic hospital	91	69.3(8.2)	58.9(19.5)	GOLD 1:14.2% GOLD 2:51.7% GOLD 3:29.7% GOLD 4:4.4%	SF-36	63.0(30.1)	50% 4.1:- 4.2:+ 4.3:+ 4.4: -

Table 3: Pain as a subdomain of Quality of Life (QoL) (*continued*)

Author	Aim	Setting & sample	N (COPD patients)	Mean age(SD) in years	FEV_1% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Rascon-Anguilar et al.[45] (2011)* USA	To evaluate HRQoL in patients with COPD compared with those with both COPD and gastro-oesophageal reflux disease (GERD) symptoms	Secondary care Patients presenting at the outpatient pulmonary department for routine health care: Patients (P): patients with COPD with GERD symptoms . Controls (C): patients with COPD without GERD symptoms .	86 P:32 C:54	 66.0(9.9) 68.8(7.0)	 40.7(17.6) 45.9(16.0)	_	SF-36	P:51.7(28.8) C:66.7(27) P<0.02	100% 3.1:+ 3.2:+ 3.3:+ 3.4:+
Janssen et al.[4] (2011)* Netherlands	To assess health status and care dependency in patients with advanced COPD or CHF and to identify correlates of an impaired health status	Secondary care Patients recruited from outpatient pulmonary department of 1 academic and 5 general hospitals	105	66.3(9.2)	34.1(13.5)	GOLD 1: - GOLD 2: - GOLD 3:26.7% GOLD 4:73.3%	SF-36 EQ-5D	SF-36_BP: 70.9 (29.5) EQ-5D: Any problems: 45.7%	100% 4.1: + 4.2: + 4.3: + 4.4: +
Cedano et al.[46] (2012)* Brazil	To evaluate and correlate the QoL of COPD patients on LTOT with their socio-demographic and clinical characteristics and level of dependence	Secondary care Convenience sample of patients on LTOT followed at the oxygen therapy outpatient pulmonary department	80	69.6(9.1)	37.4(14.1)	GOLD 1: - GOLD 2: - GOLD 3: - GOLD 4:100%	SF-36	61.2(27.4)	75% 4.1:+ 4.2:+ 4.3:+ 4.4: -

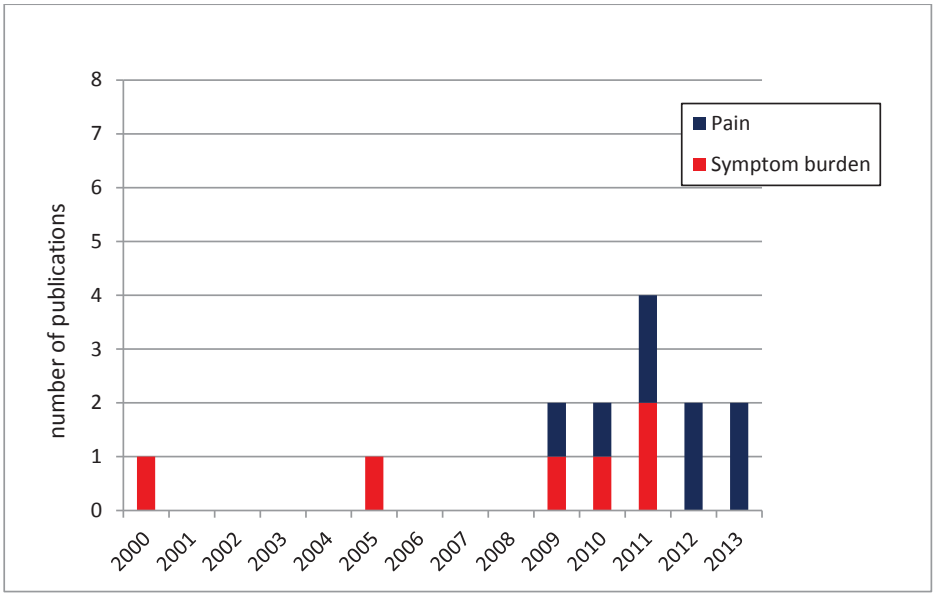
Table 3: Pain as a subdomain of Quality of Life (QoL) (*continued*)

Author	Aim	Setting & sample	N (COPD patients)	Mean age(SD) in years	FEV_1% of predicted (SD)	GOLD-stage	QOL instrument	Main outcome (SD)	MMAT score
Arimura et al.[47] (2013)* Japan	To evaluate the clinical usefulness of a concise two-question instrument to assess depressive symptoms in patients with COPD and to determine whether the instrument was related to the SF-8	Secondary care Patients recruited as a consecutive sample of clinically stable COPD patients visiting the outpatient pulmonary department of five hospitals.	52	72.7(7.5)	62.5(25.7)	GOLD 1:23% GOLD 2:40% GOLD 3:25% GOLD 4:12%	SF-8	52.2(10.0)	75% 4.1:+ 4.2:+ 4.3:+ 4.4:-

*cross-sectional study;**retrospective study; ***prospective intervention study (controlled and non-controlled); ****prospective observational study.

Abbreviations: SF-36: Short-Form health survey (SF)-36; HSQ:: Health Status Questionnaire; NHP: Nottingham Health Profile; DHP: Duke Health Profile; EQ-5D: EuroQol-5 Dimensions; MMAT: Mixed Method Appraisal Tool HRQoL: Health Related Quality of Life; LTOT: long term oxygen therapy; NSCLC: Non-small cell lung carcinoma; PR: Pulmonary Rehabilitation; 6MWT: six-minute Walking Test; LVRS: Lung Volume Reduction Surgery; GERD: Gastro-Oesophageal Reflux Disease; CHF: Chronic Heart Failure

Figure 2. Number of publications on 'pain' and 'symptom burden including pain' in patients with chronic obstructive pulmonary disease.



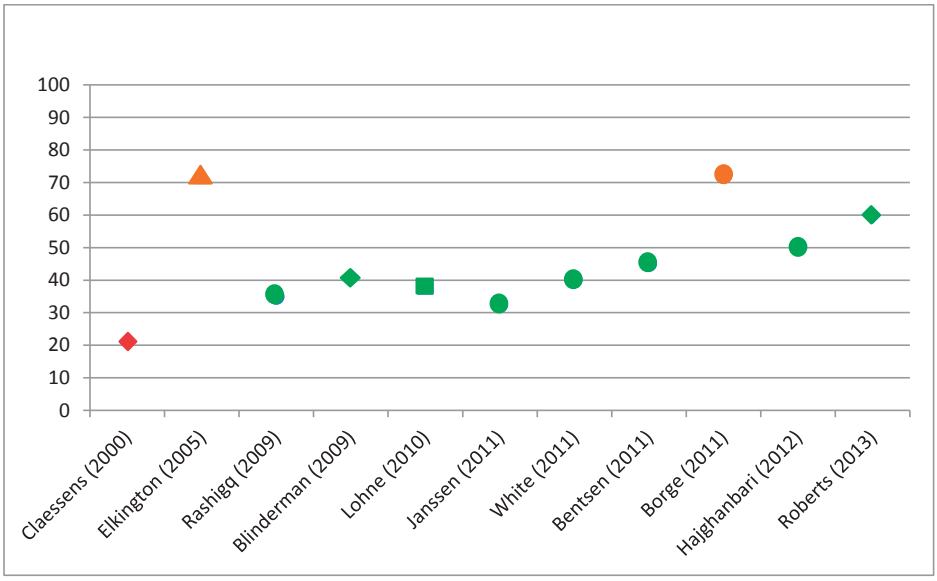
Pain measurement

Pain was measured using different instruments. Five studies on pain and symptom burden in COPD used the Brief Pain Inventory (BPI), or the body outline diagram of the BPI.[48] The BPI is a self-administered questionnaire used to assess the severity of pain [scale 0–10; cut-off points: mild pain (0–4), moderate pain: (5–6) and severe pain (7–10)] and the impact of pain on daily functioning (scale 0–10) in patients with chronic diseases or conditions. The BPI also contains a body diagram on which patients can indicate the location on which they experienced the most pain.[20,48] In five studies pain was not measured with a specific pain or symptom questionnaire, but a screening question was used, such as: 'Are you generally bothered with pain?'[9] or 'Are you usually free of pain and discomfort?'[15] Other instruments used were: the McGill Pain Questionnaire (MPQ), the Memorial Symptom Assessment Scale (MSAS), the VOICES questionnaire and the London and Leeds Pain Survey. One study measured pain using a Visual Analogue Scale (VAS).[5] Pain as a subdomain of QoL was measured using five different instruments: the SF-36 (n=19), the EuroQol-5 Dimensions (EQ-5D; n=3), the Nottingham Health Profile (NHP; n=3), the Health Status Questionnaire (HSQ; n=1) and the Duke Health Profile (DHP; n=1).

Prevalence of pain

Of the 14 studies on pain and symptom burden, 11 reported the prevalence of pain: range from 21% to 72.1% (Figure 3). Studies on prevalence of pain differed in design, setting and patient characteristics. Mean age ranged from 57.9 to 76.8 years and mean FEV_1% predicted ranged from 21% to 48%. Three studies did not report the mean FEV_1% predicted or the GOLD grade of the included patients. The MMAT scores of the studies that reported pain prevalence ranged from 50% to 100%. The reported pain prevalence of the studies with a MMAT score of 100% ranged from 32.4% to 59.8% (Figure 3). Five studies investigated the prevalence of pain in patients with COPD compared to participants from the general population,[8,9] patients with other chronic diseases,[5,23] or patients with lung cancer.[13] Bentsen *et al*[9] found a pain prevalence in patients with COPD of 45% compared to 34% in the general population (p=0.02) and HajGhanbari *et al*[8] reported that patients with COPD reported 2.5 times more pain and 3.7 times more interference of pain with daily activities, compared to healthy people. Roberts *et al*[23] also reported a higher pain prevalence in patients with COPD compared to patients with other chronic diseases (59.8% vs 51.7%; p=0.001), but in the study conducted by Janssen *et*

Figure 3. Prevalence of pain.



◆ prospective cohort study; ● cross-sectional study; ■ mixed method; ▲ retrospective post-bereavement study. **Green**: Mixed Method Appraisal Tool (MMAT)-score of 100%; **Orange**: MMAT-score of 75%; **Red**: MMAT-score of 50%.

al,[5] patients with chronic heart failure reported more pain than patients with COPD (48.8% vs 32.4%, p=0.05).

Of all included studies, 19 used the SF-36, the SF-20 or the SF-8. Of these, 17 reported scores on the bodily pain domain as a mean score (SD). In four of these studies, the SF-36_BP was measured in two separate groups of patients with COPD (cases and controls). A random-effects meta-analysis on the SF-36/20/8_BP data of the 21 studies and groups of patients with COPD, showed a mean score on the SF-36_BP of 66.7 (CI 95% 61.2; 72.2; Figure 4). The three studies that used the EQ-5D showed that 45%,[40] 46%[4] and 56%[41] of the patients with COPD reported having any problems on the subdomain pain/discomfort of the EQ-5D, respectively.

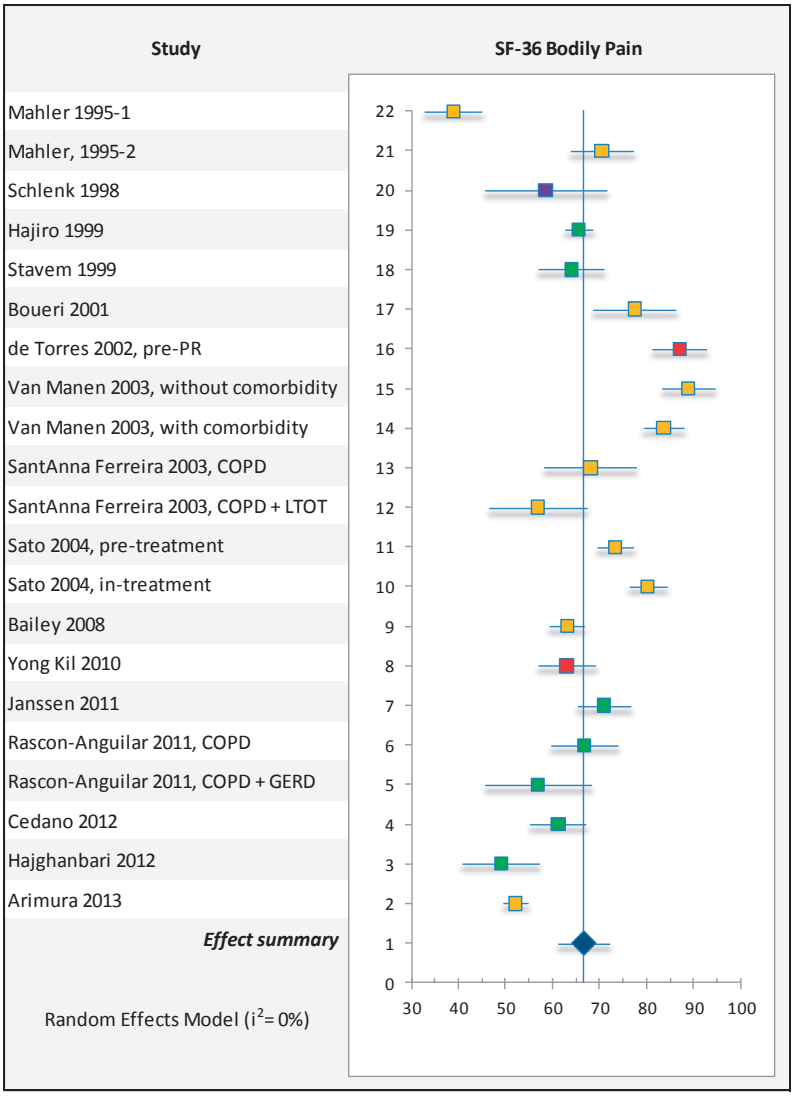
Characteristics of pain

Five studies measured pain intensity and interference using the BPI. Mean pain intensity scores ranged from 2.8 to 5.4 points (mild to moderate pain) and mean interference scores ranged from 3.6 to 5.8 points (mild to moderate interference) on a scale from 0 to 10 (higher scores indicating more pain intensity/interference). Three studies used the body outline diagram of the BPI to investigate the most prominent locations of the experienced pain.[9,17,20] Most frequently reported locations of pain were the shoulders and neck: 33% (n=15),[9] 36.4% (n=56)[20] and 50% (n=8)[17]; lumbar region: 29.2%(n=45)[20] and 47% (n=21)[9] and chest: 17.5% (n=27),[20] 36% (n=16)[9] and 38% (n=6).[17] None of the included studies investigated the type of pain (eg, neuropathic or nociceptive pain) or conducted a comprehensive pain assessment.

Factors related to pain

Of the 14 studies on pain or symptom burden, seven reported factors related to pain or correlations between pain and several variables, such as lung function, comorbidity and other symptoms (Table 4). Four of these studies reported from the same two original studies.[18,20-22] None of the studies on pain or symptom burden reported a significant relationship between lung function (FEV_1% predicted, GOLD grade) and pain prevalence or pain severity. Several studies reported a significant correlation between pain and comorbidity.[8,21,23] Bentsen *et al*[21] reported that comorbidity was a risk factor for pain in patients with COPD; patients with COPD and pain were more likely to report the presence of comorbidity and had a significantly higher number of comorbidities. However, the study from Borge *et al*[20] found no significant difference in the number of comorbidities between patients with COPD with and without pain. These conflicting results are also found for the correlation between pain severity and the number of comorbidities (Table 4).[8,18] Other variables that showed a significant correlation with pain presence or pain severity are:

Figure 4. Random effects meta-analysis of studies that examined the mean score on Short-Form health survey-36 (SF-36_BP) in patients with chronic obstructive pulmonary disease. The Forest plot shows the mean scores with 95% CIs for included study populations. The Q statistic was 19.32 with df=20 (p>0.10) and I2 was 0%. The MMAT scores are shown using different colours: green: MMAT-score: 100%; orange: MMAT-score: 75%; red: MMAT-score: 50%; purple: MMAT-score: 25%.



QoL, breathlessness, insomnia, fatigue, anxiety, depression and nutritional status (Table 4). Of the included studies on pain as a subdomain of QoL, none reported correlations between the SF-36_BP score and variables of interest. Two studies using other QoL instruments, that is, the EQ-5D[40] and the NHP[27] concluded that their analysis showed no significant correlation between pain as a subdomain of QoL and lung function.

Table 4. Factors related to pain (presence and severity)

Significant relation	*No relation*	*Conflicting results*
HRQoL[20]	*age, sex*[18,20-22]	*Comorbidity*[8,18,20-23]
Breathlessness[17,18,21]	*Lung function*[8,18,20-23]	
Insomnia[18,22]	*Smoking status*[18,20,21]	
Fatigue[18]		
Anxiety[18]		
Depression[18,23]		
Nutritional status[20]		

Abbreviations: HRQoL: health-related quality of life

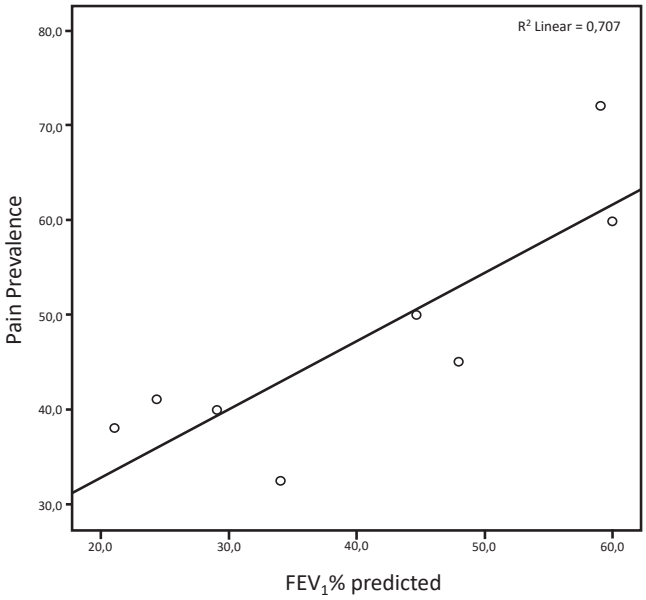
Pain management interventions

None of the included studies aimed to investigate the effect of a specific intervention on pain in patients with COPD. Bentsen *et al*[9] reported that 49% of the participants with pain received treatment with analgesics and 16% received physiotherapy. In a cross-sectional study in patients with advanced COPD, Janssen *et al*[5] found that 47% of the patients with pain (VAS score >30 mm) reported that their symptoms were addressed. Furthermore, if symptoms were treated, patients reported only moderate satisfaction with symptom treatment. One study on symptom burden in patients with severe COPD in primary care reported that all patients who suffered from 'pain every day' or 'pain on most days', were on prescribed analgesics.[19] Three studies investigated the effect of a pulmonary rehabilitation programme on health status.[32-34] All reported no effect of the intervention on the pain domain of the health status instrument used (two studies used the SF-36, one used the HSQ).

Overall relationship between pain prevalence and disease severity

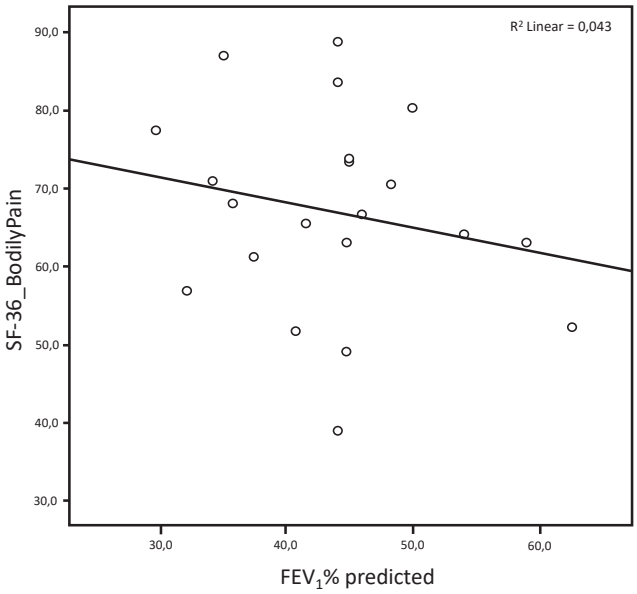
To determine the relationship between lung function and pain prevalence, we calculated the correlation coefficient between these variables. Of the 11 studies that reported on pain prevalence, seven also reported the mean FEV_1% predicted and one study reported the GOLD grade distribution,[23] which was converted to a weighted mean GOLD grade (Figure 5). There was a strong correlation between lung function (FEV_1% predicted) and pain prevalence; Spearmans r=0.79 (p=0.021).

Figure 5. Relationship between lungfunction (forced expiratory volume in 1 second; FEV1) and pain prevalence. Each data point represents a separate study. Correlation coefficient: Spearmans rho=0.79 (p=0.021)



Of the 21 studies and groups that reported SF-36/20/8 scores on the pain domain, 18 reported the mean FEV_1% predicted. In three groups of patients only the GOLD grade was reported,[34-37] which was converted to a weighted mean GOLD grade. No significant correlation was found between the SF-36_BP score and lung function: Pearson's correlation coefficient=0.21 (p=0.37; Figure 6).

Figure 6. Relationship between lungfunction (forced expiratory volume in 1 second; FEV1) and Short Form health survey-36_Bodily Pain (SF-36_BP) score. Each data point represents a separate study. Increasing units on the y-axis (e.g. higher SF-36_BP scores) refer to less severe pain and better quality of life. Pearson's correlation coefficient=0.21 (p=0.37).



Discussion

Main findings

The first main finding of this systematic review is that pain seems to be a significant clinical problem in patients with COPD, with a reported prevalence in high quality studies ranging from 32% to 60%. Second, literature on pain in patients with COPD is limited; only a few studies with a specific focus on pain in patients with COPD have recently been published. Still, little is known about the causes and characteristics of pain, factors that are related to pain and literature on the effect of interventions aimed at reducing pain in patients with COPD is lacking. Third, our data synthesis showed that studies investigating pain in patients with moderate airflow limitation reported a higher pain prevalence compared with studies in patients with severe airflow limitation. This finding could suggest that pain is more prevalent in patients with moderate COPD compared to patients with severe or very severe COPD. However, confounding and selection bias are likely to occur and much remains unclear about the relation between pain and disease severity. Fourth, our

results suggest a correlation between pain and several other symptoms, such as dyspnoea, insomnia, fatigue, anxiety and depression, QoL and comorbidity.

Strengths and limitations

To our knowledge, this is the first systematic review study on pain in patients with COPD. One strength of this study is that we included all types of studies and used a broad search method. Therefore, it seems unlikely that the search strategy we used failed to identify relevant published studies. Second, the selection strategy was objective, as it was performed by two, and in case of disagreement, by three individual members of the review team. Third, we were able to conduct a meta-analysis on the SF-36_BP data. Some limitations also need to be discussed. First, as literature on this topic is scarce, only 14 studies on pain and symptom burden in patients with COPD were included. Moreover, these studies showed substantial heterogeneity in design, setting, patient characteristics and pain measurement instruments used. Selected studies included patients with relatively severe COPD; mean FEV_1% predicted ranged from 21% to 48%. These differences in study methods might have influenced the reported pain prevalence and also limit the generalisability of the results. Furthermore, there were differences between the studies in patient selection criteria and the healthcare setting from which the patients were recruited, although most of the studies were conducted in a secondary (outpatient) care setting. Second, the appropriateness of including the SF-36_BP scores in this review is debatable. As our search strategy did not include 'QoL' as a keyword, we included only those studies on QoL that mentioned the keyword 'pain' in the abstract. This implies that our data on pain as a subdomain of QoL may not be complete. Nevertheless, we feel that the reported results do provide important information on this subject.

Interpretation of findings and relation to other literature

The wide range in pain prevalence can be explained by the heterogeneity in study design, setting, patient characteristics and instruments and definitions used to measure pain. We were interested in chronic and/or recurrent pain in patients with COPD. However, as we wanted a broad search method, we used 'pain' instead of 'chronic pain' as a major key word in our search strategy, as many studies do not clearly define pain as being 'chronic' or 'acute'. We did however exclude studies that concerned 'pain during acute bronchitis' (Figure 1). Different studies used different definitions of pain and none of the included studies presented longitudinal data on the course of pain. The wide range in pain prevalence can also be explained by differences in the quality assessment score. Three of the studies on pain and symptom burden that reported the prevalence of pain, had quality limitations as

identified with the MMAT. Furthermore, in the study conducted by Elkington *et al*[14] pain prevalence was based on reports of informants of the deceased participants. Agreement between the patient's and the proxy perception of pain is only moderate.[14,49] This by-proxy reporting of symptoms and the fact that the study included only patients in the terminal phase of their disease, could explain the relatively high level of reported prevalence of pain (72%). Claessens *et al*[13] reported a relatively low prevalence of pain (21%). However, pain was defined as 'moderately severe or extremely severe pain at least half of the time'. Borge *et al*[20] found a relatively high prevalence (72%) but used a much lower threshold, as pain was considered to be present in all patients that shaded pain on the body diagram of the BPI. Roberts *et al*[23] also reported a relatively high pain prevalence of 60%. In their cross-sectional study, recurrent pain-related healthcare utilisation (diagnosis and treatment) was considered evidence of chronic pain; data were received from the managed care claims database and from the outpatient pharmacy. Although evidence of chronic pain based on diagnosis and management can be reliable, it should be noted that, in the latter study, 28.6% patients with COPD used short-acting or long-acting opioids, compared with 17% in the control group (patients with other chronic diseases).[23] However, as the reason for prescribing opioids was not stated it is debatable whether opioid prescription was indeed aimed at treating pain, especially as it is also prescribed for chronic dyspnoea in patients with COPD.[50] Therefore, the reported prevalence of chronic pain in the study of Roberts *et al*[23] might have been an overestimation. The reported prevalence of pain should be interpreted in relation to pain prevalence in the general population, as well as in patients with cancer and other chronic diseases. Recent population-based surveys showed that 25–35% of the adults report chronic pain.[51] In patients with cancer this percentage is higher, as 50% of all patients with cancer experience chronic pain.[51] Thus, literature indicates that the prevalence of pain in patients with COPD is higher compared with the general population. Results from our meta-analysis on the SF-36_BP data also show that patients with COPD experience more pain compared to the general population: mean score of the SF-36_BP domain in the general US adult population is 75.2 (SD 23.7),[11] which is higher than the mean score we found in our random-effects meta-analysis of the SF-36_BP data in patients with COPD. A higher score on the SF-36_BP domain refers to less pain and better QoL.

We were not able to perform a meta-analysis on the results of the included studies that used other QoL instruments, because of the very small numbers of studies that used the same instrument (EQ-5D: n=3;NHP: n=2; HSQ: n=1; DHP: n=1). Results from the random-effects meta-analysis of the SF-36_BP scores showed substantial heterogeneity. It is very likely that parts of the heterogeneity is explained by

research setting, population, study design, cultural diversity and other, unknown variables.

None of the included studies on pain or symptom burden reported a significant relationship between lung function (measured as FEV_1% predicted or GOLD grade) and pain prevalence or pain severity. Interestingly, when we investigated the correlation between lung function and pain prevalence over all included studies on pain and symptom burden in patients with COPD, a strong correlation was found between lung function and pain prevalence. Studies that investigated prevalence of pain in patients with moderate COPD reported a higher pain prevalence compared with studies in patients with severe and very severe COPD. This might suggest that pain is more prevalent in patients with moderate COPD compared with patients with severe or very severe COPD. This finding has not previously been reported in literature on pain in patients with COPD. An explanation for this might be found in the hypothesis that when investigating the relationship between lung function and pain, confounding and selection bias are very likely to occur. Possible selection bias and confounding in the included studies might be an explanation for the observed relation between lung function and pain prevalence in the present study. For example, the number and severity of comorbidities may have caused selection bias: patients with very severe COPD and many comorbidities (cardiovascular and musculoskeletal such as osteoporosis) might have already died, or were not able to participate in the studies due to severely limited functional capacity. The number and severity of comorbidities might also have acted as a confounder in the relationship between pain prevalence and disease severity in the included studies. Furthermore, our results can be interpreted in line with a growing body of evidence showing that the correlation between FEV_1, symptoms and impairment of a patient's health status is weak.[52] Hence, in the recently updated GOLD Global Strategy for Diagnosis, Management and Prevention of COPD (GOLD strategy, 2014) the classification of patient's disease severity requires assessment of symptoms and exacerbation history, in addition to the degree of airflow obstruction. Our results show some evidence for a relationship between pain and comorbidity, although the included studies are not entirely consistent on this topic. Musculoskeletal disorders and comorbidities (including mechanical limitations of chest wall movement due to hyperinflation and osteoporosis) are considered possible causes of pain in patients with COPD.[8,9] However, due to the heterogeneity in the study designs we were unable to conduct a meta-analysis on pain prevalence and lung function controlling for comorbidity. In conclusion, much remains unclear about the relationship between disease severity, pain and comorbidity in patients with COPD and further research on this topic is needed.

We were unable to identify a study that investigated a specific intervention aimed at reducing pain in patients with COPD. The lack of literature on this topic is probably due to the fact that, in general, literature on pain in patients with COPD is scarce and pain seems to be a symptom that is often overlooked; this applies to daily practice and to research on the effect of comprehensive interventions, such as pulmonary rehabilitation (PR) and integrated disease management (IDM). In systematic reviews on PR and IDM in patients with COPD, pain is not mentioned as a patient-centred outcome in the field of symptom management.[53,54] Also, in national and international COPD guidelines there is almost no discussion of pain as part of a comprehensive symptom assessment. For example, the GOLD Global Strategy for Diagnosis, Management, and Prevention of COPD (GOLD guideline 2014) does not mention chronic pain and discusses opioids only in the context of the relief of dyspnoea. Also, the combined statement on PR of two major international medical societies does not mention pain as a problem in COPD management.[55] Moreover, in the Institute for Clinical Systems Improvement (ISCI) guidelines for management of COPD, pain is not discussed. Only the American Thoracic Society (ATS) clinical policy statement on palliative care for patients with respiratory diseases and critical illness includes a separate section on pain management; however, this addresses only dying patients with respiratory diseases and critical illnesses in general.[56]

Conclusion and implications

Pain in patients with COPD is a significant problem with an estimated prevalence of 32–60%. Literature on this topic is scare, and studies specifically focusing on pain in patients with COPD have only recently been published. Little is known about the factors associated with pain and no literature is available on the effect of interventions aimed at reducing pain in patients with COPD. Studies that investigated pain in patients with moderate airflow limitation reported a higher pain prevalence compared with studies in patients with severe and very severe airflow limitation. This finding might suggest that pain is more prevalent in patients with moderate COPD compared with patients with severe or very severe COPD. However, there was a substantial heterogeneity in patient characteristics and outcome assessment tools. More research on this topic is needed. Standardisation of assessment tools of pain in patients with COPD is needed. Future studies should focus on determining a more accurate prevalence of pain in patients with COPD, also in relationship to disease severity and comorbidity. Research should also pay more attention to the causes, course and characteristics of pain and clinical intervention trials are warranted. Furthermore, adequate pain recognition and treatment in clinical practice is

important and pain assessment should be incorporated into regular comprehensive symptom assessment in the clinical care of this group of patients. Finally, pain prevalence and its possible impact on QoL should be discussed in guidelines on COPD in order to raise awareness and recognition of this topic.

Appendix Chapter 6

Electronic search systematic review pain in patients with COPD

Pubmed:

("Pain"[Mesh] OR "pain"[all fields] OR "pains"[all fields] OR "Pain Measurement"[Mesh] OR "Analgesics"[Mesh] OR "analgesic"[all fields]) AND ("Pulmonary Disease, Chronic Obstructive"[Majr] OR "chronic obstructive pulmonary disease"[tiab] OR COPD[tiab] OR "Lung Diseases, Obstructive"[Majr:NoExp] OR "chronic bronchitis"[tiab] OR "chronic obstructive airway disease"[tiab] OR "chronic airway obstruction"[tiab] OR "chronic airway obstructions"[tiab] OR "COAD"[tiab] OR "chronic airflow obstruction"[tiab] OR "chronic airflow obstructions"[tiab] OR "Pulmonary Emphysema"[Majr])

EMBASE:

(exp *pain/ OR pain*.ti,ab. OR exp *pain assessment/ OR exp *analgesia/ OR analgesic.ti,ab.) AND (exp *chronic obstructive lung disease/ OR "chronic obstructive lung disease".ti. OR "chronic obstructive pulmonary disease".ti. OR COPD.ti. OR "obstructive lung disease*".ti. OR "chronic bronchitis".ti. OR "chronic obstructive airway disease".ti. OR "chronic airway obstruction*".ti. OR "COAD".ti. OR "chronic airflow obstruction*".ti. OR exp *lung emphysema/)

CINAHL

(MH "Pain+" OR TX pain* OR MH "analgesia+" OR TX analgesic) AND (MM "Pulmonary Disease, Chronic Obstructive+" OR MM "Bronchitis, Chronic" OR TI "chronic obstructive pulmonary disease" OR TI COPD OR TI "obstructive lung disease*" OR TI "chronic bronchitis" OR TI "chronic obstructive airway disease" OR TI "chronic airway obstruction*" OR TI COAD OR TI "chronic airflow obstruction*" OR MM emphysema)

PsycINFO

(DE "Pain" OR DE "Aphagia" OR DE "Back Pain" OR DE "Chronic Pain" OR DE "Headache" OR DE "Myofascial Pain" OR DE "Neuralgia" OR DE "Neuropathic Pain" OR DE "Somatoform Pain Disorder" OR TX pain OR DE "Analgesia" OR TX analgesic) AND (DE "Chronic Obstructive Pulmonary Disease" OR DE "Bronchial Disorders" OR DE "Pulmonary Emphysema" OR TX "chronic obstructive pulmonary disease" OR TX COPD OR TX "obstructive lung disease" OR TX "chronic bronchitis" OR TX "chronic obstructive airway disease" OR TX "chronic airway

obstruction" OR TX "chronic airway obstructions" OR TX COAD OR TX "chronic airflow obstruction" OR TX "chronic airflow obstructions" OR TX emphysema)

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Pain in patients with chronic obstructive pulmonary disease indicated for post-acute pulmonary rehabilitation

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Abstract

Objective: Pain is a significant problem in stable chronic obstructive pulmonary disease (COPD) and is associated with other symptoms, worse health status and lower functional status. Not much is known about pain in unstable disease. The primary aim of the present study is to investigate prevalence, characteristics and relationships of pain in patients with COPD hospitalized for an acute exacerbation (AECOPD) and indicated for post-acute pulmonary rehabilitation (PR). *Methods*: This cross-sectional observational study included 149 patients [mean age 70,8 (±7,9) years, 49% male, mean FEV_1 % predicted 35,3 (±12,6)]. Pain was assessed using the Brief Pain Inventory. Functional status and health status were measured using the six-minute walking test (6MWT), the Barthel index (BI) and the clinical COPD questionnaire (CCQ), respectively. *Results*: Pain was prevalent in 39,6% of all patients. Symptom burden was high, especially in patients with pain. Although we found no difference in objective measurements of functional status (6MWT, BI), patients with pain had clinically relevant lower health status (CCQ), attributed to the functional domain. *Conclusion*: Pain in patients hospitalized for AECOPD and indicated for post-acute PR is a relevant problem and needs more attention. Incorporation of standard pain assessment during exacerbations and post-acute PR is recommended.

Background

Pain is a clinically relevant symptom in chronic obstructive pulmonary disease (COPD) with prevalences ranging from 32-85%, depending on setting, sample and measurements used.[1,2] Pain is negatively associated with health-related quality of life (HRQoL).[1-5] Many symptoms are associated with pain, of which dyspnoea, anxiety, depression and insomnia are the most frequent.[1] Furthermore, these symptoms cluster and aggravate each other. Lohne et al first described this process of multiple concurrent symptoms reinforcing each other and called it the "vicious COPD circle".[6] In this concept, derived from a qualitative study on pain in patients with severe COPD, pain was described as "tying up the body", which made breathing difficult, leading to breathlessness and more pain. Pain also induced anxiety, depression and insomnia, causing more pain and psychological problems.[6] Recently, Lee et al reported similar results on the negative interaction between several symptoms and pain.[7]

Pain in COPD is also associated with diminished physical activity and lower functional exercise capacity,[8,9] often worsened by pain-related fear of movement.[4,7] The relationship between pain, symptoms and physical activity is important, since lifelong adherence to physical activity is essential to improve HRQoL and prognosis in COPD.

Acute exacerbations in COPD (AECOPD) play a key role. They represent a major burden for individual patients,[10] are the most frequent reason for hospital admissions and deaths among patients with COPD,[11] and negatively influence HRQoL and functional capacity,[10,11] often leading to re-hospitalizations, further decline of health status and high mortality rates.[12,13] The prevalence of pain and its relationship with other symptoms, functional capacity and HRQoL in unstable disease is however unknown, as data on pain during AECOPD are lacking.[1,2] Hypothetically, pain in patients with AECOPD might be aggravated compared to the stable state due to the mentioned vicious circle of symptoms, since acute exacerbations are defined as in increase in symptoms such as dyspnoea and cough. Post-acute pulmonary rehabilitation (PR) is an effective and safe intervention to counteract the adverse effects of hospital admission for AECOPD on symptom burden and physical functioning.[10] From this viewpoint post-acute PR could be an effective non-pharmacological intervention to reduce pain in unstable COPD, as it might counteract the pain-related vicious circles in COPD.[14] Also, as pain management is preferably undertaken using multi-domain strategies (e.g. psychological, physical, behavioural and pharmacological)[9], it might be a separate goal in post-acute PR by means of improving muscle strength, exercise capacity and coping. On the other hand, pain might negatively influence outcomes of post-acute PR in terms of

HRQoL and functional status. However, as far as we know, no studies on the role of pain in post-acute PR are available in literature.
Recently, Harrison et al did report on the role of pain in PR and concluded that a pain intervention, as part of a PR education program, seems warranted, as high pain prevalence and intensity, in combination with under-diagnosis and under-treatment, might negatively influence adherence to and outcomes of PR. Furthermore, as PR can aggravate pain in the short term, education of health care professionals and patients is important to optimize adherence to PR.[14]
In summary, pain is a relevant problem in patients with COPD, with relationships to several symptoms and diminished physical activity, causing several pain-related vicious circles. Furthermore, pain might negatively influence adherence to and outcomes of PR. However, literature on pain in unstable COPD and in relation to post-acute PR is lacking. Therefore, the primary aim of the present study is to investigate prevalence and characteristics of pain in patients with COPD hospitalized for an acute exacerbation and indicated for post-acute PR. Secondary aim is to investigate the relationship between pain, other symptoms, functional status and health status.

Methods

Study design

This cross-sectional observational study is part of a larger real-life prospective cohort study, conducted in the pulmonary department of two local hospitals to investigate the effects of a post-acute PR program on patients with COPD. Data collected during the hospital stay (the start of the study) were used. The Medical Ethics committee of Leiden University Medical Centre approved the study (P14.248) and the study design was registered in the Netherlands National Trial Register (NTR6261).

Participants

Patients were eligible when diagnosed with COPD and hospitalized with an acute exacerbation and indicated for post-acute PR based on standard criteria (Box 1). All participants signed a written informed consent. Patients were included in the study from January 2015 through December 2017.

Measurements

The following patient and disease characteristics were accessed from the patient's file: age, sex, spirometry [according to the Global Initiative for Chronic Obstructive Disease (GOLD) guidelines],[15] co-morbidity [Charlson Comorbidity Index (CCI)][16] and smoking status (yes/no). Nutritional status was measured by calculating body

Box 1. Criteria for post-acute PR

Major criteria:
1. Decline of functional status
2. Disease-specific health status is severely impaired, as measured by the CCQ, score ≥ 2.0
3. Frequent exacerbations; ≥ 2 in the last 6 months (excluding the present exacerbation)

Minor criteria:
1. Hypoxemia (excluding pre-existing chronic respiratory failure)
2. Impaired nutritional status: BMI <21 kg/m^2 and/or FFMI depletion
3. Patients at risk for clinically relevant anxiety disorder or depression; HADS >7 on either subscale

Indication for post-acute PR: 2 major criteria OR 1 major AND 2 minor criteria
Exclusion:
1. End-stage of COPD
2. Major psychiatric or cognitive disease
3. Lack of fluency in Dutch language

Abbreviations: CCQ: Clinical COPD questionnaire; BMI: body mass index; FFMI: fat-free mass index; HADS: Hospital anxiety and depression scale

mass index (BMI; kg/m^2) and assessing the fat-free mass index (FFMI; kg/m^2) by electrical bio-impedance. Impaired nutritional status was defined as FFMI <16 (men) or <15 (women) kg/m^2, or in case of missing FFMI data, BMI <21 kg/m^2.[17]

Pain

Pain was measured using the Dutch version of the brief pain inventory (BPI).[18] The BPI is a valid, reliable, comprehensive and widely used pain questionnaire in COPD studies and clinical practice.[19] First, patients are asked to indicate whether they are generally bothered by pain in the past week (yes/no), and if so, they then completed the full BPI, which consists of nine items subdivided into three components; (i) pain location using the body outline diagram on which patients can mark the location(s) of their pain, (ii) pain intensity which consists of four items that ask about pain intensity “now”, “worst level”, “least level” and “on average”, using a numeric rating scale (NRS) ranging from zero (no pain) to ten (worst pain) and (iii) pain interference with seven items evaluating how pain interferes with seven activities of daily life using a NRS ranging from zero (no interference) to ten (com-

plete interference). In addition, two items address pain treatment and pain relief by treatment, ranging from 0%(no relief) to 100% (complete relief).
Pharmacologic pain treatment was also assessed using the medical charts of all patients. Categories were based on the pain ladder of the World Health Organisation; 1) non-opioid, 2) weak opioid, and 3) strong opioid.[20] All prescriptions were coded as 'daily use' and/or 'as needed'.

Symptom burden

In addition to pain, the following symptoms were measured: dyspnoea was measured using the modified Medical Research Council (mMRC) dyspnoea scale (scores range from zero to four); moderate to severe dyspnoea was defined as having a score of ≥ two,[15] fatigue, insomnia, muscle weakness and anorexia were measured using a numeric rating scale (NRS) (scale 0-100) and were considered to be moderate to severe with a score of ≥ 40.[21,22] Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). A score of > seven points on either subscale indicates moderate to severe symptoms of anxiety or depression.[23]

Functional status

Activities of daily living (ADL) were measured using the Barthel index (BI).[24] The BI is a valid and reliable instrument to assess ADL. Total score ranges from 0 to 20, with 20 representing complete functional independence, 15-19 mild-, 10-14 moderate- and <10 severe care dependency, respectively.[25] Exercise capacity was measured with the six-minute walking test (6MWT), according to ERS guidelines. The 6MWT is a reliable, practical and widely used instrument to measure exercise capacity in patients with COPD.[26]

Disease-specific health status

Disease-specific health status was measured using the clinical COPD questionnaire (CCQ).[27] The CCQ is a validated and reliable 10-item self-administered questionnaire with three subdomains; symptoms, function and mental status. Items are scored on a Likert scale ranging from zero to six. The final score is the sum of all items divided by 10 and a score of ≥ 2.0 indicates impaired health status. The minimal clinical important difference (MCID) of the CCQ total score is ± 0.4.[28]

Statistical analysis

All data were processed using the SPSS (IBM SPSS Statistics for Windows version 23.0). Categorical variables are described as frequencies, while continuous variables were tested for normality and are presented as mean and standard deviation

(SD) or median and interquartile range (IQR) in case of skewed data. Differences between patients with and without pain were tested with independent sample t-test or chi-square test where appropriate. In case of skewed data, non-parametric tests were used. Statistical significance was defined as a p-value <0.05 (two-sided level of significance).

Results

General results

In total, 158 patients participated in the original study. Of these, nine patients (5.7%) had not completed the BPI and were excluded from the current analyses. Hence, the data of 149 patients [mean age 70.8 (±7.9) years, 49% male, mean FEV_1 % predicted 35.3 (±12.6)] were analysed (Table 1). Pain was prevalent in 59 patients (39.6%). No differences in demographic data (age, sex) and disease characteristics (FEV_1, FEV_1% predicted, co-morbidity score, nutritional status, smoking status) were found between patients with and without pain. Considering the functional status, results of the BI showed only mild care-dependency [BI:18 (15-20)], but exercise capacity was considerably limited [6MWT: 200.3(10.8)].

Table 1. Characteristics of the study population

	Total group (N=149)	Patients with pain (N=59)	Patients without pain (N=90)	*p*-value
Male***	73 (49)	25 (42.4)	48 (53.3)	0.24
Age in years *	70.8 (7.9)	69.5 (7.3)	71.7 (8.2)	0.08
FEV_1(L)	0.88 (0.35)	0.92 (0.37)	0.86 (0.33)	0.28
FEV_1 % predicted*	35.3 (12.6)	37.3 (12.6)	33.9 (12.5)	0.11
Smoking***	45 (30.2)	19 (32.2)	26 (28.9)	0.72
CCI**	2 (1-3)	2 (1-3)	2 (1-3)	0.75
BMI*	24.8 (5.4)	25.3 (6.1)	24.5 (4.9)	0.33
FFMI*	16.2 (2.6)	16.4 (2.7)	16.1 (2.5)	0.63
Impaired nutritional status***	52 (34.9)	21 (35.6)	31 (34.4)	0.89
BI**	18 (15-20)	18 (16-20)	18 (15-20)	0.34
6MWT*	200.3 (1108)	212.0 (111.5)	201.9 (114.4)	0.42

**Mean values (SD), **median (IQR), or ***counts with percentage are indicated. Level of significance: p <0.05*

Abbreviations: FEV_1% predicted: forced expiratory volume in one second as percentage of predicted value; CCI: Charlson Comorbidity Index; BMI: body mass index; FFMI: fat-free mass index; BI: Barthel index; 6MWT: six-minute walking test;

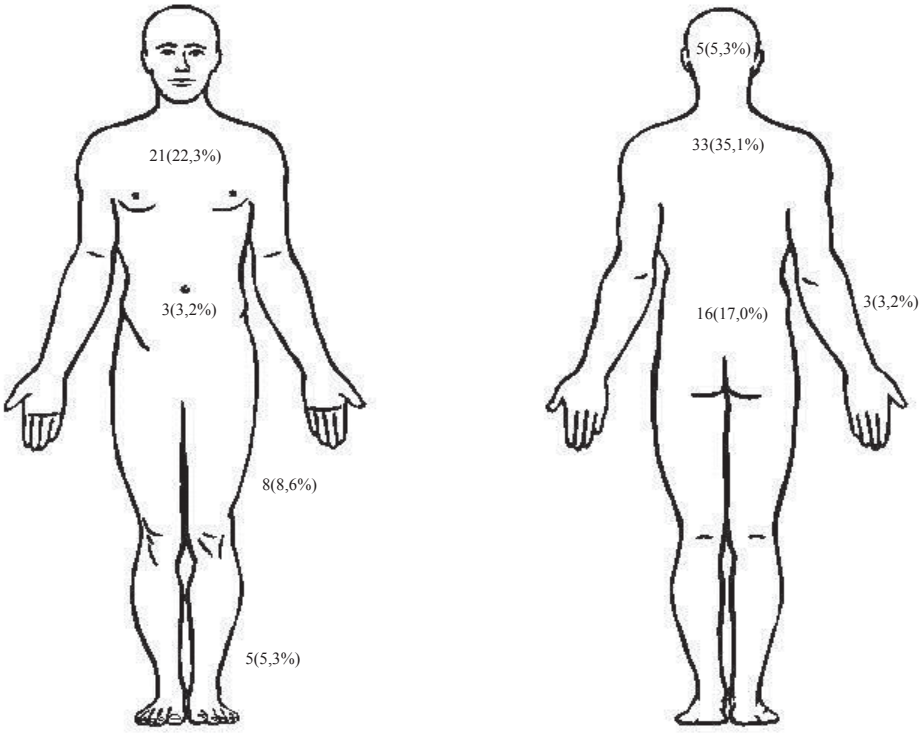
No differences in functional status were found between the two groups (p=0.34; p=0.42 respectively).

Characteristics of pain and pain treatment

In total, 94 marks were placed on the body outline diagram by 44 patients. In 15 patients with pain, the body outline diagram was blank. Pain was most frequently located in the trunk region (Figure 1). More than half (57%) of the patients with pain indicated two or more locations of pain on the body outline diagram.

Mean pain intensity scores on the BPI ranged from 2.7 (±2.3) (least pain) to 6.4 (±2.5) (worst pain). 'Average pain' and 'pain right now' showed mean scores of 4.3 (±2.3) and 4.1 (±3.1), respectively. Interference domain scores were highest for interference with normal work [5.9 (±3.3)], walking ability [5.6 (3.1)] and general activity [5.5 (3.0)]. Patients experienced the least interference with mood [3.6 (±2.9)] and relations with others [3.3 (±2.9)].

Figure 1. Reported pain locations, N(%)



Patients with pain were asked which treatment they received for their pain. In 14 patients this item was blank, three patients indicated they did not know the name of the treatment and eight patients wrote 'no treatment'. In total, 27 patients (45.7%) reported use of analgesic medication and 43 treatment items were scored: 23 non-opiod, 4 weak opioid, 8 strong and 8 other [antibiotics (n=2), corticosteroids (n=5) and physiotherapy (n=1)]. Patients were also asked to score the effect of treatment on pain relief on a scale ranging from 0-100%; the mean score was 43.5% (±32.1), indicating a mean moderate relief of pain due to pain treatment.
Data on pain prescriptens were collected from the medical files of all patients. In the total group (patients with and without pain), 67 patients (45.0%) had one or more analgestic prescription (daily use); most frequently prescibed were non-opioid analgesics: paracetamol (25.4%) and non steroidal anti-inflammatory drugs (15.9%). Analgestic prescription (daily use) was more frequent in patients with pain compared with those without pain (64% versus 38%; p=0.01). Analgestics 'as needed' were prescibed in 25.6% of the patients, with no differences between the two groups.

Differences in symptom burden (prevalence and intensity) in patients with and without pain

Almost all patients (91.3%) experienced moderate to severe dyspnoea with no differences between patients with and without pain (p=0.37). After dyspnoea, fatigue, muscle weakness and symptoms of anxiety and/or depression were most prevalent. Patients with pain suffered more often from fatigue (p=0.004), muscle weakness (p=0.01), anorexia (p=0.02) and symptoms of anxiety and/or depression (p=0.04), (Table 2). Considering symptom intensity, patients with pain had significantly higher scores for all symptoms except for dyspnoea (Table 3).

Differences in health status in patients with and without pain

Patients with pain had significantly and clinically relevant worse disease specific health status compared to patients without pain (Table 4). When analysing the differences in the scores on the three subdomains of the CCQ, only the CCQ_function subdomain showed significant and clinically relevant higher scores in patients with pain, compared to patients without pain.

Table 2. Prevalence of symptoms in patients with and without pain

Symptoms, N(%)	N	Patients with pain	Patients without pain	*p-value*
Dyspnea	149	52 (88.1)	84 (93.3)	0.37
Fatigue	137	52 (94.5)	62 (75.6)	0.004
Muscle weakness	136	44 (80.0)	47 (58.0)	0.01
Insomnia	136	37 (67.3)	43 (53.1)	0.11
Anorexia	136	31 (56.4)	29 (35.8)	0.02
Anxiety and/or depression	147	41 (70.7)	47 (52.8)	0.04

Notes: Moderate to severe fatigue, insomnia, muscle weakness, and anorexia was defined as having a NRS score of ≥ 40. Moderate to severe symptoms of anxiety or depression was considered to be present with a score of >7 on either subscale of the HADS, moderate to severe dyspnea was considered present with a score of ≥2 on the mMRC dyspnea scale. Level of significance: p <0.05
Abbreviations: mMRC: modified Medical Research Council Dyspnea Scale; NRS: numerical rating scale; HADS: Hospital Anxiety and Depression Scale

Table 3. Symptom intensity in patients with and without pain

	Total group (N=149)*	Patients with pain (N=59)*	Patients without pain (N=90)*	*p*-value
mMRC_Dyspnea (range 0-4)	3.1.(1.0)	3.1 (1.1)	3.1 (1.0)	0.60
NRS_Fatigue (range 0-100)	63.1 (24.8)	72.6 (20.4)	56.8 (25.7)	<0.001
NRS_Muscle weakness (range 0-100)	50.0 (27.7)	56.7 (25.9)	45.4 (28.1)	0.02
NRS_Insomnia (range 0-100)	41.8 (31.0)	49.8 (33.5)	36.3 (28.0)	0.01
NRS_Anorexia (range 0-100)	35.2 (22.4)	46.1 (22.9)	27.8 (20.0)	0.001
HADS_Anxiety (range 0-21)	7.8 (4.5)	8.9 (4.5)	7.2 (4.4)	0.03
HADS_Depression (range 0-21)	7.5 (4.2)	8.3 (4.6)	6.9 (3.8)	0.07

**Mean (SD). Level of significance: p <0.05*
Abbreviations: mMRC: modified Medical Research Council Dyspnea Scale; NRS: numerical rating scale; HADS: Hospital Anxiety and Depression Scale

Table 4. Health status in patients with and without pain

	Total group (N=149)*	Patients with pain (N=59)*	Patients without pain (N=90)*	*p*-value
CCQ_total (range 0-6)	3.6 (1.1)	3.9 (1.0)	3.4 (1.1)	0.04
CCQ_symptoms (range 0-6)	3.6 (1.1)	3.8 (1.1)	3.5 (1.1)	0.10
CCQ_function (range 0-6)	4.1 (1.3)	4.4 (1.1)	3.9 (1.3)	0.04
CCQ_mental (range 0-6)	2.4 (1.7)	2.6 (1.7)	2.2 (1.7)	0.14

**Mean (SD). Level of significance: p <0.05*
Abbreviations : CCQ: clinical COPD questionnaire

Discussion

Main findings

The present study is the first to measure pain in patients hospitalized for AECOPD and indicated for post-acute PR and shows that 39.6% of these patients reported pain with moderate to severe intensity and interference scores. These findings indicate that pain is also a relevant problem in this specific group of patients. Patients with pain also experienced a worse disease specific health status, compared to patients without pain, which was predominantly caused by more experienced limitations in functional status.

Interpretation of findings and relation to literature

In recent literature, two systematic reviews investigated pain prevalence in patients with stable COPD.[1,2] Prevalences varied widely, from 32 to 88%, with a pooled prevalence of 66%.[2] Compared to these results, we found a relatively low prevalence of pain. When comparing our results to individual studies that investigated pain in patients with similar characteristics (age, sex and lung function) that also used the BPI, more similarity was found. Lee et al conducted a cross-sectional study in 64 patients [mean age 71(±10) years; mean FEV_1 % predicted 37.9(±14.9)] with stable COPD (outpatient clinic) and reported a pain prevalence of 41%.[9] In two other studies,[4,29] pain prevalence was 50 and 45% in patients with similar mean age [70.0(±6.7) and 65.0(±9.2) years] but slightly better lung function [mean FEV_1 % predicted 44.7(±19.2) and 48(±16)%], respectively. However, in the cross-sectional study of Christensen et al,[30] 61% of 258 COPD patients [mean age 63.4(±9.4) years, mean FEV_1 % predicted 40.9(±19.2)] reported pain. Interestingly, the authors concluded that lower stages of COPD were associated with (more) pain and more interference. The apparent paradoxical relationship between pain and lung function was also reported in our earlier review.[1] This inverse relationship, probably also caused by selection bias, could be explained by the hypothesis that, in more severe COPD, other symptoms like dyspnoea are more distressing than pain, leading to more focus on dyspnoea and less on pain, also causing patients to be reluctant to spontaneously report pain.[6,14] Furthermore, patients with more severe disease and worse health status might experience a 'response shift' in their perception of pain, as they may have had pain for a longer period of time. Response shift refers to the phenomenon that patients suffering from chronic diseases change their internal standards as their disease progresses.[31] In summary, evidence from recent research together with the above outlined hypotheses indicate that our prevalence could have been an underestimation.

Our data showed no difference in co-morbidity between patients with and without pain. Other studies reported co-morbidity as a risk factor for pain,[32] and correlations were shown between pain and the number of co-morbidities,[4] but data are conflicting. Janssen et al reported a high prevalence of thoracic pain (53,7%), but no correlation between the CCI and thoracic pain was found.[5] A reason for this could be that the CCI measures co-morbidities in relation to mortality.

Regarding nutritional and functional status, several studies concluded that pain in COPD is associated with lower functional exercise capacity and higher BMI.[8,9,33] Our results show no differences in functional and nutritional status between patients with and without pain. Explanation for this finding could be that exacerbations and hospital admissions cause deterioration of functional and nutritional status.[10] Furthermore, in the present study, decline of functional and nutritional status were part of the selection criteria for indication of post-acute PR. The effect of the exacerbation and hospital admission on functional and nutritional status was probably dominant in comparison with the effect of pain.

In the present study, mean pain intensity and interference scores were relatively high compared to other reports in similar patients,[4,9,29,30] but within the range of the mean scores reported in our review.[1]

Pain treatment was assessed by the self-reported BPI and by collecting prescription data from the medical files of all patients. Relief from pain treatment or medication provided was 43.5% (±32.1), which is comparable to the result of Christensen et al [41.6%(±33.0].[30] Not many other studies on pain in COPD elaborated on pain treatment. In the study of Bentsen et al,[29] 48.9% of the patients with pain received analgestics (patient reported), also similar to our results. When comparing this pecentage with prescription data derived from the patient's file, patient reported analgestic use seems to cause a considerable underestimation. However, still 36% of the patients with pain did not have any analgestic prescription. Results from recent literature on this topic, together with our data, indicate that pain treatment is probably suboptimal in terms of pain relief and prescription of analgetics in patients with COPD.

In patients with pain, total symptom burden was higher compared to patients without pain; they experienced more symptoms with worse intensity of which fatigue, muscle weakness and symptoms of anxiety and depression were most frequent and most severe. This is in line with earlier studies showing correlations between different symptoms and pain prevalence.[3,6,9,30,34]

We found no difference in prevalence or severety of dyspnoea beween patients with and without pain. This is an interesting result, as many studies in stable COPD found a relation between pain and dyspnoea.[1] However, this finding can probably

be explained by the overall high prevalence of dyspoea in our study population, due to the acute state our patienst were in.

The present study is in line with earlier studies reporting that pain is negatively associated with HRQoL and health status in stable COPD,[4,5,9,33,35] as patients with pain in our study had a significantly and clinically relevant higher score on the CCQ. Interestingly, when looking at the mean scores on the subdomains of the CCQ, only the CCQ_function domain showed higher mean scores. However, no differences in more objective measurements of functional status (6MWT, BI) were found. Literature on the relation between pain and disease specific health status measured with the CCQ is scarce. Two studies did not find an association between pain and outcomes of (subdomains of) the CCQ.[22,36] The CCQ_function domain is known to correlate well with objective measurements of functional status in patients with COPD with similar age, lung function and functional status,[37] but literature on this relationship in COPD patients with pain is completely lacking. Therefore, interpretation of this particular finding is difficult but could generate new hypotheses on this subject. First, when patients with pain experience more limitations than they objectively have, this might negatively influence their motivation for rehabilitation. Furthermore, rehabilitation might be more effective in these patients when specifically addressing pain- experience, management and implications, also in relation to individual coping style. The study of Harrison et al on the role of pain in PR from a qualitative perspective, provides evidence that is in line with these hypotheses.[14]

Strengths and limitations

To our knowledge, this is the first study to investigate pain in patients with COPD hospitalized for AECOPD and indicated for post-acute PR. Furthermore, as this was a real-life study, almost no exclusion criteria were applied, indicating good generalizability within this group and setting. However, generalizability beyond this specific group and setting is limited, as only 149 patients from two hospitals were included. Selection bias may have occurred, as all patients in this group were indicated for post-acute rehabilitation. As this is a cross-sectional study and no comparison to patients within the stable state of COPD was made, it remains unclear if pain is worse following an AECOPD, only that people do experience pain during AECOPD. We also cannot determine case and effect, i.e. does pain affect HRQoL or does having poor HRQoL mean people have heightened sensitivity to the experience of pain.

Conclusions and implications

Pain in patients hospitalized for AECOPD and indicated for post-acute PR is a relevant problem. Patients with pain experience more severe limitation in the function

domain of their health status (CCQ) but no differences in objective measurements of functional status (6MWT, BI) were found. Pain in this specific group of patients needs more attention, as our study suggests that pain treatment is suboptimal. The reported prevalence of pain in patients hospitalized for AECOPD and indicated for post-acute PR is comparable to the prevalence of pain in the stable state. Therefore, incorporation of standard pain assessment in stable COPD and during exacerbations and post-acute PR is recommended, and patient education on pain in COPD and its possible implications is important. Further research should focus on assessing longitudinal data on pain in relation to exacerbations and post-acute PR as well as developing multi-domain pain treatment interventions that can be tested in (post-acute) PR programs.

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Summary and general discussion

8

Aim and outline of of this thesis

The central aim of this thesis is to investigate whether developing and implementing a specific geriatric rehabilitation program for older patients with severe COPD that also integrates palliative care aspects, the GR_COPD program, is both feasible and effective.

With this goal in mind, four studies were performed that included two different study populations, as well as a systematic review and meta-analysis of the literature.

First, the feasibility study (that included a retrospective case series of 61 consecutive patients with COPD that followed the GR_COPD program) investigated feasibility in terms of patient characteristics, suitability, safety and preliminary evaluation of patient response to the GR_COPD program. Furthermore, in this specific group and setting, the responsiveness of the clinical COPD questionnaire (CCQ) was examined in order to determine if the CCQ could be used as a primary outcome in the subsequent GR_COPD study.

Second, the GR_COPD study (that included a prospective cohort of 158 patients, hospitalized for an acute exacerbation and indicated for the GR_COPD program), investigated the effect of the GR_COPD program on disease-specific health status (measured with the CCQ), functional status and exacerbation frequency.

Third, a systematic review of the literature was made, including a meta-analysis, that examined the prevalence of pain, factors related to pain and pain management interventions in patients with COPD.

Fourth, cross-sectional data from the GR_COPD study were used to examine the prevalence, characteristics and relationships of pain in patients hospitalized for an acute exacerbation and indicated for the GR_COPD program.

Results

Main findings

Part one: The GR_COPD program

Chapters 3 and 4 present the feasibility study. The results show that patients admitted to the GR_COPD program had complex health issues: i.e. all patients suffered from advanced COPD (GOLD stage 3 or 4), co-morbidities were frequent, health status was severely impaired, and exercise capacity was limited. Furthermore, undernourishment was prevalent and many patients were at risk for an anxiety disorder or depression. These results confirm that patients admitted to the GR_COPD program have specific and complex problems and needs that can be explained by the co-occurrence of disease- and age-related problems. This underpins the need

for a suitable program that addresses these complex health issues. Preliminary evaluation of patient response to the GR_COPD program showed a clinically relevant improvement in both functional status and health status. Moreover, adherence to the program was good, there were no unexpected adverse events and over 90% of these patients were discharged home after a median length of inpatient rehabilitation of 35 days. Thus, we concluded that geriatric rehabilitation for patients with advanced COPD is feasible and is likely to offer substantial benefits.
The study in **Chapter 4** evaluated outcomes of the CCQ in relation to lung function, degree of dyspnoea and (change in) functional status. Results showed that, in this specific group of patients, the CCQ is sensitive to change in response to the GR_COPD program.
Chapter 5 presents the results of the GR_COPD study and shows that, during a three-month follow-up period, the GR_COPD program had a significant and clinically relevant treatment effect on disease-specific health status (measured with the CCQ) and exacerbation rate. This allowed us to conclude that geriatric rehabilitation, for older patients with severe COPD and hospitalized for an acute exacerbation, is effective. However, a longer follow-up period is needed to reveal whether these results can be maintained for a longer period of time. Nevertheless, we also concluded that the GR_COPD program should be implemented in clinical practice, as no alternative rehabilitation programs for this specific group of patients, are available.

Part two: Pain in patients with COPD

Chapters 6 and 7 present two studies that focused on pain in COPD. Overall symptom burden is one of the most important determinants of disease-specific health status and, therefore, adequate symptom control is of major importance, from the perspective of both palliative care and rehabilitation medicine. Patients with COPD suffer from many different symptoms, of which the most commonly known are dyspnea, cough and sputum production. We decided to focus on pain, since pain is also highly relevant but an often unrecognized, underestimated and, therefore, undertreated symptom in patients with COPD; moreover, pain has a negative impact on quality of life and possibly also on functional status.
The results of our systematic review (**Chapter 6**) confirm that pain is prevalent in patients with COPD, with moderate to severe scores on intensity and interference. Furthermore, the results show that pain is related to many other symptoms (e.g. dyspnea, insomnia, fatigue, anxiety and depression) and that pain is negatively associated with health-related quality of life. Nevertheless, much remained unknown due to the relatively few studies on pain in COPD and the considerable amount of heterogeneity in the design of the included studies.

The cross-sectional study (**Chapter 7**) on the prevalence and characteristics of pain in patients indicated for the GR_COPD program, shows that pain was also a prevalent and significant symptom in this specific population, as 40% of all patients suffered from pain, with moderate to severe scores on intensity and interference. Furthermore, compared to patients without pain, patients with pain had an overall higher symptom burden and a more impaired disease-specific health status. Although we found no difference in objective measurements of activities of daily living and exercise capacity, patients with pain experienced more limitations in functional status, as measured with the functional domain of the CCQ. Results from this study also indicate that pain treatment was probably suboptimal in terms of pain relief and prescription of analgetics. These results tend to confirm that, in patients with COPD, pain is often unrecognized, underestimated and undertreated. Thus, we concluded that, in this group of patients and setting, pain needs more attention and standard assessment of pain should be implemented into daily practice, together with patient education on this subject.

Reflection

To further discuss the outcomes of the work presented in this thesis, the postacute rehabilitation (PAC) quality framework of Jesus and Hoenig was used as a theoretical context and translated to the GR_COPD program and study.[1]

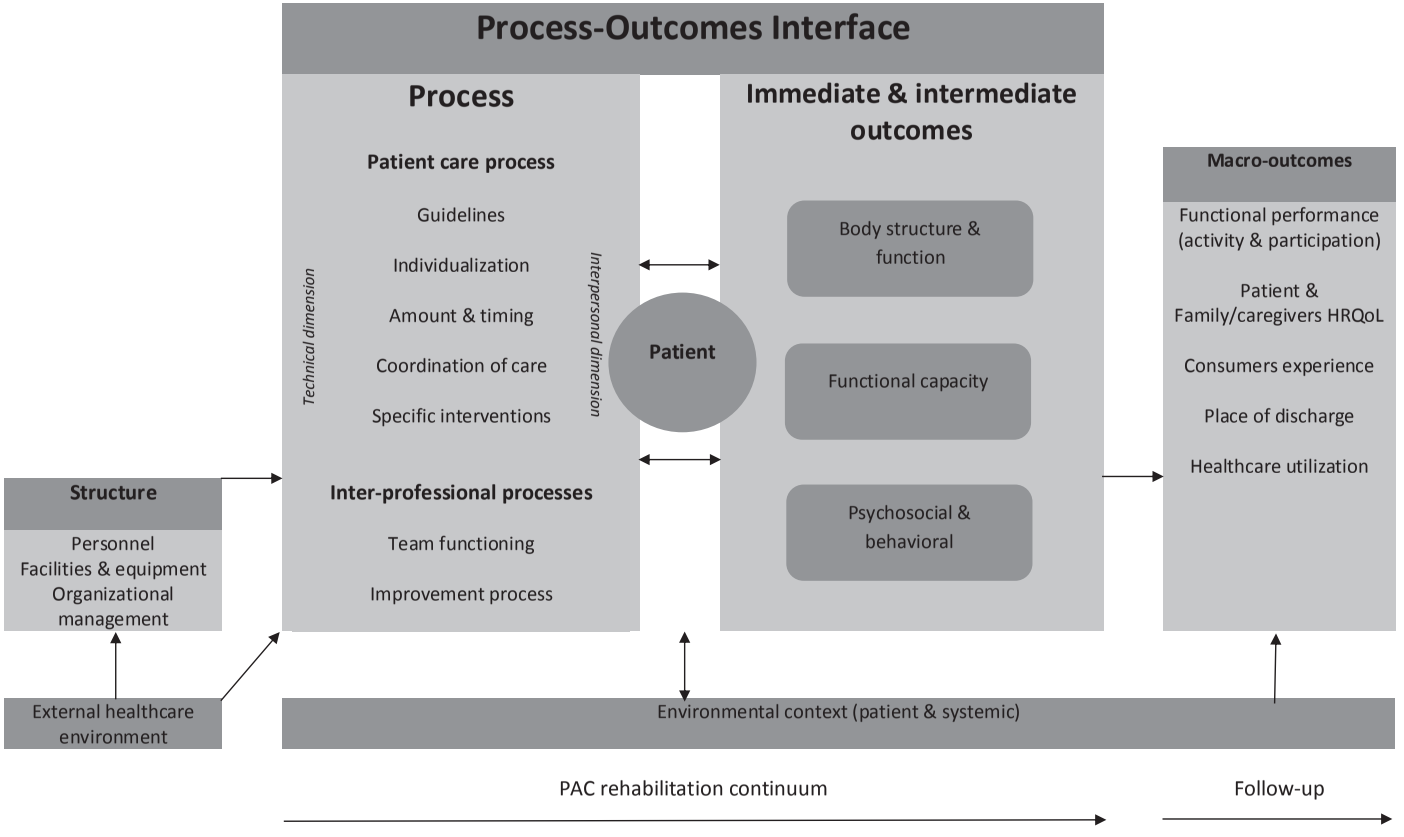
The PAC quality framework was based on the structure, process, outcome (SPO) model of Donabadian and the International Classification of Functioning, Disability and Health (ICF) model of the World Health Organization (WHO). It was developed in order to clarify what constitutes 'quality of care' in postacute rehabilitation, and to provide a sound and evidence-based framework that can be used for quality of care evaluation and improvement (Figure 1). The PAC quality framework was therefore used as a model to evaluate the results of the present work, and to develop a broader and more generic view on geriatric rehabilitation for patients with chronic diseases, in terms of implications for clinical practice and recommendations for research. Below, we discuss the different elements of the framework in a stepwise reverse order, i.e. we start with the outcomes, because these reflect what really matters: namely, benefit for our patients.

Outcomes of the GR_COPD program

Macro level

The primary outcome measure of the GR_COPD study was change in disease-specific health status, as measured by the clinical COPD questionnaire (CCQ).

Figure 1. The postacute rehabilitation (PAC) quality framework developed by Jesus and Hoenig.[1]



Abbreviations: HRQoL: health related quality of life

Our results show a clinically relevant effect of the GR_COPD program on disease-specific health status. Choosing disease-specific health status as primary outcome is important, as it reflects the patient's personal experience of disease severity and covers other domains beyond the functional domain, such as symptoms and mental status. This is also in line with literature and guidelines on pulmonary rehabilitation and palliative care in COPD, which also state that improvement of (health-related) quality of life should always be the ultimate aim of any intervention or treatment program within these domains.[2-5]

Exacerbation rate was defined as secondary outcome. Results from the GR_COPD study show a relevant effect on exacerbation rate during a three-month follow-up period: i.e. patients in the control group had an exacerbation rate of 2.7 as compared to 1.0 in the GR_COPD group. Exacerbation rate can be related to several macro outcomes. First, in patients with COPD, exacerbations are strongly related to diminished health-related quality of life and have a negative impact on functional performance and prognosis.[6,7] Second, exacerbation rate can be seen as a derivative of healthcare utilization, because exacerbations are the most frequent reason for hospital admission in these patients.[8] However, secondary analysis with a longer follow-up period that also focuses on other outcome measures more strongly related to healthcare utilization (i.e. cost-effectiveness), such as rehospitalizations and preventable follow-up care, is needed.

In the ICF-based construct of functional performance, social participation and the extent to which patients can perform tasks of daily living in their own environment (i.e. activity) are considered the primary outcomes of rehabilitation. Both activity and participation are complex concepts, not only determined by individual factors but also by the dynamics of social roles and the direct environment in which they take place. However, measurement of participation was not part of the primary analysis of the GR_COPD study. Although validated and widely used instruments are available that measure activity [e.g. functional independence measure (FIM)], no internationally used and validated tool that includes the complexity of participation in this domain is available.[1] In the Netherlands, the Utrecht scale for evaluation of rehabilitation-participation (USER-p) was developed and appears to be a valid measure to rate participation in persons with physical disabilities.[9] Integrating personal goals on the level of participation into geriatric rehabilitation programs is important, as was recently stated in the Dutch Position Paper on geriatric rehabilitation, and has already been confirmed in stroke survivors aged 70 years and older.[10,11] Therefore, validating the USER-p as outcome measure on a macro level could prove important for research in geriatric COPD rehabilitation.

It should be mentioned that the patients' and caregivers' actual experience with the program was not measured. This can be seen as an important shortcoming of our

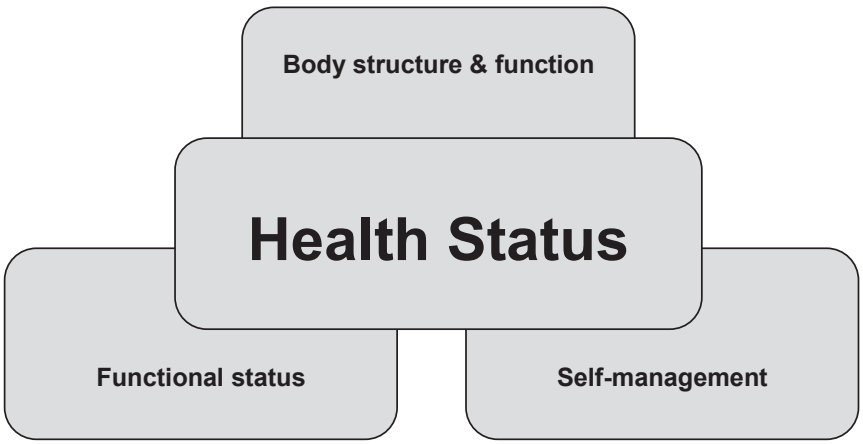
study, as the patient's perspective is an important outcome measure that directly reflects the degree of patient centeredness and, thus, the quality of healthcare.[1] In addition to the relevance of the patient's perspective, it is also important to note that the construct of 'experience' was preferred to 'satisfaction', the latter being more expectancy-dependent and more subjective.[12]

Intermediate/immediate level

Intermediate outcomes of the GR_COPD program can be categorized into three domains: i) body structure and function, ii) functional status and iii) self-management. These three domains encompass several standard treatment modules, all targeted at improving disease-specific health status as the ultimate goal (on a macro level) of the program (Figure 2). These three domains are very similar to the immediate/intermediate outcomes defined in the PAC quality framework (body structure & function; functional capacity; psychosocial & behavioural), although the third domain (i.e. self-management) needs additional clarification and elaboration (further discussed below).

Improvement in body structure and function was achieved through treatment modules that focussed on a) optimizing pharmacological treatment, inhalation techniques and oxygen use, b) prevention and treatment of co-morbidities, c) optimizing nutritional status and/or treatment of undernourishment, and d) improving symptom burden. There is considerable evidence to support the important role of symptoms in COPD driving the burden of the disease.[13] Therefore, optimal symptom control is considered to be a key target in COPD treatment and of major importance for improving health status, also from a palliative care perspective.[14]

Figure 2. Three-domain-model of the GR_COPD program.

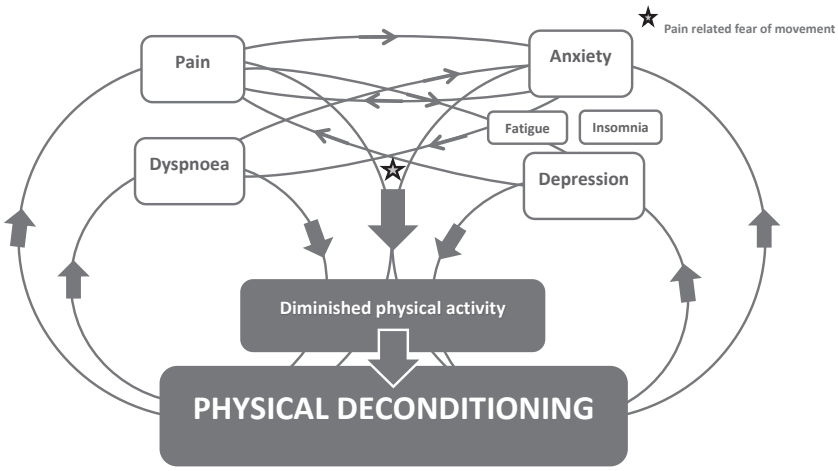


Symptom burden in patients with advanced COPD is known to be high: this is also confirmed by our data (**Chapters 3, 4 and 7**). Participants of the GR_COPD study suffered from many symptoms, the most prevalent being dyspnoea, fatigue, muscle weakness and pain (**Chapter 7**). Furthermore, in patients with COPD, symptoms (including pain) seem to cluster, thereby aggravating each other, causing several 'vicious circles in COPD' (Figure 3). In this concept, originally based on the study of Lohne et al, and further developed based on the results from our systematic review (**Chapter 6**), cross-sectional data from the GR_COPD study (**Chapter 7**) and (more recently) studies on pain in COPD, physical deconditioning is seen as the underlying process that could explain the observed co-occurrence of pain and many other symptoms. This process is mediated by diminished physical activity and pain-related fear of movement, and is often aggravated by co-morbidities and poor nutritional status.[15-18]

The central role of symptoms in the burden of COPD emphasizes that standard systematic assessment and follow-up of symptom burden should be part of clinical care for patients with COPD during the stable phase of the disease, and also during exacerbations and rehabilitation (**Chapter 7**). This requires a valid multidimensional symptom assessment instrument and specific interventions aimed at optimal control of several symptoms, such as pain, fatigue, dyspnoea, insomnia, anxiety and depression.

The GR_COPD study could not establish any treatment effect on functional status (**Chapter 5**). Considering the fact that postacute rehabilitation in general primarily focusses on functional recovery and functional performance, this result is some-

Figure 3. The vicious circles in COPD.



what surprising and might even be concerning. Functional status as intermediate outcome refers to the ability of the patients to function (i.e. perform. activities of daily living such as washing, getting dressed, going to the bathroom, walking and eating) regardless of social roles or environmental variables.[1] We defined functional recovery as improvement in two functional domains: 1) change in the level of care dependency concerning activities of daily living, as measured with the Barthel Index (BI), and 2) change in exercise capacity, as measured with the six-minute walking test (6MWT). When analysing the results of the BI and 6MWT we concluded that, although both outcome measures had improved to a clinically-relevant extent, the BI is probably less suitable as an outcome measurement in this specific group of patients because of (amongst other reasons) its ceiling effect. Results of the 6MWT showed a high amount of missing data and a wide range, leading to limited statistical power. Based on these results, the relevance of the BI and the 6MWT as outcomes in geriatric COPD rehabilitation can be questioned, also because of the possible limited correlation of these instruments to activity and participation. When the GR_COPD study was designed, choosing these instruments to measure (improvement in) functional status was based on international literature and guidelines on pulmonary rehabilitation (6MWT) and generic geriatric rehabilitation (BI). Thus, we conclude that, based on our results, together with the construct of activity and participation from the PAC framework, additional instruments are needed.

For this, the Utrecht scale for evaluation of rehabilitation (USER) and the USER-participation (USER-p), might be a more suitable choice for measuring functional status and participation, and improvement of these outcomes in response to geriatric COPD rehabilitation. The USER was developed in the Netherlands, and is a valid and reliable instrument to measure immediate/intermediate outcomes of rehabilitation on an individual level, and can also be used to measure the effectiveness of specific rehabilitation programs.[10] The USER consists of several domains including activities of daily living, mobility, cognition, psychosocial functioning and several symptoms (including fatigue and pain). The USER is also part of the Standard Measurement Plan for Geriatric rehabilitation, developed at the University Network for the Care Sector South Holland (UNC-ZH) that is currently being implemented and tested in several geriatric rehabilitation units.

Improvement of self-management, as the third intermediate outcome of the GR_COPD program, was pursued by the following treatment modules: education, peer-group support, smoking cessation support, training of energy saving techniques, general advice concerning healthy aging (e.g. nutrition, exercise), and assessment of compliance and coping responses (e.g. patients compliance with care recommendations, adaptive coping responses). Motivation for the program and psychological status, expressed by symptoms of anxiety and depression and

cognitive impairment, are also known to affect macro outcomes of postacute rehabilitation.[1] Furthermore, the interaction between motivation and psychological status is of interest and importance. For instance, symptoms of depression can predict uptake and non-completion of rehabilitation, and cognitive impairment increases the risk for dropout during pulmonary rehabilitation.[19,20] From a broader perspective, research questions should move from focussing on effectiveness of postacute rehabilitation for patients with COPD to how referral, uptake and adherence can be improved, also in relation to patients' motivation and preferences in terms of setting and timing.[6,21] In the GR_COPD study, indication for the program was based on a set of standard criteria, probably resulting in a relatively high referral rate (although evaluation of the referral rate was not part of the study). Also, the feasibility study showed good adherence, as only one patient dropped out due to lack of motivation. However, uptake of the program can be interpreted as being relatively low: of the 158 included patients only 78 were motivated for the GR_COPD program. This finding again raises the important discussion concerning which variables influence and constitute patients' motivation for rehabilitation, and how to improve uptake.
The GR_COPD study was not aimed at measuring the direct effects of the program on self-management, or one or more of its individual components. Also, we did not investigate the relationship between (components of) self-management and psychological status as independent variables and health status as a dependent primary outcome measure, nor did we investigate the effect of specific self-management and psychological treatment modules on an intermediate or macro outcome level. However, more knowledge on the effectiveness of these specific elements of the GR_COPD program (also in relation to motivation and uptake) is important since improvement of self-management is a key component of treatment in general for chronic conditions, such as COPD.[1,5] The PAC quality framework does not present an evidence-based conceptual understanding and approach for definitions and quality evaluation of self-management; this emphasizes the need for the development of concepts that describe and explain the complex interactions between motivation, psychological status and self-management in this specific group of patients and setting.

Patient care process: evaluation of the GR_COPD program

The GR_COPD program was developed as a structured care pathway, in close collaboration with the pulmonary department of the adjacent hospital. Coordination of care across settings enables smooth transitions and helps to synchronize the care provided by different healthcare providers interfacing with the patients. The resultant synergies are known to have a positive effect on patients' outcomes.[1]

The GR_COPD program was based on (inter)national guidelines on comprehensive evidence-based pulmonary rehabilitation.[5,22] Implementation and dissemination of these guidelines into clinical practice was assured by repeated knowledge transition from the pulmonary department to the multidisciplinary rehabilitation team, and vice versa. Furthermore, the feasibility study (**Chapters 3 and 4**) was developed to evaluate the program and the results were also used for quality improvement.

Although guidelines should direct practice, rehabilitation should always be tailored to patients' needs and possibilities and, therefore, programs need to be individualized. This also applies to the treatment plan of the GR_COPD program, which is based on an individual comprehensive assessment. Outcomes from this assessment, combined with the experience of the rehabilitation team, are used as input for the complex process of individualized clinical reasoning about the wide variety of variables that constitute a patient's disabilities and limitations. At the next level, individualization should be part of the process of defining specific rehabilitation goals, i.e. use patient-centred goal setting and shared decision-making. Structured goal setting in rehabilitation has the potential to improve macro outcomes via higher levels of motivation and self-efficacy.[23] Although patient-centred goal setting does take place within the GR_COPD program, this is not done in a formalized way [e.g. by using an instrument that facilitates the goal-setting process, such as the Canadian Occupational Performance Measure (COPM) or Goal Attainment Scale (GAS)] and, therefore, implementation cannot be guaranteed. In the Standardized Measurement Plan for Geriatric Rehabilitation, the COPM is one of the core instruments. Preliminary results of pilot studies show that the COPM is feasible in this population.[24]

The GR_COPD program was developed as a modular program that combines specific interventions of rehabilitation medicine and palliative care. The program is aimed at restoring patients' health status to the level before hospital admission or, in other patients, to counteract or stabilize the gradual decline in health status that preceded hospital admission and prevent hospital readmissions (**Chapter 2**). The GR_COPD program consists of several standard treatment modules within the three domains (Figure 2). Using standardized treatment modules that specify exactly what kind of treatment is provided, facilitates quality monitoring and presumably improves outcomes.[1] However, the complexity of most disabilities, and the rehabilitation process itself, challenge the use of standardized treatment modules. Nevertheless, using a modular program (categorized into the three domains) seems to be a suitable and workable structure for this specific group of patients. Moreover, it can be argued that geriatric rehabilitation after an acute exacerbation of a chronic ('acute-on-chronic') disease (e.g. heart failure, renal failure, Parkinson's disease, oncological diseases) is different from geriatric rehabilitation after an acute event,

such as a hip fracture or stroke. Besides focussing on functional recovery and improvement of body structures and body functions, rehabilitation after an 'acute-on-chronic' event should also be aimed at improving self-management strategies (i.e. educate the patient how to live well with a chronic disease) and should also integrate palliative care aspects into the rehabilitation plan.

In **Chapter 2** we described the palliative care aspects of the GR_COPD program. The palliative care needs of patients with advanced chronic organ failure can be divided into five domains: 1) symptoms, 2) care dependency, 3) family caregiving, 4) co-morbidities. and 5) advance care planning.[25] Although all of these domains were implemented into the structure of the GR_COPD program, this was not carried out in a standardized systematic way in daily practice. Implementation of a more standardized systematic assessment of the five palliative care needs defined by Janssen et al might be beneficial to patients and could improve outcomes of the GR_COPD program. Therefore, a validated instrument for the assessment of multidimensional symptom burden, and specific interventions aimed at optimal control of specific symptoms (such as pain, fatigue and insomnia), are needed. An intervention that facilitates implementation of advance care planning into daily practice was recently developed and evaluated, and should be implemented into practice.[26]

Interprofessional processes

Interprofessional processes support the care process and outcomes, and encompass team functioning and improvement processes. However, since evaluating the quality of the interprofessional process of the GR_COPD program was beyond the aims of this research project, this element is not addressed in detail. Nevertheless, the design of the GR_COPD program does meet all the conditions that define good quality of team functioning in postacute rehabilitation, such as deliberate care planning (e.g. multidisciplinary treatment plans), care coordination (e.g. weekly interdisciplinary team meetings), team leadership (e.g. coordination of interdisciplinary care by the elderly care physician) and sociologic factors (e.g. rehabilitation climate as part of organizational culture).

Structure of the GR_COPD program

Organizational management

When the GR_COPD program was first developed, geriatric rehabilitation was part of a government-guided long-term care reimbursement system without financial incentive for efficient or high-quality geriatric rehabilitation. In 2011, a bundled payment system was introduced to improve the quality of service delivery and, ultimately, the quality of care. Considering the process of service delivery, develop-

ing structured care pathways was one of the main goals. However, this requires effective collaboration between different stakeholders, e.g. nursing homes with specialized nursing facilities (SNF), specialized rehabilitation centres and hospitals. Although the GR_COPD program was developed in close collaboration with the pulmonary department of the adjacent hospital (secondary care), structural collaboration with a pulmonary rehabilitation centre (tertiary care) or general practitioners and other primary care stakeholders was not part of the developmental process. Moreover, structural cooperation in daily practice on a patient, outcome and quality level was only present between the SNF and the adjacent hospital. Developing and implementing cooperation on a large scale with multiple healthcare providers and stakeholders from different domains of the healthcare system is challenging, especially in a changing external healthcare environment.[27,28] Nevertheless, from a patient's and evidence-based perspective, integrated care pathways that cover all domains of healthcare should always be pursued, as they improve quality of care and contribute to deliverance of the right type of care, at the right moment, in the right setting, for the right patient.

Patient centeredness

In the PAC quality framework, patient-focussed quality definitions are considered to be of key importance and, therefore, the patient is placed in the centre of the framework. First, a patient-centred rehabilitation process, with alignment with patients' care needs, values and perspectives, is crucial, Second, patients can be seen as co-creators of their own rehabilitation process and directly influence outcomes and quality of care. Therefore, involvement of the patient (and family/caregiver) in the rehabilitation process, mediated by individual goal setting, shared decision-making, improvement of self-management and context-based care, is needed.[11] This process should be fostered by healthcare providers. Recently, patients are increasingly involved in the development of patient- reported outcome measures (PROMs), also in line with value-based healthcare.[29,30] The GR_COPD program was developed as a patient-centred program. The treatment plan is based on a thorough individual assessment that includes the patient's preferences, needs and goals, also in the context of psychosocial status and participation. Furthermore, the program is aimed at improving self-management and disease-specific health status, using a disease-specific PROM (i.e. the CCQ) as outcome. Nevertheless, processes that actually constitute patient centeredness were not yet transparent and, thus, the quality of implementation cannot be objectively measured and evaluated. This calls for implementation of innovative techniques that, ideally, facilitate and foster patient centeredness (e.g. goal setting and self-management), improve the quality of the process (i.e. ensure that patient centeredness was indeed part

of daily practice) and improve (macro) outcomes (i.e. are (cost)-effective). An innovative technique that has the potential to combine these outcomes, is eHealth.[31] eHealth can be defined as the use of information and communication technologies for health and can, when integrated into usual care (i.e. blended eHealth), improve self-management in patients with chronic diseases, such as COPD.[32] Developing and implementing blended eHealth interventions aimed at improving, facilitating and monitoring patient centeredness in geriatric rehabilitation, can be seen as a new and important field of interest, both from a practice and evidence-based perspective.

Methodological consideration

When interpreting the results of this thesis, some important limitations should be considered. We discuss these limitations in relation to the three study designs that were used.

Limitations of the feasibility study

The first and most important limitation of the feasibility study (designed as a real-life study describing a consecutive series of patients all receiving the GR_COPD program, but with no control group) is population bias due to the selection procedure, which was not based on strict inclusion criteria and might negatively affect generalizability. The lack of a control group, although self-evident when considering the design and aims of this study, can be seen as a second limitation: it is plausible that those that received usual care also experienced significant improvement. Thirdly, when considering the guidelines on conducting feasibility studies, one important recommended objective was not incorporated into this study: we could not report on recruitment rate, as data from patients that were indicated but not motivated for the program, were not collected.

Limitations of the systematic review and meta-analysis

First, because our review was the first systematic review study on pain in patients with COPD, at the time of performing the search strategy the literature on this topic was scarce; only 14 studies on pain and symptom burden in patients with COPD could be included and, of these, only 11 reported on the prevalence of pain in COPD. Also, because the included studies showed considerable heterogeneity in design, setting, patient characteristics and pain measurement instruments used, this probably affected the validity and reliability of our results. As a consequence, the estimated prevalences of pain in patients with COPD showed a large range (21-

72% overall; 32-60% in high-quality studies). Furthermore, the appropriateness of including data from quality of life instruments that included a separate pain domain is debatable. Because our search strategy did not include 'quality of life' as a keyword, we included only those studies on quality of life that mentioned the keyword 'pain' in the abstract. This implies that our data on pain as a subdomain of quality of life are probably incomplete. However, there has been a recent increase in studies specifically focussing on pain in COPD; this allows to more accurately determine the prevalence of pain in COPD, and helps the development and implementation of treatment interventions that specifically target pain in patients with COPD.

Limitations of the GR_COPD study

The design of the GR_COPD study is an important limitation. Because randomization was considered unethical, lack of comparability in outcome risk factors between the GR_COPD and control group might have led to confounding. Therefore, we chose to use propensity scores (PS) analysis and included sensitivity analysis for unmeasured confounding. PS analysis is recommended when conducting observational real-life studies that evaluate treatment benefits and harms in older adults. Although an additional sensitivity analysis showed similar results, confounding cannot be fully excluded as we did not perform other recommended strategies to address unmeasured confounding (e.g. active comparator design). Another important limitation is the generalizability to other patients with COPD; although positively influenced by the fact that this was a real-life study and lenient exclusion criteria were applied, this influence may have been limited due to selection bias caused by the indication criteria applied. Moreover, patients willing to participate might have been a selective group, even though no differences were found in demographics and baseline CCQ and HADS scores between the included and not included patients. Finally, results from both the feasibility study and the GR_COPD study question the appropriateness and relevance of the instruments used to measure functional status (i.e. the Barthel Index and the 6MWT). This limitation was mainly reflected in the observed ceiling effect of the Barthel Index and the wide range in values of the 6MWT combined with a relatively high amount of missing data (40%). Furthermore, since no valid set of outcome measures for this group of patients and setting is available, this makes it difficult to compare our results on functional status with other studies in general.

Conclusion, implications and recommendations

Based on the results of the work in this thesis we conclude that a disease-specific geriatric rehabilitation program that integrates rehabilitation with palliative care aspects (the GR_COPD program) is needed, is feasible, and shows beneficial effects on disease-specific health status and exacerbation rate, in older patients with COPD hospitalized for an acute exacerbation. These results imply that the GR_COPD program should be available to all patients within this specific group.

We used the PAC quality framework to structure implications for daily practice and recommendations for research. *First*, considering the macro outcomes of the program, it is recommended to use the CCQ as primary patient-related outcome measure (PROM), in clinical practice and in research. PROMs related to activity and participation (macro outcome) and to functional recovery (intermediate outcome) for this specific group of patients are needed, because integration of personal goals on the level of activity, participation and functional recovery into the treatment plan is important. There is evidence that using the USER and USER-p as outcome measures on an intermediate and macro level is promising, and further research should focus on evaluating the validity, reliability and responsiveness of these instruments in geriatric rehabilitation. Furthermore, measurement of patients' and caregivers' experience with the program is important and should be implemented into practice and used as an outcome measure in studies on geriatric rehabilitation.

Second, within the process-outcome interface, it is recommended to use the three-domain model with a specific focus on self-management (Figure 2) in disease-specific geriatric rehabilitation programs for patients that suffer from acute exacerbations of chronic ('acute-on-chronic') diseases. Furthermore, palliative care aspects should be integrated into the treatment plan by incorporating standardized symptom assessment and advance care planning methods. Research should focus on developing a valid multidimensional symptom assessment instrument for patients with COPD or, more generally, for patients with chronic organ failure. Specific interventions aimed at optimal symptom control (e.g. pain, fatigue and insomnia) and facilitating implementation of advance care planning into practice, should be developed and tested. *Third*, research should focus on obtaining more knowledge about the effectiveness of specific interventions of the GR_COPD program, especially concerning self-management and palliative care. This requires development of a conceptual approach to the complex interaction between motivation, psychological status and self-management in this specific group of patients and setting. *Fourth*, on an organizational level, models of cooperation between multiple healthcare providers and stakeholders that cover all domains of rehabilitation medicine (community and hospital care, tertiary (pulmonary) reha-

bilitation centres) on a patient, outcome and quality level, should be developed and implemented into practice. *Finally*, eHealth is a novel but promising field of interest with considerable potential in terms of improving patient centeredness, quality of care and saving costs. Therefore, future research should also focus on development, implementation and evaluation of blended eHealth interventions in geriatric rehabilitation.

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Samenvatting

Samenvatting

Deel I: Het GR_COPD zorgpad

Gezien de wereldwijde vergrijzing en stijging van het aantal kwetsbare ouderen met chronische aandoeningen en multimorbiditeit, is er in toenemende mate behoefte aan revalidatieprogramma's die specifiek gericht zijn op deze groeiende groep ouderen met vaak complexe problematiek, lage belastbaarheid en beperkte prognose. Geriatrische revalidatiezorg heeft zich de laatste jaren sterk ontwikkeld en geprofessionaliseerd. Hierbinnen past het ontwikkelen en wetenschappelijk evalueren van doelgroep specifieke revalidatie programma's. Eén van de patiëntengroepen waarvoor dit zinvol kan zijn betreft oudere patiënten met chronisch obstructief longlijden, ofwel COPD. COPD is de afkorting van de Engelse term *Chronic Obstructive Pulmonary Disease*, en wordt gekenmerkt door een chronische, meestal progressieve, luchtwegobstructie die niet volledig reversibel is. De belangrijkste symptomen van COPD zijn kortademigheid, hoesten en het opgeven van sputum. COPD is een wereldwijd groeiend probleem met stijgende prevalentie-, morbiditeits- en mortaliteitscijfers, met name onder ouderen. Het beloop en de prognose van COPD wordt voor een groot deel bepaald door acute exacerbaties, welke gedefinieerd zijn als een acute toename van de respiratoire symptomen waarvoor behandeling en/of ziekenhuisopname geïndiceerd is. Exacerbaties hebben belangrijke klinische gevolgen, waaronder een negatief effect op de kwaliteit van leven, de functionele status en de prognose van patiënten.

Onderzoek laat zien dat revalidatie direct na een ziekenhuisopname vanwege een acute exacerbatie COPD (postacute longrevalidatie) een effectieve en veilige behandeling is en de negatieve effecten van een exacerbatie (deels) kan herstellen. Echter, laag belastbare, kwetsbare oudere patiënten met vaak ernstig COPD en multimorbiditeit, opgenomen in het ziekenhuis vanwege een acute exacerbatie, ontvangen in de dagelijkse praktijk vaak geen postacute longrevalidatie. Reden hiervoor is vaak diezelfde matige belastbaarheid en kwetsbaarheid, waardoor deze patiënten vaak niet in staat zijn deel te nemen aan intensieve revalidatie programma's, die bovendien vaak niet in de buurt van hun eigen woonomgeving beschikbaar zijn. Daar komt bij dat er bij deze doelgroep vaak ook sprake is van tijdelijke zorgafhankelijkheid en dat, mede gezien de beperkte prognose, het integreren van palliatieve zorg aspecten in het revalidatieprogramma geïndiceerd is maar in de praktijk maar moeizaam tot stand komt.

In 2009 heeft Zorggroep Solis, in samenwerking met de longafdeling van het Deventer Ziekenhuis, het ketenprogramma "Geriatrische revalidatie voor patiënten met ernstig COPD" (het GR_COPD zorgpad) ontwikkeld. Doel van dit revalidatieprogramma is het verbeteren van de kwaliteit van leven van oudere patiënten

met (zeer) ernstig COPD, na een ziekenhuisopname in verband met een acute exacerbatie. Tevens wordt gestreefd naar een betere functionele status en het voorkomen van complicaties, zoals een progressieve achteruitgang van de algehele gezondheidsstatus en recidiverende ziekenhuisopnames. Om deze doelen te behalen worden revalidatie- en palliatieve zorg aspecten geïntegreerd aangeboden in het behandelprogramma.
Het centrale doel van dit proefschrift is om te onderzoeken of het GR_COPD zorgpad haalbaar en effectief is. Met dit doel voor ogen werden vier studies ontworpen en uitgevoerd met twee verschillende onderzoekspopulaties, evenals een systematische review en meta-analyse van de literatuur.

Hoofdstuk 2 beschrijft het GR_COPD zorgpad zoals dat is ontworpen en geïmplementeerd. Het GR_COPD zorgpad is een multidisciplinair patiënt-georiënteerd revalidatieprogramma en wordt aangeboden binnen de setting van de geriatrische revalidatiezorg (GRZ). Het zorgpad bestaat uit een modulair behandelprogramma dat gebaseerd wordt op een individueel breed assessment bij opname. De verschillende behandelmodules kunnen worden gecategoriseerd in de volgende drie domeinen: 1) somatische status, 2) functionele status en 3) zelfmanagement. Het uiteindelijke doel van het behandelprogramma is het verbeteren van de algehele gezondheidsstatus van de patiënt. Aan de hand van drie case-studies wordt geïllustreerd hoe het programma in de praktijk is opgezet en wat de meerwaarde van het GR_COPD zorgpad kan zijn voor individuele patiënten. Hierbij wordt ook verduidelijkt hoe de integratie van revalidatie en palliatieve zorg in de praktijk wordt toegepast.

Hoofdstuk 3 presenteert de resultaten van een retrospectieve pilot studie van 61 patiënten met COPD die het GR_COPD zorgpad volgden. De studie onderzocht de haalbaarheid van het zorgpad, waarbij met name gekeken werd naar de volgende vragen: 1) patiëntkenmerken: Worden de juiste patiënten in het GR_COPD zorgpad opgenomen?, 2) beloop: Laten geselecteerde uitkomstmaten een verbetering op patiënten-niveau zien gedurende het zorgpad? 3) ontslagbestemming: Lukt het in voldoende mate om patiënten terug naar huis te ontslaan? De resultaten van deze studie laten zien dat er bij patiënten die werden opgenomen voor het GR_COPD zorgpad sprake was van complexe problematiek: alle patiënten hadden ernstig of zeer ernstig COPD, multimorbiditeit kwam frequent voor, bij veel patiënten was er sprake van een slechte voedingsstatus en overall was de inspanningscapaciteit ernstig beperkt. Bovendien was er gemiddeld genomen sprake van een verhoogd risico op het voorkomen van een angststoornis en/of depressie en was de ziekte-specifieke gezondheidsstatus ernstig verminderd. Deze resultaten

bevestigen dat patiënten opgenomen voor het GR_COPD zorgpad specifieke en complexe problemen hebben die kunnen worden verklaard door het naast elkaar voorkomen van COPD en leeftijdsgebonden aandoeningen, zoals multimorbiditeit en lage belastbaarheid. Deze uitkomsten bevestigen de behoefte aan een doelgroep-specifiek programma dat deze complexe gezondheidsproblemen aanpakt. Het beloop van een aantal relevante uitkomstmaten van het GR_COPD zorgpad toonde een klinisch relevante verbetering van zowel de functionele status als de ziekte-specifieke gezondheidsstatus. Bovendien was de adherence goed, waren er geen adverse-events en kon meer dan 90% van de patiënten naar huis na een gemiddelde opnameduur van ongeveer 5 weken. Conclusie van de pilot studie was dan ook dat het GR_COPD zorgpad haalbaar is en waarschijnlijk substantiële verbetering voor patiënten kan bieden.

In **hoofdstuk 4** wordt dieper ingegaan op het in de pilot studie gebruikte meetinstrument voor de ziekte-specifieke gezondheidsstatus, de Clinical COPD Questionnaire (CCQ). Het meten van de gezondheidsstatus vanuit het perspectief van de patiënt wordt in toenemende mate gezien als een belangrijke maat voor de ernst van een aandoening, zowel in de dagelijkse praktijk als in wetenschappelijk onderzoek. De CCQ is ontwikkeld als ziekte-specifieke maat voor de gezondheidsstatus van patiënten met COPD. Het is een eenvoudige 10-item vragenlijst en bestaat uit drie domeinen: symptomen, functionele status en mentale status. Bij patiënten met mild tot matig ernstig COPD correleert de CCQ goed met de functionele status en heeft een goede voorspellende waarde voor wat betreft exacerbaties en mortaliteit. Er was echter nog weinig bekend over het gebruik en uitkomsten van de CCQ bij oudere patiënten met multimorbiditeit en (zeer) ernstig COPD, en over de uitkomsten van de CCQ bij deze groep in relatie tot uitkomsten van postacute revalidatie. Doel van de aanvullende analyse van de pilot studie was dan ook het onderzoeken van uitkomsten en de responsiviteit van de CCQ in deze specifieke groep en setting om zo te bepalen of de CCQ als een primaire uitkomstmaat gebruikt kan worden in de daaropvolgende GR_COPD studie. De resultaten laten zien dat, in deze specifieke groep patiënten, een verbetering op de CCQ goed correleert met verbeteringen in de functionele status en het inspanningsvermogen. Op basis van deze resultaten hebben wij geconcludeerd dat de CCQ in deze groep patiënten gevoelig is voor verandering in reactie op het GR_COPD zorgpad en gebruikt kan worden als primaire uitkomstmaat in de vervolgstudie.

Hoofdstuk 5 presenteert de resultaten van de GR_COPD studie, een prospectieve vergelijkende cohortstudie naar de effecten van het GR_COPD zorgpad op de ziekte-specifieke gezondheidsstatus als primaire uitkomstmaat. Secun-

daire uitkomstmaten waren de functionele status en de exacerbatie-frequentie. De studie werd uitgevoerd op de longafdeling van twee ziekenhuizen, namelijk het Deventer Ziekenhuis en het Isala Ziekenhuis in Zwolle. In beide regio's is het GR_COPD zorgpad beschikbaar voor patiënten. Alle patiënten die in aanmerking kwamen voor deze studie waren opgenomen in het ziekenhuis vanwege een acute exacerbatie COPD en hadden een indicatie voor het GR_COPD zorgpad. Deze indicatie werd gesteld op basis van een aantal standaard criteria. Vervolgens werd bepaald of patiënten ook gemotiveerd waren voor het zorgpad. Uit de pilotfase van het onderzoek was al gebleken dat ongeveer de helft van de patiënten met een indicatie voor revalidatie niet gemotiveerd was voor deelname aan dit specifieke programma. In de vervolgstudie werden deze patiënten beschouwd als controle. Randomisatie voor het GR_COPD zorgpad zou op basis van wetenschappelijke inzichten wellicht de voorkeur hebben gehad, maar was in de praktijk niet haalbaar. Veel van deze patiënten verkeren na ziekenhuisopname wegens een acute exacerbatie in een dusdanig slechte algehele gezondheidsstatus dat het onthouden van revalidatie niet ethisch zou zijn geweest. In de gekozen onderzoeksopzet moest echter wel gecorrigeerd worden voor confounding, aangezien het te verwachten is dat de groep met motivatie voor het zorgpad zou verschillen van de groep zonder motivatie. Op basis van de literatuur hebben we er daarom voor gekozen om hiervoor te corrigeren middels de propensity-score. De propensity-score geeft, op basis van een aantal van tevoren vastgestelde mogelijke confounders, zoals leeftijd, geslacht, de ernst van de aandoening en functionele beperkingen, de kans weer dat een bepaalde patiënt kiest voor het zorgpad. Correctie voor confounding vindt vervolgens plaats door het wegen van de onderzoekspopulatie op basis van de propensity-score. In totaal konden158 patiënten worden geïncludeerd in deze studie, van wie er 78 gemotiveerd waren voor het GR_COPD zorgpad en de resterende 80 patiënten de controlegroep vormden. Tijdens de analyse bleek dat de twee groepen in veel opzichten van elkaar verschilden, zoals in leeftijd, geslacht, longfunctie, voorgeschiedenis, rookgedrag en exacerbatiefrequentie. Na correctie met de propensity-score waren er geen significante verschillen meer tussen de twee groepen, voor wat betreft gemeten confounders. Hierna kon met een propensity-score gewogen lineaire regressie het behandeleffect worden bepaald. De resultaten hiervan tonen aan dat het GR_COPD zorgpad een significant en klinisch relevant behandeleffect heeft op de ziekte-specifieke gezondheidsstatus, gemeten met de CCQ, en de exacerbatie-frequentie, gedurende een follow-up periode van drie maanden. Op basis van de resultaten van dit onderzoek hebben wij geconcludeerd dat het GR_COPD zorgpad, voor oudere patiënten met ernstig COPD, opgenomen in het ziekenhuis vanwege een acute exacerbatie, effectief is. Er is echter vervolgonderzoek nodig om vast te stellen of deze resultaten ook

gedurende een langere periode kunnen worden behouden, en ook is onderzoek nodig naar de kosteneffectiviteit van het zorgpad. Bovendien lieten de resultaten geen significant effect zien van het zorgpad op de functionele status. Dit kan deels verklaard worden door de kenmerken van de gebruikte uitkomstmaten, zoals het bestaan van het plafond-effect bij de Barthel Index, de gebruikte maat voor het meten van de zelfstandigheid. Daarnaast bleek de gebruikte test voor het meten van het inspanningsvermogen, de zes-minuten-wandeltest, een grote spreiding te vertonen en bovendien voor een deel van de patiënten een te grote belasting te zijn, waardoor het aantal missing waarden voor deze uitkomstmaat relatief groot was. Desalniettemin hebben we geconcludeerd dat het GR_COPD zorgpad breder geïmplementeerd kan worden in de klinische praktijk, mede gezien het feit dat er geen alternatieve revalidatieprogramma's voor deze specifieke groep patiënten beschikbaar zijn. Vervolgonderzoek naar geschikte uitkomstmaten van de functionele status die bij deze specifieke doelgroep goed correleren met doelen op participatie en activiteiten- niveau, is van belang.

Deel II: Pijn bij patiënten met COPD

Binnen het onderzoek van dit proefschrift is een specifiek focus aangebracht op pijn bij patiënten met COPD. Achtergrond hiervan is dat in de literatuur in toenemende mate gepleit wordt voor betere integratie van revalidatie en palliatieve zorg voor deze groep patiënten met een chronisch progressieve aandoening. Veel oudere patiënten met (zeer) ernstig COPD hebben een hoge symptoomlast, slechte kwaliteit van leven en een beperkte prognose. Inzet van palliatieve zorg is dus geïndiceerd, maar blijft in de praktijk vaak uit, mede doordat het individueel voorspellen van de prognose moeilijk is en revalidatie en palliatieve zorg vaak als aparte domeinen zijn georganiseerd in de gezondheidszorg. Optimale symptoomcontrole wordt beschouwd als een belangrijk doel van de behandeling, zowel vanuit het perspectief van revalidatie als palliatieve zorg. Het is bekend dat patiënten met COPD last hebben van veel symptomen, waarvan dyspneu, hoesten en sputumproductie het meest bekend zijn. Uit de recente literatuur kwam naar voren dat pijn ook een relevant, maar vaak niet herkend, onderschat en daardoor vaak onder-behandeld symptoom lijkt te zijn bij patiënten met COPD. Bovendien zou pijn gecorreleerd zijn aan veel andere symptomen en deze mogelijk kunnen verergeren. Dit fenomeen wordt de 'vicieuze COPD-cirkel' genoemd. In dit concept bemoeilijkt pijn de ademhaling, wat leidt tot meer kortademigheid, verkramping van spieren en daardoor nog meer pijn. Via deze weg kan pijn ook leiden tot inactiviteit, of angst voor bewegen, met een verdere achteruitgang van conditie en spierkracht tot gevolg. Pijn lijkt ook angst, depressie en slapeloosheid te veroorzaken, of te verergeren, en deze symptomen hebben op zichzelf vaak weer een negatief effect

op pijn. Pijn lijkt ook samen te hangen met een verminderde kwaliteit van leven en hypothetisch zou pijn de uitkomsten van (postacute) longrevalidatie negatief kunnen beïnvloeden, maar mogelijk kan revalidatie juist bijdragen aan het verminderen van pijn, mits hiervoor voldoende aandacht is binnen het behandelprogramma. Veel was echter nog onduidelijk over pijn bij COPD, zoals een preciezere prevalentie, ook in relatie tot de ernst van de COPD en de setting, de oorzaken van pijn en de relatie met co-morbiditeit, en de relatie tussen pijn en andere symptomen. Tevens was onduidelijk welke interventies pijn bij patiënten met COPD kunnen verminderen en of er interventies bekend zijn die mogelijk ook effectief zouden kunnen zijn in het verminderen van de negatieve gevolgen van pijn bij COPD.

In **hoofdstuk 6** worden de resultaten gepresenteerd van onze systematische review en meta-analyse van de wetenschappelijke literatuur naar pijn bij COPD, waarbij specifiek gekeken is naar de prevalentie van pijn, factoren gerelateerd aan pijn en interventies gericht op het verminderen van (de gevolgen van) pijn bij patiënten met COPD. De resultaten van deze systematische review bevestigen dat pijn relatief veel voorkomt bij patiënten met COPD. De ernst en belemmeringen van pijn zijn gemiddeld genomen matig tot ernstig te noemen. Verder laten de resultaten van de systematische review zien dat pijn gerelateerd is aan veel andere symptomen, zoals kortademigheid, slapeloosheid, vermoeidheid, angst en depressie en dat pijn negatief geassocieerd is met kwaliteit van leven. De relatie met co-morbiditeit blijft onduidelijk, alhoewel sommige studies een duidelijk verband lieten zien met het voorkomen en de ernst van pijn. In de onderzochte afzonderlijke studies werd geen relatie gevonden tussen pijn en leeftijd, geslacht, roken en de longfunctie. Onze meta-analyse toonde wel een negatieve correlatie aan tussen de ernst van de luchtwegobstructie, als maat voor de ernst van COPD, en pijn; met andere woorden, geïncludeerde studies met patiënten met minder ernstige luchtwegobstructie rapporteerden een hogere prevalentie van pijn, in vergelijking met studies met patiënten met ernstig en zeer ernstig COPD. Dit zou er op kunnen wijzen dat pijn bij patiënten met mild of matig ernstig COPD vaker voorkomt in vergelijking met patiënten met (zeer) ernstig COPD. Veel blijft echter ook onduidelijk over pijn bij COPD. Zo vonden we geen enkele studie die een interventie, gericht op het verminderen van (de gevolgen van) pijn bij COPD, beschreef of had onderzocht. Opvallende uitkomst was ook het relatief lage aantal onderzoeken dat zich specifiek heeft gericht op pijn bij COPD. Bovendien was er sprake van een aanzienlijke heterogeniteit van de geïncludeerde studies in studie opzet en de gehanteerde methodes, zoals bijvoorbeeld de gebruikte meetinstrumenten en de setting van waaruit patiënten werden gerekruteerd.

Hoofdstuk 7 presenteert de resultaten van een cross-sectionele studie naar de prevalentie, de karakteristieken en de relaties van pijn bij patiënten die waren geïncludeerd in de GR_COPD studie. Dit onderzoek laat zien dat pijn ook in deze specifieke populatie een veel voorkomend en significant symptoom is, met een prevalentie van ongeveer 40% en matige tot ernstige scores voor wat betreft de ernst van pijn en belemmeringen als gevolg van pijn. Bovendien hadden patiënten met pijn in vergelijking met patiënten zonder pijn een algehele hogere symptoomlast en een slechtere ziekte-specifieke gezondheidsstatus. Een opvallend resultaat van dit onderzoek is dat we geen verschil vonden in objectieve maten van activiteiten van het dagelijks leven en inspanningscapaciteit, maar dat patiënten met pijn weldegelijk meer beperkingen in hun functionele status ervaarden, in vergelijking met patiënten zonder pijn. De resultaten van dit onderzoek wijzen er ook op dat de behandeling van pijn zeer waarschijnlijk niet optimaal was. Veel patiënten met pijn kregen geen pijnmedicatie voorgeschreven, en patiënten met pijnmedicatie rapporteerden een matige effect hiervan op hun pijn. Deze resultaten lijken te bevestigen dat pijn bij patiënten met COPD vaak niet wordt herkend en onvoldoende wordt behandeld. Conclusie van deze studie is dat pijn ook bij deze patiënten vaak voorkomt en meer aandacht behoeft. Het standaard in kaart brengen van pijn, voor, tijdens en na een exacerbatie, en als onderdeel van het revalidatieprogramma, wordt geadviseerd en zal moeten worden geïmplementeerd in de dagelijkse praktijk. Tevens is vervolgonderzoek nodig naar interventies gericht op het verminderen van (de gevolgen van) pijn bij deze groep patiënten, welke ook geïntegreerd zouden kunnen worden in het GR_COPD zorgpad.

Conclusies en aanbevelingen

Op basis van de resultaten van de studies beschreven in dit proefschrift is onze belangrijkste conclusie dat voor oudere patiënten met ernstig COPD, opgenomen in het ziekenhuis vanwege een acute exacerbatie, een ziekte-specifiek geriatrisch revalidatieprogramma dat revalidatie integreert met palliatieve zorgaspecten (het GR_COPD zorgpad) nodig en haalbaar is. Bovendien heeft het GR_COPD zorgpad gunstige effecten op de ziekte-specifieke gezondheidsstatus en de exacerbatiefrequentie. Deze resultaten impliceren dat het GR_COPD zorgpad beschikbaar zou moeten zijn voor alle patiënten binnen deze specifieke doelgroep.

Op basis van de uitkomsten van de CCQ in deze specifieke patiënten groep wordt het aanbevolen om de CCQ te gebruiken als primaire patiënt-gerelateerde uitkomstmaat, zowel in de klinische praktijk als in wetenschappelijk onderzoek.

Vervolgonderzoek moet zich in de eerste plaats richten op de vraag of de huidige resultaten ook op de langere termijn te behouden zijn. Daarnaast is het van belang

om de kosteneffectiviteit van het GR_COPD zorgpad te onderzoeken. Ook daarvoor is een langere follow-up periode noodzakelijk.
Vervolgonderzoek is ook nodig om te bepalen wat relevante uitkomstmaten zijn met betrekking tot functioneel herstel en participatie voor deze specifieke groep patiënten.
Pijn komt veel voor bij patiënten met COPD en heeft belangrijke klinische consequenties. Dit betekent dat pijn bij COPD meer aandacht behoeft, zowel in de klinische praktijk als in wetenschappelijk onderzoek. Gestandaardiseerd assessment van de symptoomlast, in alle fasen en stadia van de aandoening, is van belang. Onderzoek moet zich richten op de ontwikkeling van een valide en betrouwbaar multidimensionaal instrument voor het meten van de symptoomlast van patiënten met COPD. Specifieke interventies gericht op optimale symptoomcontrole (zoals pijn, vermoeidheid en slapeloosheid), moeten worden ontwikkeld, geëvalueerd en geïmplementeerd, bijvoorbeeld als onderdeel van het GR_COPD zorgpad.

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Curriculum vitae

Eléonore (Leonoor) Françoise van Dam van Isselt werd geboren op 7 juni 1970 in Rotterdam. Ze doorliep haar middelbare schooltijd in Zeist, op het Herman Jordan Lyceum, en behaalde in 1989 haar VWO diploma. In datzelfde jaar begon ze met haar studie geneeskunde aan de Universiteit van Utrecht, waar zij in 1995 haar doctoraal examen behaalde en begin 1998 haar artsexamen. Tijdens haar studie maakte ze verschillende reizen naar het buitenland en deed onderzoek bij de vakgroep MDL van het AZU en de maatschap vaatchirurgie van het St. Antonius Ziekenhuis in Nieuwegein. Om eerst meer klinische ervaring op te doen alvorens een definitieve keuze te maken m.b.t. een vervolgopleiding, werkte ze na haar artsexamen ruim anderhalf jaar als AGNIO cardiologie, longziekten en interne geneeskunde in Ziekenhuis Hilversum. Toen zij in 1999 zou starten met de huisartsenopleiding, kreeg de avonturier in haar de overhand en vertrok ze voor een wereldreis per zeilboot. Ruim een jaar later, terug in Nederland, werkte ze tijdelijk als arts-onderzoeker bij het Julius Centrum voor Huisartsgeneeskunde van de Universiteit Utrecht, en deed onderzoek naar prognostische factoren van COPD in de huisartsenpraktijk. Na een verhuizing naar Deventer besloot Leonoor te gaan werken op de acute opname afdeling van verpleeghuis Casa Bonita in Apeldoorn. Wat bedoelt was als het opdoen van aanvullende ervaring in afwachting van de huisartsopleiding, bleek een gouden greep. In 2004 startte Leonoor bij Stichting Sutfene in Zutphen met de opleiding tot verpleeghuisarts aan de Radboud Universiteit van Nijmegen, welke zij in 2007 afrondde. Tijdens haar opleiding deed zij, samen met prof. dr. Jos Schols, onderzoek naar de consultfunctie van de verpleeghuisarts. Vanaf 2008 werkt Leonoor bij Zorggroep Solis, in Deventer, waar ze in 2009 het GR_COPD zorgpad mede hielp opzetten. In 2012 startte zij met dit promotieonderzoek als buitenpromovendus aan de afdeling Public Health en Eerstelijnsgeneeskunde (PHEG) van het Leids Universitair Medisch Centrum (LUMC). Vanaf september 2018 is zij aangesteld als post-doc onderzoeker aan diezelfde afdeling met als onderzoeksthema eHealth in de geriatrische revalidatiezorg.

Leonoor is getrouwd met Erik de Romph en samen kregen zij drie kinderen, Elena (2001), Stan (2002) en Tos (2005).

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