# Proactive palliative care for patients with COPD

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Colofon

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Life is not measured by the number of breaths we take,
but by the moments that take our breath away.

George Carlin

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# General Introduction

# 1

The quality of life of patients with advanced Chronic Obstructive Pulmonary Disease (COPD) is poor, and often even worse than patients with inoperable lung cancer.[1] Patients with cancer commonly receive palliative care towards the end of life, incorporating their physical, psychological, social, and spiritual needs. Research has shown that an early or proactive approach to palliative care improves the quality of life of patients with cancer.[2,3] However, for patients with COPD such care is not common practice.[1,4] This thesis contains several studies in order to move towards the use of proactive palliative care for patients with COPD.

## COPD

### Definition and outline

COPD is defined as *"a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases."*[5] Although smoking is a major risk factor for COPD, non-smokers may also develop the disease as a result of exposure to air pollution and/or a genetic predisposition.[6-9] The severity of COPD is graded according to the degree of airflow limitation as mild, moderate, severe, or very severe.[5] However, airflow limitation is only poorly correlated with the symptom burden and the other problems these patients encounter, such as functional limitation, number of exacerbations, and the presence of co-morbidities.[10] The characteristic symptoms of COPD are chronic and progressive dyspnea, coughing and sputum production, while fatigue and anxiety are also highly prevalent in more advanced disease.[11,12] The distress these symptoms cause is, beside functional impairment and poor psychological well-being, associated with impairment of quality of life.[11] COPD has an unpredictable course characterized by episodes of gradual decline punctuated by acute severe exacerbations.[13] Patients with COPD often suffer from co-morbidities such as cardiovascular diseases, depression, osteoporosis, diabetes and lung cancer.[14] The occurrence of exacerbations and co-morbidities contribute to the severity of the disease and have a significant impact on prognosis.[14-16]

### Demographics and prognosis

The global prevalence of moderate to very severe COPD is estimated to be around 10% in people aged 40 years or older.[17] The risk of developing COPD between the ages of 40 and 80 was reported to be 12.7% for men and 8.3% for women.[18] COPD is expected to be the fourth leading cause of death worldwide by 2030.[19] The prognosis of patients with COPD is poor; the mortality rate in the year following hospitalization for an acute exacerbation of COPD (AECOPD) is around 22%.[20,21] A large cohort study showed that after their first hospitalization for AECOPD, 50% of patients had died within 3.6 years, while 75% of patients had died within 7.7 years.[22]

## Managing COPD

The management of COPD is disease-oriented and mainly focuses on symptom control. It includes the reduction of risk factors, especially smoking cessation; pharmacological treatments, such as inhaled bronchodilators and glucocorticosteroids; and non-pharmacological treatments, including pulmonary rehabilitation, long-term oxygen therapy, and surgical treatment.[5]

## Challenges for care

Generally speaking, clinicians are faced with the following challenges in the provision of quality care for patients with COPD:

*Addressing low socioeconomic status*

Environmental risk factors for developing COPD, such as tobacco smoking and indoor and outdoor pollution, are more common in people with a lower socioeconomic status (SES), i.e., people with a lower average level of education and less financial means.[23] As a result, having these social and economic disadvantages increases the risk of developing COPD.[24] It is therefore not surprising that people of low SES account for the majority of all COPD patients.[25] In addition, lower SES is associated with lower health literacy and poorer health outcomes.[26,27] Patients with the lowest SES are twice as likely to experience poor health outcomes from COPD, such as morbidity and mortality, as those of the highest SES.[23] Reducing these health disparities requires a multidisciplinary effort to encourage healthy lifestyles, target environmental risk factors, and optimize the prevention and management of COPD.[28]

*Informing patients about the progressive course of COPD*

Patients with advanced COPD often have poor understanding of their disease.[29] They sometimes assume that deterioration is a normal part of ageing instead of a disease-related factor,[30] and tend to be unaware of the progressive course of COPD and the possibility of dying from this disease.[29] Informal caregivers of patients with COPD have also reported being under-informed about the diagnosis, expected course, and prognosis.[31] Good clinician-patient communication addressing these topics is necessary to educate patients and their informal caregivers about COPD and to consequently enable them to take an active role in the management of the disease.[29]

*Installing an integrated multidisciplinary collaboration*

COPD has an unpredictable course.[13] During the stable phase, patients are treated by a General Practitioner (GP), while during a severe acute exacerbation they are often hospitalized and treated by a pulmonologist. In addition, patients often face co-morbidities, such as cardiovascular disease or diabetes, which complicate the management of COPD.[14,32] As a result, they are also treated by other medical specialists, such as cardiologists and endocrinologists. Consequently, an integrated multidisciplinary well-coordinated approach is necessary to manage the disease and provide the best care possible.[33]

## PALLIATIVE CARE

### Definition

The World Health Organization (WHO) defines palliative care as *"an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care: provides relief from pain and other distressing symptoms; affirms life and regards dying as a normal process; intends neither to hasten or postpone death; integrates the psychological and spiritual aspects of patient care; offers a support system to help patients live as actively as possible until death; offers a support system to help the family cope during the patients illness and in their own bereavement; uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated; will enhance quality of life, and may also positively influence the course of illness; is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications."*[34]

### Quality of life

The main objective of palliative care is to improve the quality of life of patients with a life-threatening illness and their families. The WHO defines quality of life as *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment."*[35]

### Advance care planning

Advance care planning (ACP) is an important aspect of palliative care which involves patient-clinician communication about end-of-life care.[36] ACP conversations inform patients about their diagnosis, prognosis, and treatment options, as well as the consequences of these options.[30] If well informed, patients have the opportunity to express their values and preferences for life-sustaining treatments with the goal of improving the quality of their end-of-life care.[30]

### History of palliative care

In the past, acute diseases were the primary causes of death. Since living conditions and healthcare have improved, people are living longer and the primary causes of death today are chronic diseases.[37] This change from acute to chronic causes of death led to the development of palliative care.[37] Initially, the focus of palliative care was on patients with incurable cancer.[37,38] After cure of the cancer was not possible anymore, the emphasis of care shifted not only to symptom control but also incorporated psychological, social and spiritual support for patients and their families.[39] By the end of the 20th century, this kind of care was mainly provided by community services working alongside GPs, specialized palliative care teams and hospices.[37] At the beginning of the present century, a consensus arose that access to palliative care should be based on needs rather than diagnosis, and that palliative care should become a gradually increasing part of care from diagnosis to death, rather than being concerned only with the terminal phase.[37,38] In 2002 the WHO incorporated this view into their new definition of palliative care, described above.[34] Palliative care options should therefore be considered early in the disease trajectory alongside disease-oriented care, and should be promoted for patients with non-malignant diseases too. As a result, palliative care has become more integrated into hospital and GP services.[37]

### Effectiveness on quality of life

In 2008, a systematic review was performed by Zimmermann and colleagues to investigate the effectiveness of specialized palliative care.[40] They identified four studies specifying quality of life as a primary outcome,[41-44] all of which focused on patients with cancer. In one of these studies, a structured multidisciplinary intervention was found to improve the quality of life of these patients.[44] Between 2008 and 2012, two more studies examined the effectiveness of palliative care, with quality of life as a primary outcome measure.[2,3] These studies undertaken by Bakitas and colleagues and Temel and colleagues concerned early or proactive approaches to palliative care for patients with cancer. In both studies, patients received palliative care concurrently with oncology treatments either upon diagnosis or with a life expectancy of at least six months. This early or proactive palliative care approach was found to improve not only their quality of life, but also the mood of the patients.[2,3] Temel and colleagues even showed that patients receiving early or proactive palliative care had less aggressive care at the end of live but longer survival.[3] No studies examining the effectiveness of palliative care on quality of life were found with a specific focus on patients with COPD.

## PROACTIVE PALLIATIVE CARE FOR PATIENTS WITH COPD

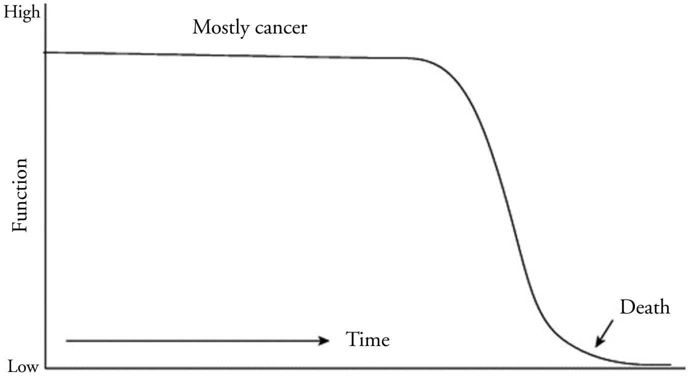
Palliative care in general is still developing; however, for patients with non-malignant diseases, such as COPD, the delivery of palliative care is not yet common practice and is still in the initial phases. Patients with COPD are rarely offered palliative support and have limited access to specialized palliative care services.[1] On occasions when they are offered palliative care it is often limited to a reactive instead of a proactive approach.[45] Proactive palliative care is about the early identification of patients to be able to anticipate on their palliative care needs and wishes thereby preventing and relieving suffering.[34] In this section the circumstances of patients with COPD and the barriers and challenges to developing a proactive palliative care approach for this patient group are outlined.

## Symptom burden and quality of life

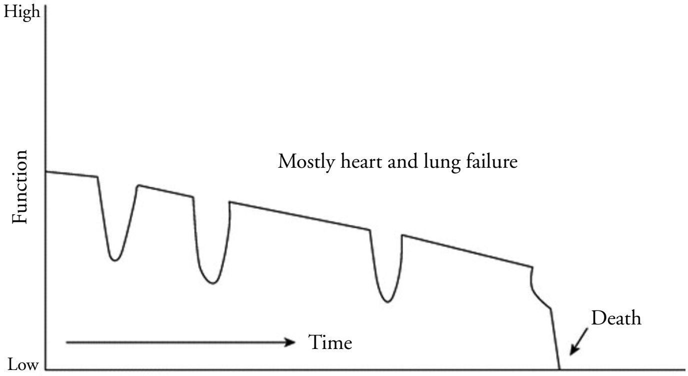
The symptoms experienced by patients with COPD in their last year of life are at least as severe as those of patients with lung cancer.[4] Post-bereavement interviews with informal caregivers of patients with COPD and lung cancer were used to compare symptoms.[4] Patients in both groups experienced breathlessness, anorexia, pain, low mood, insomnia, and coughing, and although patients with lung cancer were more likely to be anorexic, patients with COPD more frequently experienced and were troubled by breathlessness.[4] Patients with advanced COPD also had an impaired quality of life.[1] Self-reported quality of life questionnaires showed that patients with advanced COPD even had lower activity levels in their daily life and worse physical, emotional and social functioning than patients with inoperable lung cancer.[1]

## Disease trajectory

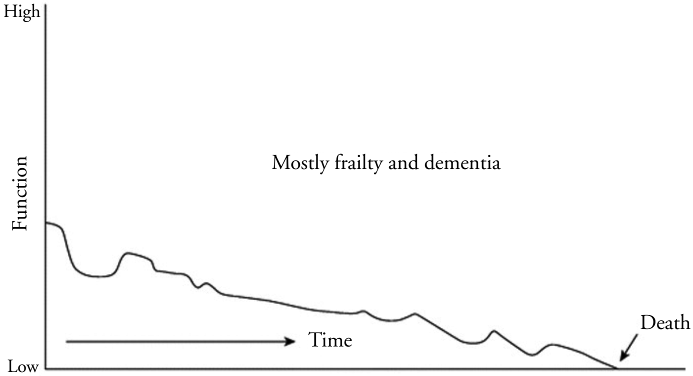
Although the symptom burden and quality of life of patients with advanced COPD are as bad as, or even worse than, those of patients with lung cancer, they less commonly receive palliative care.[1,4] This disparity in care likely reflects distinct disease trajectories.[46] For progressive chronic diseases three typical end-of-life disease trajectories have been described: cancer, organ failure, and the frail elderly trajectory (see Figure 1).[13,47,48] During the course of their disease, patients with cancer often experience a steady progression and usually have a clear terminal phase involving a rapid decline until death (Figure 1, upper panel), whereas patients with frailty or dementia suffer a prolonged gradual decline until death (Figure 1, lower panel). In contrast, patients with organ failure, such as COPD, experience a gradual decline, punctuated by acute severe exacerbations and some recovery, with a more sudden, seemingly unexpected death (Figure 1, middle panel). The physical, psychological, social, and spiritual needs of patients and their caregivers are likely to vary between these distinct disease trajectories. Different models of care are therefore necessary to reflect the differences in care needs.[13] This implies that patients with COPD require a different approach to palliative care than patients with cancer.



Short Period of Evident Decline



Long-Term Limitations with Intermittent Serious Episodes



Prolonged Dwindling

**Figure 1** End-of-life disease trajectories of progressive chronic diseases. Reproduced with permission.[47]

## Barriers and challenges

Patients with COPD experience a gradual functional decline punctuated by acute severe exacerbations during which disease-oriented care remains necessary and the need for palliative care gradually increases.[13,49] This implies that the traditional model of care based on a dichotomy involving an abrupt transition from active, life-sustaining care to palliative care does not work for patients with COPD.[33] Since it is acknowledged that access to palliative care should be based on needs rather than diagnosis, this kind of care should also be made available for patients with COPD. Nowadays, palliative care can be delivered early in the disease trajectory alongside disease oriented care. However, the occurrence of acute severe exacerbations, any one of which may be fatal, complicates the delivery of proactive palliative care in two ways. First, the uncertainty of the prognosis in terms of survival caused by these exacerbations hinders the timely identification of patients who would benefit from proactive palliative care.[36,50] Second, the healthcare professionals involved in the care of the patient during the stable phase differ from those involved in care during hospitalization for acute exacerbations, which endangers the continuity of palliative care delivery.[51]

The disease trajectory of COPD often takes decades. Initially, the patient and the informal caregiver are capable of managing the disease themselves. In this stage it is important for clinicians to educate them about the disease and its course so they can take an active role in their own disease management.[29] Starting palliative care or talking about the end of life during this stage seems unrealistic and might even be undesirable; however, as the disease progresses and the functional status of the patient declines, a time will come when the patient and the informal caregiver might benefit from a proactive palliative care approach. The timely identification of patients requiring such an approach not only enables adequate support for the patient and the informal caregiver, but also facilitates the initiation of ACP conversations and communication between healthcare professionals,[30,36] which is necessary to ensure the continuity of the proactive palliative care delivery.[52] However, it has not yet been determined how to identify patients with COPD in need of proactive palliative care and how to organize such a coordinated healthcare plan.[33,53] In 2011, the Lung Alliance Netherland, the Dutch society for chronic lung diseases, developed a guideline which provides recommendations to support healthcare professionals involved with the palliative care of patients with COPD.[54] This guideline describes the best care for patients with COPD in the palliative phase, while also recognizing the difficulties about when to begin palliative care and how it should be organized.[54] Therefore, major challenges for delivery of proactive palliative care to patients with COPD are the identification of patients who need such care, and the organization of proactive palliative care itself.

## Identification

General tools for the identification of patients in need of proactive palliative care have previously been developed.[55,56] Most of these tools consist of a clinical prediction of survival by means of the surprise question (Would I, as healthcare professional, be surprised if my patient would die in the next year?), as well as general and disease-specific prognostic indicators of decline.[56,57] However, these tools are not specifically intended for, or not validated in, the COPD population.[55,56]

Moreover, prognostic tools for use in stable COPD disease have been developed to enable the adjustment and optimization of care.[58,59] However, these tools only have a poor to fair predictive performance for mortality within one year, indicating that they do not predict short-term survival well and are therefore not suitable for the identification of patients with COPD who might benefit from proactive palliative care.[58,59]

Since hospitalization for AECOPD is associated with significant mortality, research has focused on the identification of predictors of mortality after such an event.[60,61] Recently several clinical important predictors of post-hospital mortality have been identified.[60-62] Hospitalization for AECOPD may therefore create an opportunity to identify patients with poor prognosis who may profit from a proactive palliative care approach.[60] In addition, during hospitalization for AECOPD patients have a poor health status and are probably more willing to talk about end-of -life issues.[63] Consequently, since healthcare professionals are present, they have the opportunity to engage in conversations about palliative care needs with patients.[30]

## Organization

Towards the end of life, patients with COPD are faced with increasing symptom burden and functional limitations while also experiencing more frequent exacerbations.[64] Decreases in mobility means they are often homebound until they enter an acute phase requiring hospitalization.[36] This unpredictable course requires community-based care with continuity of care during hospitalization.[65] Continuity of palliative care can therefore only be achieved with a coordinated, integrated, multidisciplinary care approach.[33,52] GPs, pulmonologists, respiratory nurse specialists, and palliative care specialists should collaborate to optimize palliative care delivery for patients with COPD. However, there is no consensus on how this coordinated care should be successfully organized across the entire illness trajectory.[33] Since pulmonologist have a central role in COPD management, they are advised to take the lead in organizing this coordinated, integrated, multidisciplinary approach to palliative care and in developing services for patients with COPD.[66]

## Proactive assessment of problems and needs

A proactive approach to palliative care not only considers the current problems and needs of patients, but also anticipates future problems and needs to prevent and relieve suffering.[34] This requires a thorough assessment in which the person, their disease, and their social context are considered. Important elements of this assessment include an evaluation of the patient's physical, psychological, social, and spiritual problems and needs, an assessment of the family's strength and burdens, a discussion of the expected disease scenarios and the advantages and disadvantages of several options for intervention, a discussion about the expected dying scenarios, and the evaluation of the patient's ACP wishes. Such a multidimensional assessment can be quite challenging for clinicians. Recently, a tool was developed to help clinicians make a structured multidimensional overview of the patient's current and possible future problems, needs, and ACP wishes (Figure 2).[67] This simple tool can help clinicians to develop a proactive palliative care plan in which all dimensions are considered.[68]

| **Somatic domain** | **Social and Financial domain** |
|---|---|
| Actual problems:<br>Expected problems:<br>Scenario of dying:<br>Patient's own wishes: | Actual problems:<br>Expected problems:<br>Patient's own wishes |
| **ADL and Care provision** | **Psychological and Existential domain** |
| Actual problems:<br>Expected problems:<br>Patient's own wishes | Actual problems:<br>Expected problems:<br>Patient's own wishes |

**Figure 2** Multidimensional assessment tool for proactive palliative care planning. Modified from Thoonsen et al (2011).[67]

## ACP conversations

A study investigating treatment preferences found that hospitalized patients with advanced COPD and lung cancer were equally likely to prefer a treatment based on comfort, yet patients with COPD were much more likely to be intubated or to receive cardiopulmonary resuscitation.[69] To improve care for patients with COPD, it is important that ACP conversations take place during which patients can discuss their preferences for end-of-life care with their physician. However, these ACP conversations occur only infrequently, and often take place late in the disease trajectory, such as in the intensive care unit.[70,71] This implies that the patient and family did not have the chance to consider their future needs and wishes, and shared decision-making is often difficult in such an acute situation. There are several clinician and patient-related barriers to the timely communication of these topics.[30,72] One important barrier is the difficulty predicting the prognosis, which can falsely reassure clinicians into thinking that they can postpone these difficult discussions..[73] Clinicians also expressed concern that early ACP may take away patients' hope and lead to unnecessary anxiety and depression. On the other hand, patients mentioned their assumption that clinicians will initiate these conversations, as well as their guilt about their smoking-related disease.[30,72] Clinician awareness of these barriers to communication may improve occurrence and quality of discussions about end-of-life care.[74]

## Research

Research in vulnerable patient groups, such as patients in the palliative phase, must deal with significant ethical and methodological concerns.[75,76] As a result studies investigating these patients have difficulties in gaining informed consent, poor recruitment rates and high attrition rates.[75,76] This is an important reason why there is hardly any research into end-of-life care in patients with COPD, which in turn hinders service development.[33] Good quality research into patients with COPD is therefore necessary to facilitate the improvement of outcomes and end-of-life care in this patient group.

## OBJECTIVES OF THIS THESIS

The objective of this thesis is: to explore the views, needs and wishes of pulmonologists concerning proactive palliative care for patients with COPD; to examine the identification of patients with COPD for proactive palliative care; and to examine the effectiveness of proactive palliative care on the well-being of patients with COPD.

A survey study, pilot study, and a pragmatic cluster controlled trial were designed to answer the following research questions:

1. What is the view of pulmonologists regarding: proactive palliative care for patients with COPD in general; the identification of patients with COPD for proactive palliative care; the content of proactive palliative care for patients with COPD; and the organization of proactive palliative care for patients with COPD?
2. Are potential indicators of poor prognosis documented consistently in the medical records of patients hospitalized for an AECOPD?
3. What is the effect of proactive palliative care on patients with COPD in terms of quality of life, psychological distress, the number and length of hospital admissions, survival and the number of patients who made ACP choices?
4. Is it possible to develop a valid multivariable tool to identify patients with COPD in need of proactive palliative care and what is the discriminating power of this tool in predicting death for any cause within one year (as a proxy for palliative care needs)?

## OUTLINE OF THIS THESIS

In **Chapter 2** the views of pulmonologists in the Netherlands regarding palliative care for patients with COPD are described, particularly regarding the identification of patients with COPD for palliative care and the content and organization of palliative care for patients with COPD. **Chapter 3** contains a detailed description of the methodology used to perform the pragmatic cluster controlled trial. To undertake this trial, we used a set of indicators to identify patients hospitalized for an AECOPD who have a poor prognosis and who might therefore benefit from proactive palliative care. These indicators were selected a priori, based on information from the literature. In **Chapter 4** the results of a pilot study investigating the feasibility of using this set of indicators for our prospective trial are presented. In addition to elucidating the consistency of documentation for each indicator in the medical records, the percentage of patients with poor prognoses and the prognostic value of the set of indicators were also explored. **Chapter 5** presents the results of the pragmatic cluster controlled trial, in which we assessed the effects of proactive palliative care on the wellbeing of patients with COPD. The primary objective was to assess the effects of proactive palliative care on the quality of life of these patients, while the secondary outcome measures were: psychological distress, the number and length of hospital readmissions for AECOPD, survival, and the number of patients who made ACP choices. **Chapter 6** comprises a report on the development of a tool to identify patients with COPD who require proactive palliative care. In response to our paper describing this work, some authors wrote a letter to the editor; therefore, this chapter also includes this letter and our reply to it. Finally, **Chapter 7** is the general discussion, in which the clinical implications of this thesis and future directions for education and research are discussed.

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# The View of Pulmonologists on Palliative Care for Patients with COPD: A Survey Study

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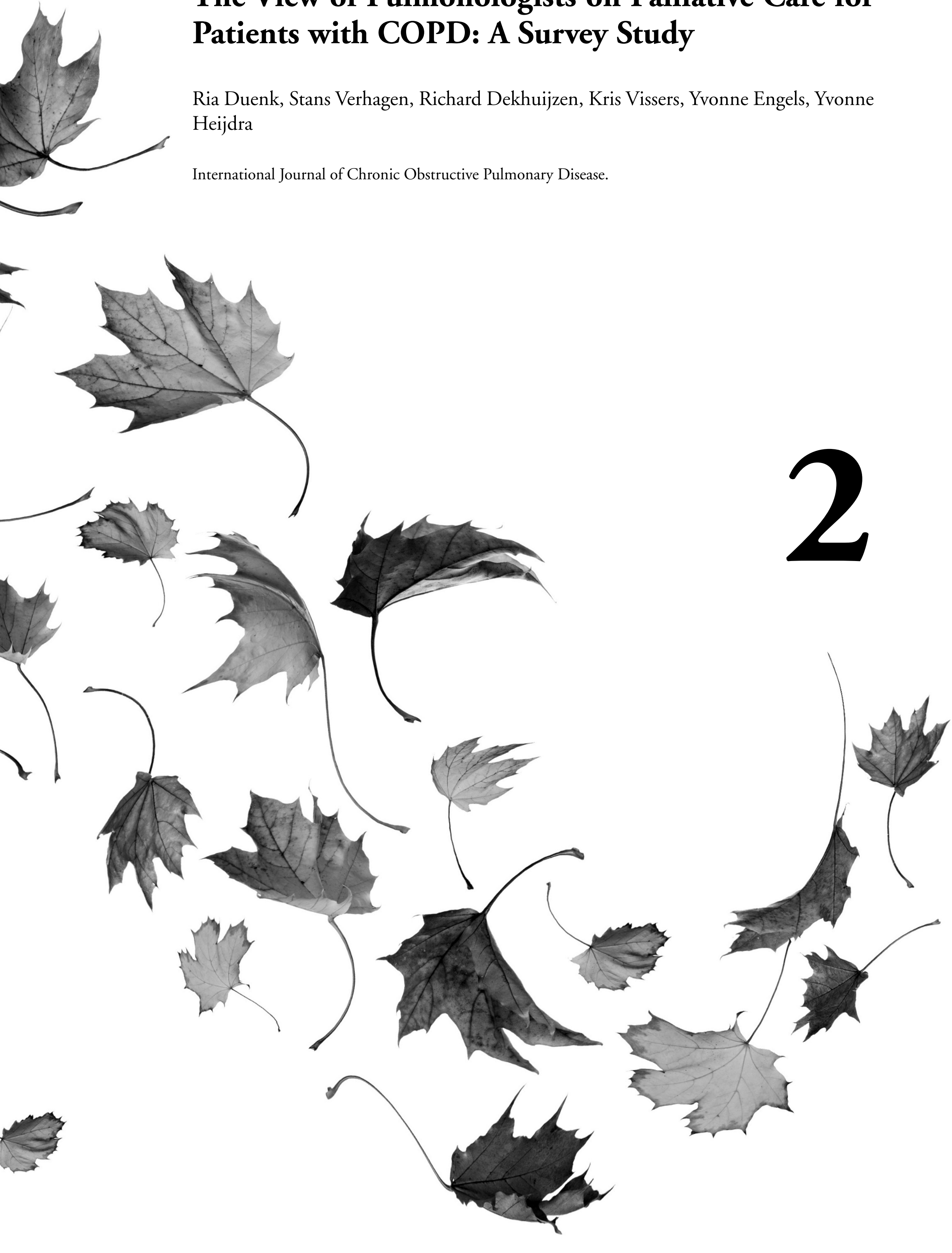

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## ABSTRACT

**Introduction:** Early palliative care is not common practice for patients with Chronic Obstructive Pulmonary Disease (COPD). Important barriers are the identification of patients for palliative care and the organization of such care in this patient group.

**Objective:** Pulmonologists have a central role in providing good quality palliative care for patients with COPD. To guide future research and develop services their view on palliative care for these patients was explored.

**Methods:** A survey study was performed by members of the Netherlands Association of Physicians for Lung Diseases and Tuberculosis (NVALT).

**Results:** The 256 respondents (31.8%) covered 85.9% of the hospital organizations in the Netherlands. Most pulmonologists (92.2%) indicated to distinguish a palliative phase in the COPD trajectory, but there was no consensus about the different criteria used for its identification. Aspects of palliative care in COPD considered important were Advance Care Planning conversation (82%), communication between pulmonologist and **general practitioner** (77%) and identification of the palliative phase (75.8%), while the latter was considered the most important aspect for improvement (67.6%). Pulmonologists indicated to prefer organizing palliative care for hospitalized patients with COPD themselves (55.5%), while 30.9% indicated to prefer cooperation with a Specialized Palliative Care Team (SPCT). In the ambulatory setting a multidisciplinary cooperation between pulmonologist, general practitioner and a respiratory nurse specialist was preferred (71.1%).

**Conclusion:** To encourage pulmonologists to timely initiate palliative care in COPD we recommend to conduct further research into more specific identification criteria. Furthermore, pulmonologists should improve their skills of palliative care and members of the SPCT should be better informed about the management of COPD to improve care during hospitalization. Communication between pulmonologist and general practitioner should be emphasized in training to improve palliative care in the ambulatory setting.

**Keywords:** Proactive palliative care, Pulmonologists, Identification, Organization, Cooperation

# INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive life-threatening disease and the third leading cause of death worldwide.[1] Symptoms at the end of life are as severe as or even worse than those of patients with advanced cancer.[2] Even so, compared to patients with cancer, palliative care is not common practice for patients with COPD.[3] This may be due to the fact that historically the focus of palliative care has been on oncology.[4] But, according to the definition of the World Health Organization (WHO), palliative care is intended for any life-threatening disease by means of early identification, assessment and treatment of pain and other problems, physical, psychosocial and spiritual in order to prevent and relief suffering.[5] The palliative phase thus comprises of a much longer period than the terminal or dying phase only. It implies that palliative care, as opposed to hospice care, is not limited to the terminal phase and can be given at an early stage alongside curative care. So, also patients with COPD may benefit from early palliative care without denying active disease-oriented treatment.

Important barriers in the provision of palliative care for patients with COPD are the identification of patients for palliative care and the organization of such care.[6] COPD has a gradual decline punctuated by acute severe exacerbations, any one of which may be fatal.[7,8] This unpredictable disease course hampers clinicians to timely initiate discussions about palliative care.[9,10] A debate has started among professionals whether prognosis, curability, palliative needs or a combination of these factors should mark the start of a palliative trajectory in patients with COPD but consensus has not yet been established.[11] Consensus also needs to be established about the optimal organization of palliative care.[9] Patients with advanced COPD are often homebound until they enter an acute phase with hospitalization. This requires community-based care with continuity of care during hospitalization.[12] Continuity of palliative care thus can only be achieved with a coordinated, collaborative, multidisciplinary care approach.[13] Therefore, general practitioners (GPs), pulmonologists, respiratory nurse- and palliative care specialists should collaborate to optimize palliative care delivery for patients with COPD. How this coordinated care should be successfully organized across the entire illness trajectory is not yet decided.[14,15]

To facilitate delivery of palliative care to patients with COPD for clinicians, the Lung Alliance Netherland (LAN), the Dutch society for chronic lung diseases, developed a guideline on palliative care for patients with COPD in 2010.[16] This guideline also provides recommendations about the start and the organization of palliative care based on literature but it is unknown to what extent clinicians use this guideline.

Since pulmonologists have a central role in providing good quality care for patients with COPD, they are in the front line to recognize palliative care needs in this patient group. For that reason it has been advised that they take the lead in developing services.[17] Therefore, the objective of this study was to explore the view of pulmonologist in the Netherlands on: 1) palliative care for patients with COPD in general, 2) identification of patients with COPD for palliative care, 3) important aspects of palliative care for patients with COPD, and 4) organization of palliative care for patients with COPD.

## METHODS

### Study design

A national survey was performed to explore the view of pulmonologists in the Netherlands on palliative care for patients with COPD.

### Study procedure

Mail and postal addresses of all pulmonologists and pulmonologists in training (it) were obtained from the Netherlands Association of Physicians for Lung Diseases and Tuberculosis. (NVALT). Of all 846 members registered at the NVALT 42 were excluded because they worked in a foreign practice (n=25), were a tuberculosis physician (n=15) or a epidemiologist (n=2) (see Figure 1). In total 804 members, 575 pulmonologists (66.1% male, 33.9% female) and 229 pulmonologists it (31% male, 69% female) were invited to participate in the study in April 2015. They received the digital NVALT newsletter with a link to a digital survey. An e-mail reminder was send two weeks later. In June 2015 a paper version of the survey was send to invite non-responders to participate. All questionnaires received before the 15th of August 2015 were included in the analysis.

### Survey

The survey consisted of demographic characteristics and questions about proactive palliative care for patients with COPD (Supplementary material). The demographic characteristics were assessed based on the position (pulmonologist or pulmonologist it), clinician (active or non-active), gender, name and place hospital, location hospital if appropriate, and the number and gender of pulmonologists working in their association of pulmonologists (or if not applicable, hospital).

The questions about proactive palliative care for patients with COPD concerned the view of pulmonologists or pulmonologist it on the following four main subjects: 1) palliative care for patients with COPD in general (five questions), 2) identification of patients with COPD for palliative care (one question) , 3) content of palliative care for patients with COPD (two questions), and 4) organization of palliative care for patients with COPD (five questions).

The questions about palliative care for patients with COPD in general concerned whether pulmonologists or pulmonologist it think that palliative care for patients with COPD is desirable, whether they distinguish a palliative phase in the COPD disease trajectory, if not why, whether they use the guideline palliative care for patients with COPD (2011) and, if not why. The view of pulmonologists and pulmonologists it concerning the organization of palliative care for patients with COPD started with the question whether the hospital has a Specialized Palliative Care Team (SPCT) at their disposal, and if yes, whether this team is also involved in the care of patients with COPD. Next, their opinion was asked about who should organize the delivery of palliative care for patients with COPD respectively during hospitalization and in the ambulatory setting.

In total 13 questions were presented in this second part: 12 multiple choice- and one last open question about what aspects of palliative care in COPD they thought were missing or should be developed in the near future. In seven multiple choice questions only one answer was possible. In the other five multiple choice questions, multiple answers were possible and the opportunity was given for an open answer under the choice "other namely".

### Statistical analyses

Descriptive statistics were conducted. Non-continuous variables were reported as frequencies. Statistical analyses were performed with SPSS 20.0 (IBM SPSS Statistics, Armonk, NY, USA).

## RESULTS

### Study population

In total 256 of 804 pulmonologists and pulmonologists it (31.8%) completed the survey (see Figure 1). The responding pulmonologists and pulmonologists it covered 73 of the 85 hospital organizations (85.9%) of all general and academic hospitals in the Netherlands. A hospital organization consists of one or more hospital locations which fall under the same board of directors.

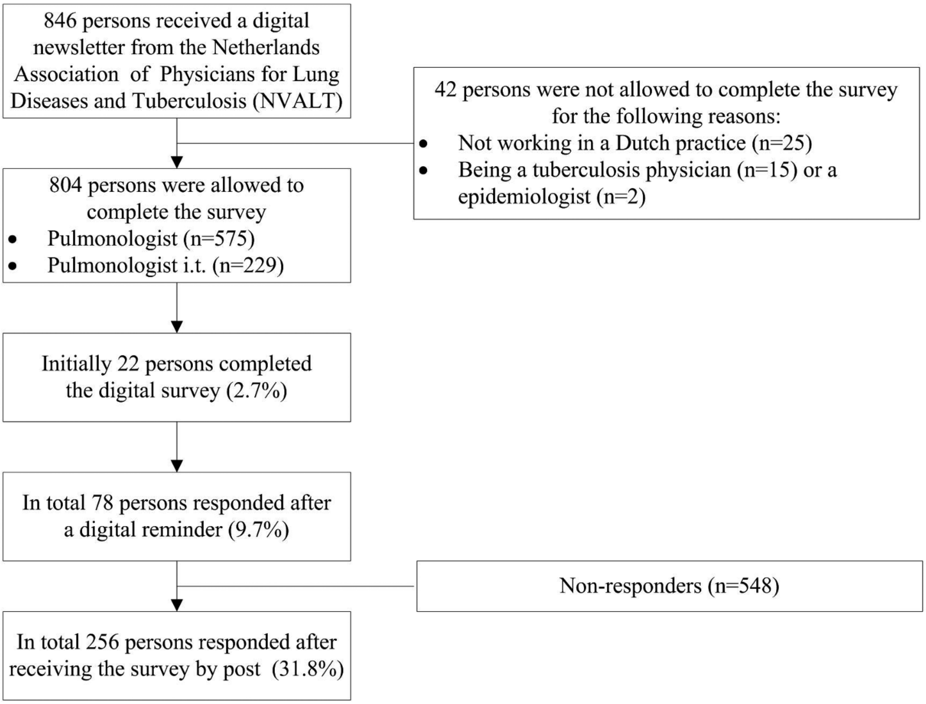


**Figure 1** Study flow diagram.
**Abbreviations:** it, in training.

## Demographic characteristics

The characteristics of the study population are presented in Table 1. Of the study population of 256 respondents, 197 were pulmonologists (60.4% male, 39.6% female) and 59 pulmonologist it (28.8% male, 71.2% female). Two pulmonologists were not active clinicians since one was a researcher and the other retired.

**Table 1** Characteristics of the study population

| Study population (*N*=256) | N (%) |
|---|---|
| Position | |
| Pulmonologist | 197 (77) |
| Pulmonologist it | 59 (23) |
| Clinician | |
| Active | 254 (99.2) |
| Gender | |
| Male | 136 (53.1) |
| Work place | |
| General hospital | 202 (78.9) |
| Academic hospital | 45 (17.6) |
| Categorical hospital * | 8 (3.1) |
| Missing | 1 (0.4) |

**Notes:** * specialized pulmonary hospital (sleep, rehabilitation or cancer).
**Abbreviations**: it, in training.

## Palliative care for patients with COPD in general

In total 253 respondents (98.8%) answered that palliative care for patients with COPD is desirable and 236 respondents (92.2%) answered that they distinguish a palliative phase in the COPD trajectory. The 19 respondents (7.4%) that did not distinguish a palliative phase in the COPD trajectory gave as reasons (more than one answer possible): that there is no distinction between curative and palliative care (63.2%), that they find the criteria for the start of palliative care difficult (26.3%), that an SPCT is not available for patients with COPD (5.3%), and/or other reasons (15.8%).

The percentage of pulmonologists that use the guideline palliative care for patients with COPD are presented in Figure 2.

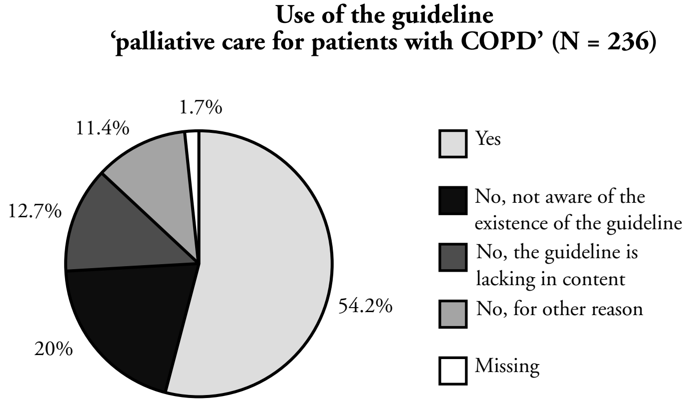


**Figure 2** The percentage of pulmonologists that use the guideline palliative care for patients with COPD.

## Identification of patients with COPD for palliative care

Each of the formulated criteria mentioned in the survey to possibly identify patients with COPD for palliative care was indicated by a larger or smaller part of the 236 respondents who distinguished a palliative phase in the COPD trajectory. Besides, all respondents indicated to use more than one criteria. The criteria and the percentage of respondents that mentioned to use each criterion to identify patients with COPD for palliative care are presented in Figure 3. Of all respondents 11.4% mentioned to use also other criteria such as: a combination of factors (2.5%), no treatment options left (2.1%) and the surprise question (=negative answer to the question: would I (as pulmonologist) be surprised if the patient would die in the next year?) (1.7%).

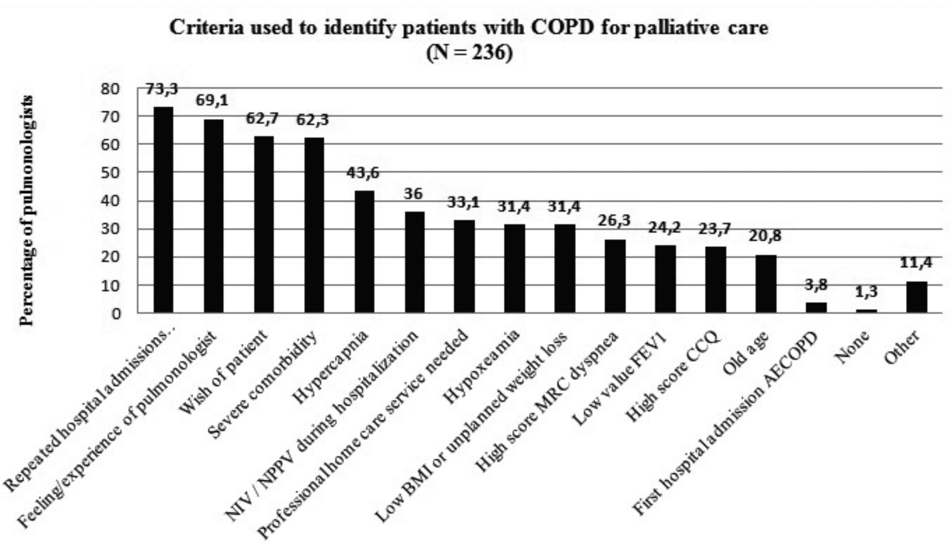


**Figure 3** The criteria and the percentage of respondents that mentioned to use each criterion to identify patients with COPD for palliative care.

**Abbreviations:** AECOPD, acute exacerbation COPD; BMI, body mass index; CCQ, Clinical COPD Questionnaire; FEV1, forced expiratory volume in 1 second; MRC dyspnea, Medical Research Council dyspnea questionnaire; NIV, non invasive ventilation; NPPV, non invasive positive pressure ventilation.

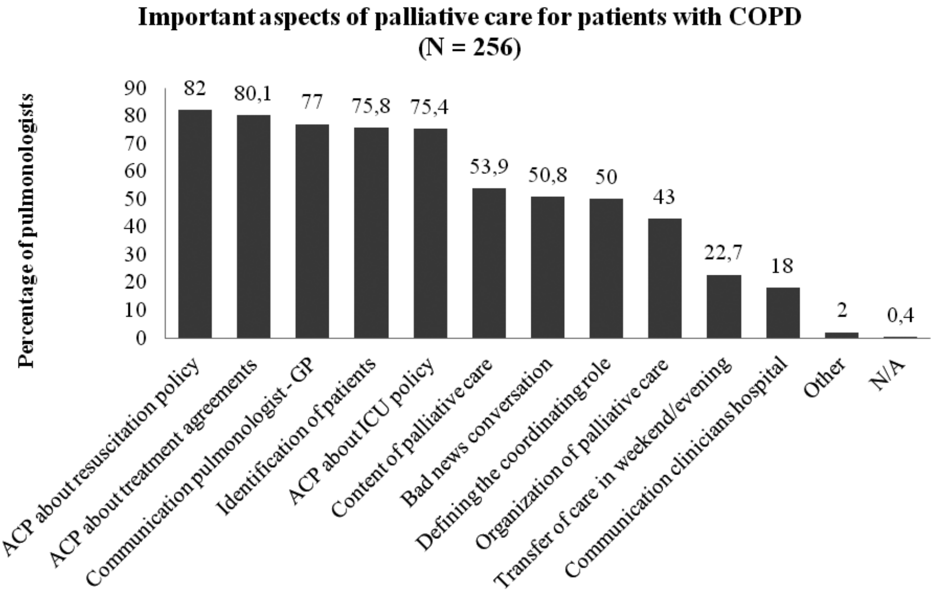
## Aspects of palliative care for patients with COPD

### *Important aspects*

Each formulated aspect of palliative care was at least chosen once. Besides, each respondent indicated more than one aspect. (see Figure 4). Of all respondents 2% also mentioned other aspects to be important. These were mainly remarks of involved pulmonologists concerning the aspect content of palliative care such as the response “involvement of informal caregivers”.

### *Improvement desirable*

Each formulated aspect of palliative care was chosen by at least one respondent as being desirable to improve. Besides, each respondent chose more than one aspect (see Figure 4). Of all respondents 2% mentioned that improvement is desirable for other aspects. These were mainly remarks of involved pulmonologists concerning improvement of the aspect content of palliative care such as the response “options for relief of suffering”



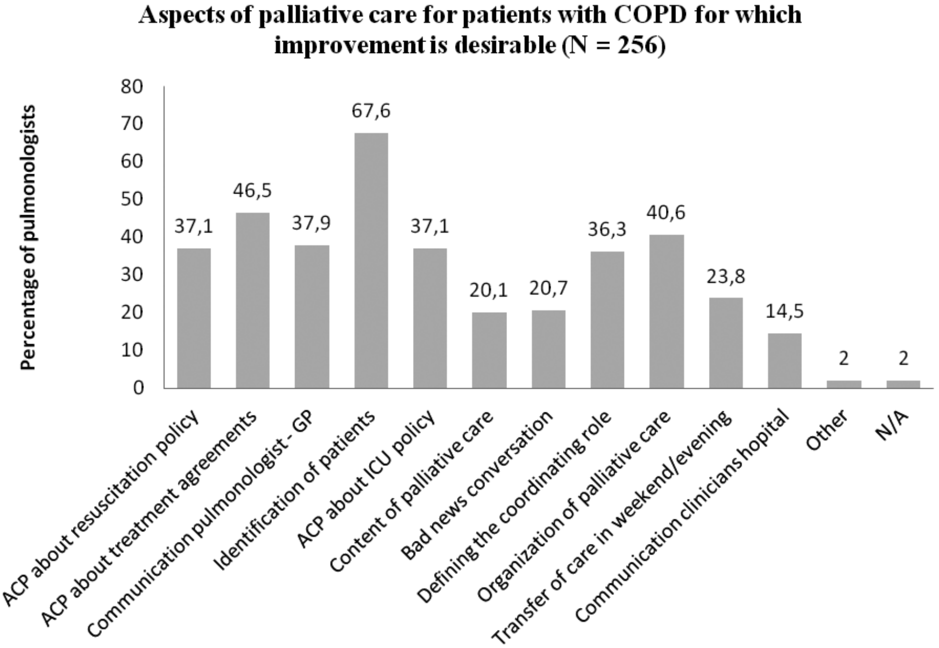


**Figure 4** The aspects of palliative care for patients with COPD and the percentage of respondents that mentioned which aspects were important and for which aspects improvement is desirable.

**Abbreviations:** ACP, advance care planning; GP, general practitioner; ICU, intensive care unit; N/A, not applicable.

## The organization of palliative care for patients with COPD

### *Specialized Palliative Care Team (SPCT)*

Of all respondents 87.1% indicated the presence of an SPCT in the hospital, while 53.1% indicated the involvement of the SPCT in the care of patients with COPD. (Figure 5). Respondents from 70 of the in total 73 hospital organizations (95.9%) indicated that they have an SPCT at their disposal but within 11 hospital organizations (15.1%) respondents were not in full agreement about this. Within these 70 hospital organizations the respondents of 32 hospital organizations (45.7%) were not unanimous when asked whether the SPCT in their organization was involved in the care of patients with COPD. Besides, some of the pulmonologists who confirmed this question placed a remark saying: theoretically this is possible but in practice it is less common.

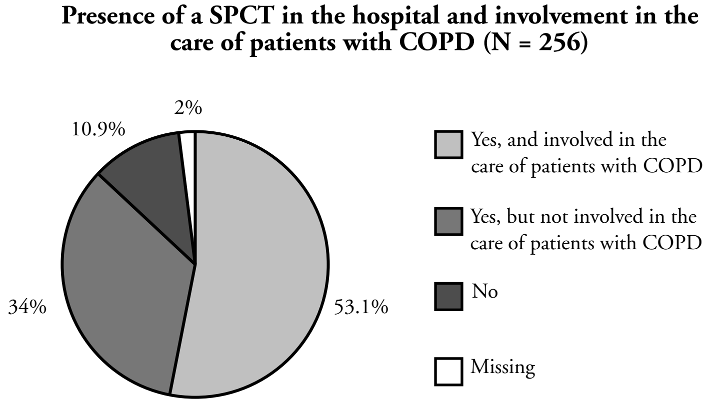


**Figure 5** The percentage of respondents that indicated the presence of an SPCT in the hospital and the involvement of the SPCT in the care of patients with COPD.
**Abbreviations:** SPCT, specialized palliative care team.

### *During hospitalization*

The opinion of respondents about who should organize palliative care for patients with COPD during hospitalization is presented in Figure 6. Most respondents (55.5%) considered the pulmonologist to perform this task.

### *In the ambulatory setting*

The opinion of respondents about who should organize palliative care for patients with COPD in the ambulatory setting is presented in Figure 6. Most respondents (71.1%) considered a multidisciplinary cooperation between pulmonologist, GP and respiratory nurse specialist to perform this task.

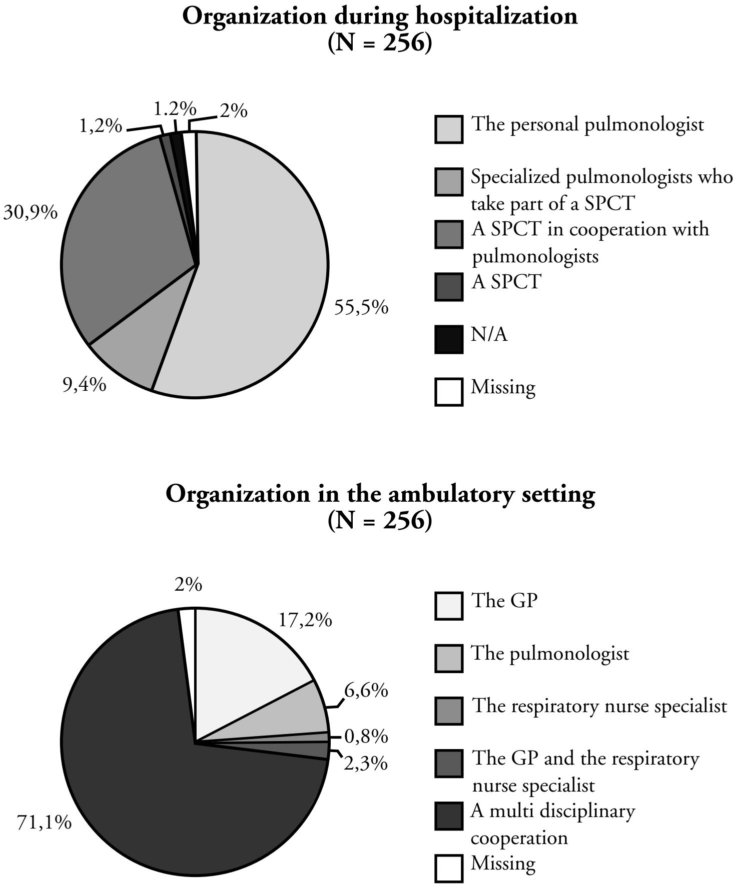


**Figure 6** The opinion of respondents about who should organize palliative care for patients with COPD during hospitalization and in the ambulatory setting.

**Abbreviations:** GP, general practitioner; N/A, not applicable; SPCT, specialized palliative care team.

# DISCUSSION

Palliative care for patients with COPD is not yet common practice.[3] Since pulmonologists have a central role in providing good quality palliative care for patients with COPD their view on this subject is important.[17] There are already survey studies that explore their current working situation regarding palliative care for patients with COPD.[18,19] This survey study however is the first to also take the view and wishes of pulmonologists into account in order to guide future research and service development.

Almost all pulmonologists indicated that palliative care for patients with COPD is desirable. To ensure that the best available evidence is translated into everyday clinical practice a Dutch clinical guideline palliative care for patients with COPD has been developed in 2010.[16] However, about half of the pulmonologists indicated not to use this clinical guideline, most often because they were not aware of its existence. This is cause for concern since low awareness of clinical guidelines may subsequently result in low adherence to guideline recommendations and potentially suboptimal healthcare.[20] In general adherence to COPD guidelines are sub-optimal and as a consequence barriers to guideline adherence in COPD have been identified.[20] We recommend to take such barriers into account in order to optimize strategies to ensure effective implementation and better use of clinical guidelines in COPD.

To facilitate timely identification of palliative care in COPD, prognostic models to estimate survival have been developed.[21] Unfortunately, these population models are of little value to predict survival for individual patients. As such, validated evidence-based criteria to determine the prognosis in advanced COPD are not yet available.[9,21] A discussion has started among clinicians whether a transition point for the initiation of palliative care in the COPD trajectory exists.[22-25] Some clinicians argue that in response to the prognostic difficulty more specific criteria of end-stage COPD need to be explored.[23] Other clinicians argue that searching further for prognostic criteria that may not exist, will lead to prognostic paralysis.[24,25] Instead, they promote an integrated early palliative care approach according to needs alongside disease-oriented care.[25] Nevertheless, the majority of pulmonologists in our study indicated that they do distinguish a palliative phase in the COPD trajectory (92.2%).

Several tools have been proposed to identify patients with COPD for palliative care.[9,21,26,27] The formulated identification criteria in our survey were selected on basis of this literature. All pulmonologists indicated to use several criteria. Four criteria were mentioned by about three quarters of the pulmonologists, being: repeated hospital admissions for an acute exacerbation of COPD (AECOPD), feeling / experience of the pulmonologist that palliative care is needed, wish of the patient, and severe comorbidity. All other formulated criteria were mentioned by about one third of the pulmonologists while some pulmonologists also mentioned as additional aspects no treatment options left and a negative answer to the surprise question (would I, as pulmonologist, be surprised if my patient would die in the next year?). The fact that criteria of prognosis as well as curability and palliative needs were chosen by the pulmonologists reflects the absence of consensus about the way of identification of patients with COPD for palliative care.[11]

The pulmonologists also indicated which aspects of palliative care for patients with COPD they considered important and for which aspects improvement is desirable. Aspects mentioned to be important by over three-quarters of the pulmonologists were: Advance Care Planning (ACP) conversation, communication between pulmonologist and GP, and identification of patients for palliative care. For improvement, only one aspect, identification of patients for palliative care, was mentioned by almost three quarters of the pulmonologist. The aspects thereafter mentioned for improvement by about two fifth of the pulmonologists were: ACP conversation, organization of palliative care, communication between pulmonologist and GP, and defining the coordinating role. It seems that pulmonologists not only consider identification of patients for palliative care important but also the most important aspect for improvement. Therefore, we suggest to conduct further research into more specific criteria to timely initiate the palliative trajectory. Having such criteria might encourage pulmonologists less familiar with palliative care in COPD to get started. Recently variables have been identified that could be indicative of poor prognosis for patients hospitalized for an AECOPD and possibly be useful to identify patients for palliative care.[28] However, the problem of identification of patients with COPD for palliative care is not to predict individual prognosis but to timely start palliative care. Future prospective studies which incorporate these potentially relevant variables should therefore focus on identifying criteria for a timely start of palliative care in order to assure that patients with COPD in need of a palliative approach are not missed out. We think that this way an integrated early use of palliative care alongside disease-oriented care can be accomplished. Beside identification of patients for palliative care, other areas of concern for improvement should preferentially be ACP conversations, communication between pulmonologist and GP, defining the coordinating role and the organization of palliative care.

In order to be able to answer the question, how to organize palliative care in COPD, it is necessary to know the facilities available in the Netherlands. The percentage of hospitals with an SPCT at their disposal for instance has increased from 39% in 2013 to 77% in 2015.[29] This growth will probably continue since it is the standard of a foundation emphasizing collaboration in oncology (Stichting Oncologische Samenwerking; SONCOS), that every hospital should have an SPCT by January 2017.[30] According to this standard an SPCT should at least consist of two medical specialists and one nurse specialist palliative care. In our survey 87.1% of the pulmonologists, representing 70 of the 73 participating hospital organizations (95.9%), indicated the presence of an SPCT in their hospital. However pulmonologists within 11 hospital organizations (15.7%) were not unanimous. The fast increase of hospitals with an SPCT and the fact that we did not define the composition of a SPCT may be the reason of this inconsistency. In the hospital organizations with an SPCT 61% of the pulmonologists, representing 53 of the 70 hospital organizations, indicated the involvement of the SPCT in the care of patients with COPD. This percentage should however be considered with caution since the pulmonologist within 32 hospital organizations (45.7%) were not unanimous. Some pulmonologists even indicated that theoretically consultation is possible but in practice less common. So, although palliative care by an SPCT in hospitals is in development it seems that the involvement in care of patients with COPD is not yet common practice.

When asked who should organize palliative care for patients with COPD during hospitalization, more than half of the pulmonologists mentioned the pulmonologist. About three-tenth of the pulmonologists preferred to organize this in cooperation with a SPCT while about one-tenth preferred specialized pulmonologists who take part of an SPCT. An SPCT, as primarily responsible entity, was hardly mentioned. It shows that during hospitalization pulmonologists want to be involved in the organization of palliative care for patients with COPD while there is also room for the involvement of an SPCT. In practice the input of an SPCT is often demanded in more complex disease trajectories.[31] Since palliative care in COPD is not common practice this implies that pulmonologists should improve their skills of palliative care and members of the SPCT should be better informed about the management of COPD.[11]

To ensure continuity of palliative care for patients with COPD in the ambulatory setting a coordinated multidisciplinary care approach has been recommended.[14] Almost three quarters of the pulmonologists in our study recognized this since they preferred a multidisciplinary cooperation between pulmonologist, GP and respiratory nurse specialist in the ambulatory setting. To accomplish successful cooperation, we recommend emphasizing the aspects communication between pulmonologist and GP and defining the coordinating role in training.

Finally, as palliative care is multidisciplinary care, we recommend to also explore the view of other health care professionals involved in palliative care for patients with COPD, as well as their incentives and barriers regarding the provision of early palliative care.

Several strengths and limitations should be considered to be able to interpret the findings. This is the first survey study to explore the view and wishes of pulmonologists regarding palliative care for patients with COPD. Furthermore, 85.9% of hospital organizations were represented by the responding pulmonologists. Like in most surveys, we did not use a validated questionnaire. It is possible that certain questions were not totally unambiguously and therefore not always interpreted in the same way. Although comparable with other survey studies,[32,33] the overall response rate of 31.8% is low and raises concerns whether the results can be generalized to the Dutch population of pulmonologists. Those pulmonologists who participated were probably more interested in palliative care in COPD than non-responders and will have provided a more favorable view. For this reason, the low response rate will not have influenced our findings that the identification of patients with COPD for palliative care and the organization of such care need improvement.

## CONCLUSION

Pulmonologists considered palliative care for patients with COPD desirable. Still many of them did not know about the existence of the guideline palliative care for people with COPD. We therefore recommend that more attention should be paid to the implementation of such guidelines. Most of the pulmonologists distinguished a palliative phase in the COPD trajectory. Many different criteria were used and there was no consensus whether prognosis, curability and/or palliative needs should mark the start of palliative care in COPD. The identification of patients with COPD for palliative care was not only seen as important but also seen as the most important aspect for improvement. We therefore recommend to conduct further research into more specific criteria to timely initiate the palliative trajectory.

The organization of palliative care was also mentioned as an aspect for improvement. During hospitalization, pulmonologists indicated that they wanted to be involved in the organization of palliative care for patients with COPD while there was also room for input of an SPCT. Since palliative care in COPD is not common practice we recommend pulmonologists to improve their skills of palliative care and members of the SPCT to be better informed about the management of COPD. In the ambulatory setting, most pulmonologists preferred a multidisciplinary cooperation between pulmonologist, GP and respiratory nurse specialist. Since pulmonologist indicated ACP conversations, communication between pulmonologist and GP and defining the coordinating role as improvement aspects, we recommend to emphasize these aspects in training.

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# SUPPLEMENTARY MATERIAL

## Survey for pulmonologists

Demographic situation:

1. What is your position?
   ☐ Pulmonologist
   ☐ Pulmonologist in training

2. Are you clinically active?
   ☐ Yes
   ☐ No

3. Name hospital
   ……………………………………………………………

4. Location (if applicable)
   ……………………………………………………………

5. Place of residence hospital
   ……………………………………………………………

6. Gender
   ☐ Male
   ☐ Female

7. a. How many pulmonologists work in your association of pulmonologists (or hospital)?
   ……………………………………………………………

   b. Number of males / females?
      ………… Males
      ………… Females

Questions palliative care for patients with COPD:

1. Is in your opinion palliative care for patients with COPD desirable?
   ☐ Yes
   ☐ No

2. Do you distinguish a palliative phase in the COPD disease trajectory?
   ☐ Yes *(go to question 4)*
   ☐ Sometimes *(go to question 4)*
   ☐ No *(go to question 3)*

3. If not, what is the reason of this? (more than one answer possible) *(go to question 7)*
   ☐ In my opinion, there is no distinction between curative and palliative care in COPD
   ☐ I don't have time for it
   ☐ I find the criteria for the start of palliative care in COPD difficult
   ☐ A Specialized Palliative Care Team (SPCT) is not available for patients with COPD
   ☐ Other, namely………………………………

4. Do you use the guideline palliative care for people with COPD (2011)?
   ☐ Yes *(go to question 6)*
   ☐ No *(go to question 5)*

5. If not, what is the reason for this? (more than one question possible)
   ☐ I was not aware of the existence of this guideline
   ☐ I find this guideline unclear
   ☐ Applying the guideline takes too much time
   ☐ The scientific basis of the guideline is to my opinion questionable
   ☐ The criteria for the start of palliative care in COPD are unclear
   ☐ Other, namely………………………………

6. What criterion/criteria do you use for the start of palliative care in patients with COPD? (more than one answer possible)
   ☐ First hospital admission for an acute exacerbation COPD (AECOPD)
   ☐ Repeated hospital admissions for an AECOPD
   ☐ Hypoxemia (stable and/or at discharge)
   ☐ Hypercapnia (stable and/or at discharge)
   ☐ NIV / NPPV necessary during hospitalization
   ☐ Professional home care service needed for personal care
   ☐ Severe comorbidity
   ☐ Low value FEV1
   ☐ Low BMI or unplanned weight loss
   ☐ Old age
   ☐ High score CCQ (= Clinical COPD Questionnaire)
   ☐ High score MRC dyspneu questionnaire
   ☐ Feeling/experience of pulmonologist
   ☐ Wish of patient
   ☐ Other, namely……………………………….
   ☐ None

7. In your opinion, what are important aspects of palliative care for patients with COPD? (more than one answer possible)
   ☐ Identification of patients for palliative care
   ☐ Bad news conversation
   ☐ Advance Care Planning (ACP) conversation about resuscitation policy
   ☐ ACP conversation about treatment agreements
   (e.g. enteral tube feeding, antibiotics, hospitalization, palliative sedation, mechanical ventilation)
   ☐ ACP conversation about ICU policy
   ☐ Content of palliative care
   ☐ Organization of palliative care
   ☐ Defining the coordinating role
   (e.g. pulmonologist/ respiratory nurse specialist/ specialized palliative care team/ GP)
   ☐ Communication with other professionals within the hospital
   ☐ Communication between pulmonologist and GP
   ☐ Transfer of care in the weekend/ evening
   ☐ Other, namely……………………………….
   ☐ N/A

8. In your opinion, for which aspects of palliative care for patients with COPD is improvement desirable? (more than one answer possible)
   ☐ Identification of patients for palliative care
   ☐ Bad news conversation
   ☐ Advance Care Planning (ACP) conversation about resuscitation policy
   ☐ ACP conversation about treatment agreements
   (e.g. enteral tube feeding, antibiotics, hospitalization, palliative sedation, mechanical ventilation)
   ☐ ACP conversation about ICU policy
   ☐ Content of palliative care
   ☐ Organization of palliative care
   ☐ Defining the coordinating role
   (e.g. pulmonologist/ respiratory nurse specialist/ specialized palliative care team/ GP)
   ☐ Communication with other professionals within the hospital
   ☐ Communication between pulmonologist and GP
   ☐ Transfer of care in the weekend/evening
   ☐ Other, namely……………………………….
   ☐ N/A

9. Does the hospital have a Specialized Palliative Care Team (SPCT) at their disposal?
   ☐ Yes
   If yes, are they also involved in the care of patients with COPD?
   ☐ Yes
   ☐ No
   ☐ No

10. Who should in your opinion organize the delivery of (proactive) palliative care for patients with COPD <u>during hospitalization</u>? (only one answer possible)
    ☐ The personal pulmonologist. Every pulmonologist provides (proactive) palliative care to their own patients with COPD
    ☐ A specialized pulmonologist who take part of a SPCT
    ☐ A SPCT in close cooperation with pulmonologists
    ☐ N/A

11. Who should in your opinion organize the delivery of (proactive) palliative care for patients with COPD in the ambulatory setting? (only one answer possible)
    ☐ The GP
    ☐ The pulmonologist
    ☐ The respiratory nurse specialist
    ☐ The GP and the respiratory nurse specialist
    ☐ A multi disciplinary cooperation (GP / pulmonologist / respiratory nurse specialist)
    ☐ N/A

12. What aspects of palliative care in COPD did you miss or do you think should be developed in the near future?

# PROLONG: A Cluster Controlled Trial to Examine Identification of Patients with COPD with Poor Prognosis and Implementation of Proactive Palliative Care (Study Protocol)

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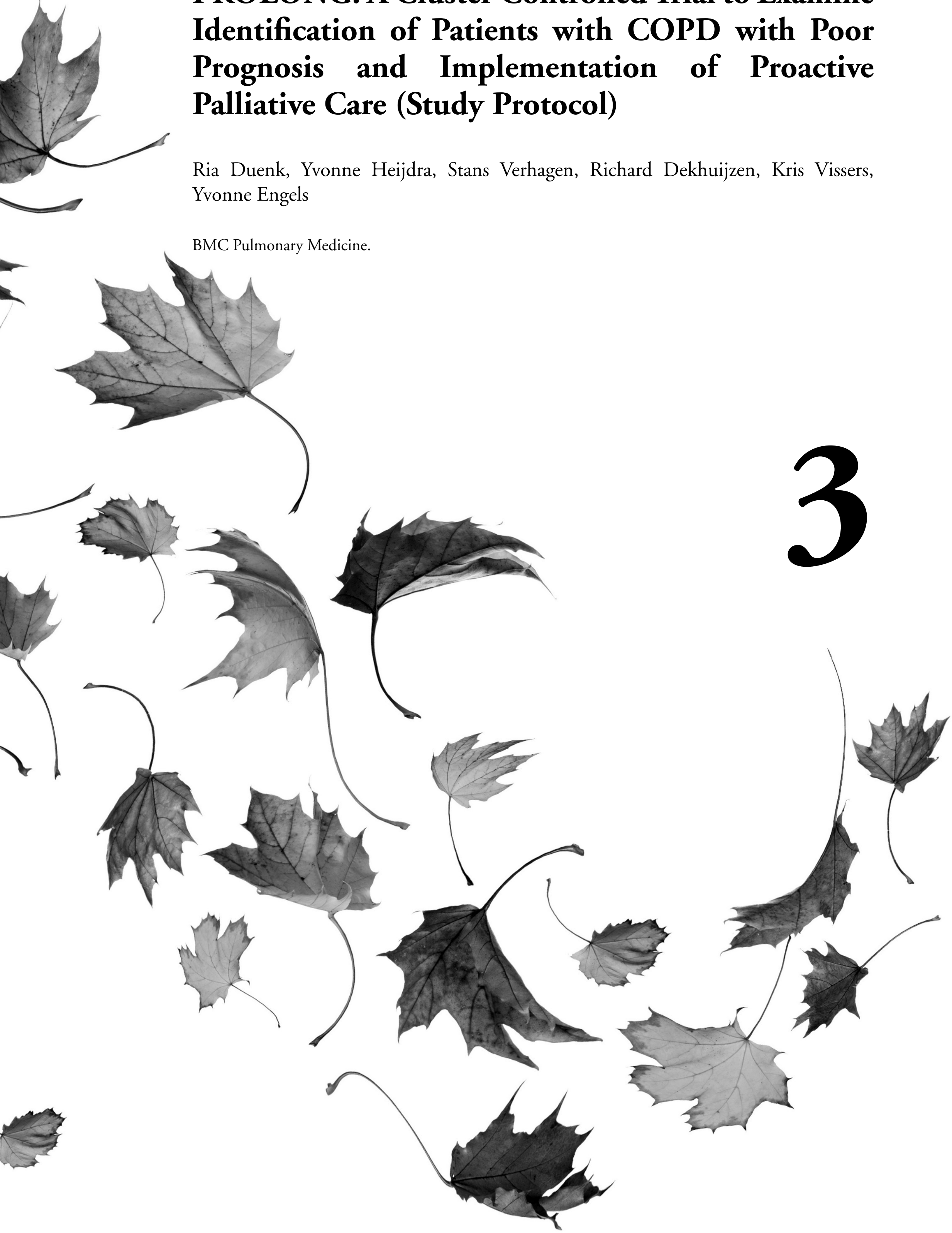
BMC Pulmonary Medicine.

# 3



## ABSTRACT

**Background:** Proactive palliative care is not yet common practice for patients with COPD. Important barriers are the identification of patients with a poor prognosis and the organization of proactive palliative care dedicated to the COPD patient. Recently a set of indicators has been developed to identify those patients with COPD hospitalized for an acute exacerbation who are at risk for post-discharge mortality. Only after identification of these patients with poor prognosis a multi disciplinary approach to proactive palliative care with support of a specialized palliative care team can be initiated.

**Methods/design:** The PROLONG study is a prospective cluster controlled trial in which 6 hospitals will participate. Three hospitals are selected for the intervention condition based on the presence of a specialized palliative care team. The study population consists of patients with COPD and their main informal caregivers. Patients will be included during hospitalization for an acute exacerbation. All patients in the study receive standard care (usual care). Besides, patients in the intervention condition who meet two or more criteria of the set of indicators for proactive palliative care will have additionally regular consultations with a specialized palliative care team. The objectives of the PROLONG study are: 1) to assess the discriminating power of the proposed set of indicators (indicator study) and 2) to assess the effects of proactive palliative care for qualifying patients with COPD on the wellbeing of these patients and their informal caregivers (intervention study). The primary outcome measure of the indicator study is time to death for any cause. The primary outcome measure of the intervention study is the change in quality of life measured by the St George Respiratory Questionnaire (SGRQ) three months after inclusion.

**Discussion:** The PROLONG study may lead to better understanding of the conditions to start and the effectiveness of proactive palliative care for patients with COPD. Innovative aspects of the PROLONG study are the use of a set of indicators for proactive palliative care, the active involvement of a specialized palliative care team and the use of a patient-tailored proactive palliative care plan.

**Trial registration:** Netherlands Trial Register (NTR): NTR4037

**Keywords:** COPD, Exacerbation, Indicators, Prognosis, Proactive palliative care, Quality of life

## BACKGROUND

In 2002 the World Health Organization (WHO) introduced a new definition of palliative care. They emphasized in this definition the importance of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual in order to prevent and relief suffering.[1] This means that palliative care is not limited to the terminal phase and can be delivered beside curative care to patients with a life-threatening illness. It implicates that palliative care is not only restricted to reactive symptom relief. By anticipating on expected disease scenario's and the specific needs and wishes of a patient, problems can be prevented and hence quality of life improves. The clinical use of this proactive palliative care is growing in care for patients with cancer. Still a proactive approach is not very common for patients with Chronic Obstructive Pulmonary Disease (COPD), even though the symptoms that occur in the end stage of COPD are as severe or even worse than in the final stage of lung cancer.[2,3] Both groups of patients prefer a treatment with the emphasis on comfort instead of life prolongation, but to patients with COPD this is offered less frequently.[4] For instance patients with COPD receive less opioids and benzodiazepines than patients with lung cancer for their dyspnea complaints,[5] and they die more often at an Intensive Care Unit (ICU).[6]

Several barriers are described with respect to offering proactive palliative care to patients with COPD.[7] A first important barrier is the identification of patients with COPD who can benefit from proactive palliative care, as it is difficult to predict the remaining length of survival of these patients.[8] For that reason, recognizing the appropriate time to start proactive palliative care may not be obvious for clinicians. A second important barrier is the organization of proactive palliative care for COPD patients. The majority of hospitals in Europe have no formalized approach regarding palliative care issues for patients with COPD: these patients have less universal access to specialist palliative care services than those with malignant lung diseases.[9-11]

In general, an important problem in the transition or referral to palliative care services is that the term "palliative care" is often associated with terminal or end stage care only. This can be an impediment to early implementation of proactive palliative care as proposed by the WHO. Especially for patients with COPD who do not perceive COPD as an illness that disrupts life.[12] Hence the term 'supportive care'" may be a term more conducive to referral and may facilitate integration between curative care and palliative care for patients with COPD.[13-15] Therefore, in this study we will speak of supportive care in contact with participating patients with COPD.

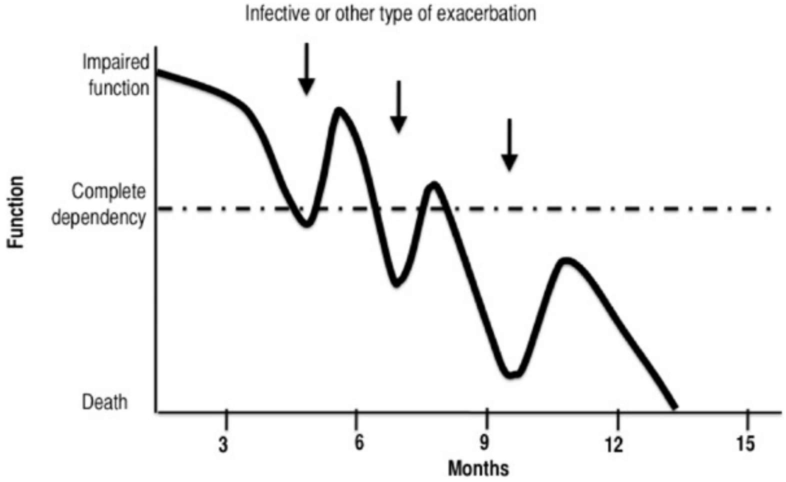


**Figure 1** COPD disease trajectory.

## Identification of patients with COPD for proactive palliative care

COPD illustrates the 'organ failure' end-of-life trajectory in which a gradual decline is punctuated by acute severe exacerbations, any one of which may be fatal.[16,17] The patient may survive the majority of these exacerbations as long as he shows resilience and rebounds to (at least part of) his former condition. As it is unclear which exacerbation will be fatal, death may seem to occur suddenly (Figure 1).[18] This uncertain prognosis makes it difficult for clinicians to initiate discussions about palliative care and end–of–life care planning.[19,20] In stable COPD, population models of 6 month survival do exist but they are of limited value to predict death for individual patients.[21] It is therefore proposed to address proactive palliative care at certain milestones in the course of the disease,[22] such as the occurrence of an acute exacerbation COPD (AECOPD).[20] An AECOPD is defined as 'an acute worsening of the patient's condition from the stable state, which is sustained and may warrant the patient to seek additional treatment'.[23] Exacerbations cluster in time with a high risk of recurrence within 8 weeks of recovery,[24] and show an increasing frequency as the disease progresses.[25] Recovery after an AECOPD is often to a suboptimal condition as before the exacerbation and after each exacerbation more care may be required to support the patient and the family. Therefore each admission to the hospital for an AECOPD creates an opportunity to identify patients at high risk of subsequent readmission or post-discharge mortality and hence who can benefit from a proactive palliative care approach. Several studies focused on the identification of predictive factors associated with hospital readmission or mortality for patients with an AECOPD. The findings of these studies are summarized in a recent review.[26] One of the conclusions is that in-hospital mortality is related to the patient's acute physiological state and to the development of acute comorbidity while post-discharge mortality particularly reflects the severity of the underlying COPD, as well as concomitant specific comorbidities. Important factors influencing the frequency of readmission include functional limitation and poor health-related quality of life. A profile emerges of the types of patients hospitalized for an AECOPD at high risk of subsequent readmission or post-discharge mortality.[19]

In accordance with these findings and based on existing literature,19, 26-29 we developed a set of indicators for lung specialists to improve the identification of patients hospitalized for an AECOPD for whom proactive palliative care might be beneficial. We hypothesize that the presence of two or more of the following indicators (or prognostic conditions) should be a reason to start proactive palliative care: 1) hypoxaemia or hypercapnia at discharge; 2) treatment of the exacerbation with Non Invasive Ventilation (NIV); 3) patient needs professional home care service for personal care after discharge; 4) a negative answer to the surprise question: 'Would I (as lung specialist) be surprised if this patient would have a subsequent readmission for AECOPD within 8 weeks and/or would die in the next year?; 5) the diagnosis of a severe comorbidity such as: a) non-curable malignity or b) cor pulmonale (proven or non proven) or c) proven Chronic Heart Failure (CHF) or d) diabetes mellitus with neuropathy or e) renal failure, clearance < 40 Glomerular Filtration Rate (GFR); 6) Clinical COPD Questionnaire (CCQ) total, day version > 3 ; 7) Medical Research Council dyspnea questionnaire (MRC dyspnea) = 5; 8) Forced Expiratory Volume in 1 second (FEV1), measured before AECOPD < 30% of predicted; 9) Body Mass Index (BMI) < 21 or unplanned weight loss (> 10% weight loss in last 6 months or > 5% in last month); 10) previous hospital admissions for AECOPD (last 2 years > 2 and/or last year > 1); 11) Age > 70 years.

In this study the discriminating power of this set of indicators will be examined. We hypothesize that the set of indicators can predict readmission within 8 weeks and/or death within 1 year for patients hospitalized for an AECOPD.

### Organization of proactive palliative care for patients with COPD

Provision of palliative care for patients with COPD in Europe is variable, and overall very small.[11] The majority of hospitals in Europe do not have a formalized approach to palliative care issues for patients with chronic lung disease. Besides patients with advanced non-malignant respiratory disease have less universal access to specialist palliative care services than those with malignant lung disease.[9-11] In a survey performed in the UK, the minority of hospital units had a formal referral pathway for palliative care and only about 13% had a policy of initiating end-of-life discussions with appropriate patients.[30] Although variation in care may be influenced by many factors including availability, access and reimbursement issues, such geographic variations suggest a lack of consensus concerning the best approach to palliative care for patients with COPD.[19]

Therefore, recent studies have focused on the best approach and content of palliative care for patients with COPD. It is suggested to start palliative care early beside curative care.[31] Furthermore, good proactive palliative care should at least consist of: 1) a standardized inventory of current and future care needs and a structured organization of proactive palliative care; 2) advance care planning (ACP), which involves the patient(-family)-clinician communication about end-of-life care and the completion of advanced directives.[20] Important components of ACP are discussions about the expected course of the disease and prognosis and counseling concerning preferences for care at the end of life, including spiritual care;[19] 3) development and implementation of a patient-tailored proactive palliative care plan. There are several problems from the patient as well as from the clinician perspective when it comes to satisfactory implementation of ACP and a patient-tailored proactive palliative care plan.[7] First, there are clinician and patient related barriers to discuss ACP.[32] Patients for instance avoid ACP discussions out of fear of suboptimal treatment in case of emergencies while clinicians are concerned that early ACP will take away patients' hope.[20] Discussions about ACP are therefore unlikely to occur and when they do occur they are likely to be of poor quality.[19] Second, not all clinicians have a special interest in or are qualified to perform proactive palliative care. Finally, delivering proactive palliative care beside curative care for patients with COPD may increase the workload and clinicians may be faced with shortage of time.[7] In order to overcome these problems it is suggested that a multidisciplinary approach to proactive palliative care with better access to specialist palliative care services will help patients with COPD navigate through the continuum of chronic disease management and will improve quality of end-of-life care.[7, 10]

Unfortunately, no research data is available on the beneficial effects of a multidisciplinary approach to proactive palliative care for patients with COPD in terms of reducing the healthcare utilization (for example, hospital readmission) or improving quality of life. However, in a study in male patients predominantly diagnosed with cancer but also with cardiovascular and pulmonary diseases, the benefits of palliative care provision appeared effective compared with usual care.[33] Patients receiving palliative care were less likely to be admitted to the ICU during hospitalization, had lower inpatient cost per day and received better medical care provision compared to usual care patients. Hence proactive palliative care may avoid admission to the ICU for patients with COPD and may help to reduce health care costs. More research data is available concerning the beneficial effects of an early introduction of palliative care for patients with cancer. In a recent study,[34] the effect of introducing early palliative care among patients diagnosed with metastatic non-small-cell lung cancer was examined in a randomized controlled trial (RCT). As compared to patients receiving standard care, patients receiving early palliative care had a better quality of life, less depressive symptoms, less aggressive care at the end of life and longer survival.

In the present study the effects of proactive palliative care performed by a specialized palliative care team for patients with COPD on the wellbeing of these patients and their informal caregivers will be examined. We hypothesize that proactive palliative care for patients with COPD will: increase the quality of life of these patients, decrease the number and length of acute hospital admissions and ICU admissions, prolong survival of these patients, decrease the number of patients that die in the ICU, and decrease the level of overburdening of their informal caregivers.

## METHODS/DESIGN

### Objectives

The PROLONG study exists of two parts, an indicator study and an intervention study, each with its own primary and secondary objectives:

***Objectives indicator study***

1. The primary objective is to assess the discriminating power of a set of indicators that indicates the start of proactive palliative care for patients with COPD.
2. The secondary objective is to examine to what extend individual indicators (or clusters) indicative are for the need of proactive palliative care.

***Objectives intervention study***

1. The primary objective is to assess the effects of proactive palliative care delivered by a specialized palliative care team on the wellbeing of patients with COPD with poor prognosis and their informal caregivers.
2. The secondary objective: is to assess survival rate in COPD patients with proactive palliative care integrated with standard care versus standard care only.

### Study design

The study consists of a controlled trial (assessment) with hospital as cluster, with a pre- and a post-test assessment. In total 6 hospitals will participate, 3 hospitals in the intervention condition and 3 hospitals in the control condition. Hospitals are selected for the intervention condition based on the presence of a specialized palliative care team. In the hospitals in the control condition standard care (usual care) will be delivered to patients with COPD by their treating lung specialists. In the hospitals in the intervention condition all patients with COPD will receive standard care by their treating lung specialist and those patients that are indicated for proactive palliative care by our set of indicators will also be supported by a specialized palliative care team on a regular base. Baseline measurements of the intervention study will be assessed from all participating patients during hospitalization for AECOPD before start of the intervention. Follow-up measurements will take place every three months, starting from the moment of discharge for a period of one year or until death. The primary outcome measure of the indicator study is time to death for any cause. The primary outcome measure of the intervention study is the change in quality of life measured by the St George Respiratory Questionnaire (SGRQ) at three month after baseline. As pre-test assessment, data will be obtained from the databases of the participating hospitals over a one year period preceding the assessment. These data on hospital-level are necessary to be able to compare hospitals at baseline. As post-test assessment, retrospectively the medical files of all participating patients will be examined over the assessment period. The assessment will take 18 month; 6 month for inclusion and 12 months for follow-up. The post-test assessment will be performed in the 3 months after the assessment.

## Study population

Patients with a hospital admission for AECOPD will be invited to participate. If they agree to participate, their main informal caregiver will also be asked to participate.

### *Inclusion criteria*

In order to be eligible to participate, a patient must meet the following criteria:

1. Being admitted to the hospital for AECOPD, and
2. Aged 18 years or older.

### *Exclusion criteria*

A patient that meets any of the following criteria will be excluded from participation:
Not speaking the Dutch language, or

1. Having severe cognitive disorders, or
2. At moment of inclusion being treated by a specialized palliative care team.

## Intervention

In the hospitals in the intervention condition, members of the specialized palliative care teams will receive a special training in the provision of proactive palliative care for patients with COPD. The training will be provided by academic palliative care professionals of the Radboudumc in Nijmegen. These trainings consist of two consecutive meetings of three hours each. The first meeting will take place in the month before start of the assessment. The second meeting will take place in the first month of the assessment. The following topics will be discussed:

- How to communicate end of life aspects with patient and family;
- How to create a patient-tailored proactive palliative care plan;
- How to anticipate on illness- and dying scenarios proactively;
- How to organize transfer of care to lung specialist and general practitioner (GP);
- How to perform a proactive palliative care plan in cooperation with the lung specialist.

During the controlled trial patients in the intervention condition who are assigned for proactive palliative care will meet with a member of the specialized palliative care team within one week after enrollment and at least monthly thereafter in the outpatients setting for at least one year or until death. The main informal caregiver of the patient will be asked to be present at those meetings. Guidelines for the proactive palliative care meetings in the ambulatory setting are adapted from the general guidelines palliative care in the Netherlands.[35]

## Study parameters

### *Outcome measures indicator study*

1. Primary outcome measures:
    - Length of time from the moment that a patient hospitalized for AECOPD meets two or more criteria of the set of indicators to death for any cause.
2. Secondary outcome measures:
    - Length of time from the moment that a patient hospitalized for AECOPD meets two or more criteria of the set of indicators to the first unexpected readmission to the hospital for AECOPD.
    - The sensitivity and specificity of the set of indicators, that indicate the start of proactive palliative care for patients hospitalized for COPD, in predicting death for any cause within 1 year.
    - The sensitivity and specificity of the set of indicators, that indicate the start of proactive palliative care for patients with COPD, in predicting the first unexpected readmission to hospital for AECOPD within 8 weeks.
    - Length of time from the moment that a patient hospitalized for AECOPD meets two or more criteria of the set of indicators to death as a result of pulmonary insufficiency.
    - The sensitivity and specificity of the set of indicators, that indicate the start of proactive palliative care for patients hospitalized for COPD, in predicting death as a result of pulmonary insufficiency within 1 year.
    - The contribution of individual indicators (or clusters), in predicting death for any cause within 1 year.
    - The contribution of individual indicators (or clusters), in predicting the first unexpected readmission to hospital for AECOPD within 8 weeks.
    - The contribution of individual indicators (or clusters), in predicting death as a result of pulmonary insufficiency within 1 year.

### *Outcome measures intervention study*

1. The primary outcome measure is:
    - Change in quality of life (St George Respiratory Questionnaire (SGRQ))[36] of the patient 3 months after inclusion
2. The secondary outcome measures are:

    <u>Patient-related</u>
    - Change in quality of life (SGRQ) of the patient 6, 9 and 12 months after inclusion
    - Change in quality of life at the end of life (McGill Quality of Life questionnaire (McGill QOL))[37] 3, 6, 9 and 12 months after inclusion
    - Change in psychological wellbeing (Hospital Anxiety and Depression Scale (HADS))[38] 3, 6, 9 and 12 months after inclusion
    - Change in illness understanding 3, 6, 9 and 12 months after inclusion

- Number and length of unexpected hospital admissions
- Number and length of unexpected ICU admissions
- Are the choices of Advance Care Planning (ACP) documented in the medical file? (when yes/when no)
- Place of death (ICU/hospital/hospice/nursing home/at home)
- Is preferred place of death known? (when yes/when no)
- Has this wish come true? (when yes/when no)
- Length of survival of COPD patients with proactive palliative care integrated with standard care versus standard care only

Informal caregiver-related

- Change in informal caregiver burden (Self-Perceived Pressure from Informal Care questionnaire (SPPIC))[39] 3, 6, 9 and 12 months after inclusion
- Change in psychological wellbeing (HADS) at 3, 6, 9 and 12 months after inclusion
- Change in illness understanding at 3, 6, 9 and 12 months after inclusion

***Other study parameters***

In order to take account of possible confounding variables, other parameters are: age, gender, marital status, socio-economic status, smoking history, condition of living (single, or living together), and place of living (home, residential home, or nursing home).

## Randomization

Randomization will not take place. Hospitals will be selected for the intervention condition based on the presence of a specialized palliative care team in the hospital. In order to be able to compare the hospitals in the control- and the intervention condition a pre-test assessment will be performed.

## Study procedure

A description of the procedure is given to assess the defined study parameters.

***Pre-test assessment***

The following data on hospital level will be obtained from the databases of the participating hospitals retrospectively over a period of one year (1-1-2013 till 1-1-2014):

- Number of hospitalizations for AECOPD (including ICU admissions)
- Number of unique patients hospitalized for AECOPD (including ICU admissions)
- Total number of days of hospitalization of patients with an AECOPD (including ICU admissions)
- Number of hospitalizations in the ICU (exclusively) for AECOPD
- Number of unique patients hospitalized for AECOPD in the ICU (exclusively)
- Total number of days of hospitalization of patients with an AECOPD in the ICU (exclusively)

- Total number of patients hospitalized for AECOPD that have died in the hospital (in the ICU or on the nursing unit)

### *Training*

Before start of the controlled trial (see Figure 2), members of the specialized palliative care teams in the hospitals in the intervention condition will receive a special training in provision of proactive palliative care for patients with COPD.

### *Controlled trial (assessment)*

#### *Patient*

Patients in the control condition will receive standard care (usual care) only. Patients in the intervention condition will receive standard care and, only if they meet two or more criteria of the set of indicators for proactive palliative care they will receive proactive palliative care integrated with standard care. The procedure in the control condition will be first described before describing the procedure in the intervention condition.

In the hospitals in the control condition eligible patients will be recruited the second day after hospital admission. The treating lung specialist will give each eligible patient oral and written information about the study. The written information consists of an information leaflet and two informed consent forms: one for the patient and one for the informal caregiver. In the information leaflet a description of the study, including the nature of participation and phone numbers for study contacts, are given for the patient and the informal caregiver. The lung specialist will obtain written informed consent from the patient prior to enrollment. If a patient has consented, a lung nurse will distribute questionnaires for completion on the sixth day of hospital stay or in case the patient is discharged earlier on the day before leaving the clinic. After hospital discharge the patient will be asked by the study coordinator to complete questionnaires every 3 month until the end of the study or until death. The questionnaires will be sent to the patient by mail. A stamped retour envelope will be enclosed.

In the hospitals in the intervention condition the same procedure will be followed as in the hospitals in the control condition. In addition lung specialists will check if a patient meets two or more criteria of the set of indicators for proactive palliative care on the sixth day of hospital admission or in case the patient is discharged earlier on the day before leaving the clinic. If so, the lung specialist will inform the specialized palliative care team. Patients who are assigned for proactive palliative care will preferably meet for the first time with a physician of the specialized palliative care team before being dismissed from the hospital. If this is not possible the first meeting will take place within 1 week after enrolment. Thereafter, the specialized palliative care team will meet with the patient monthly in the outpatients setting for at least 1 year or until death.

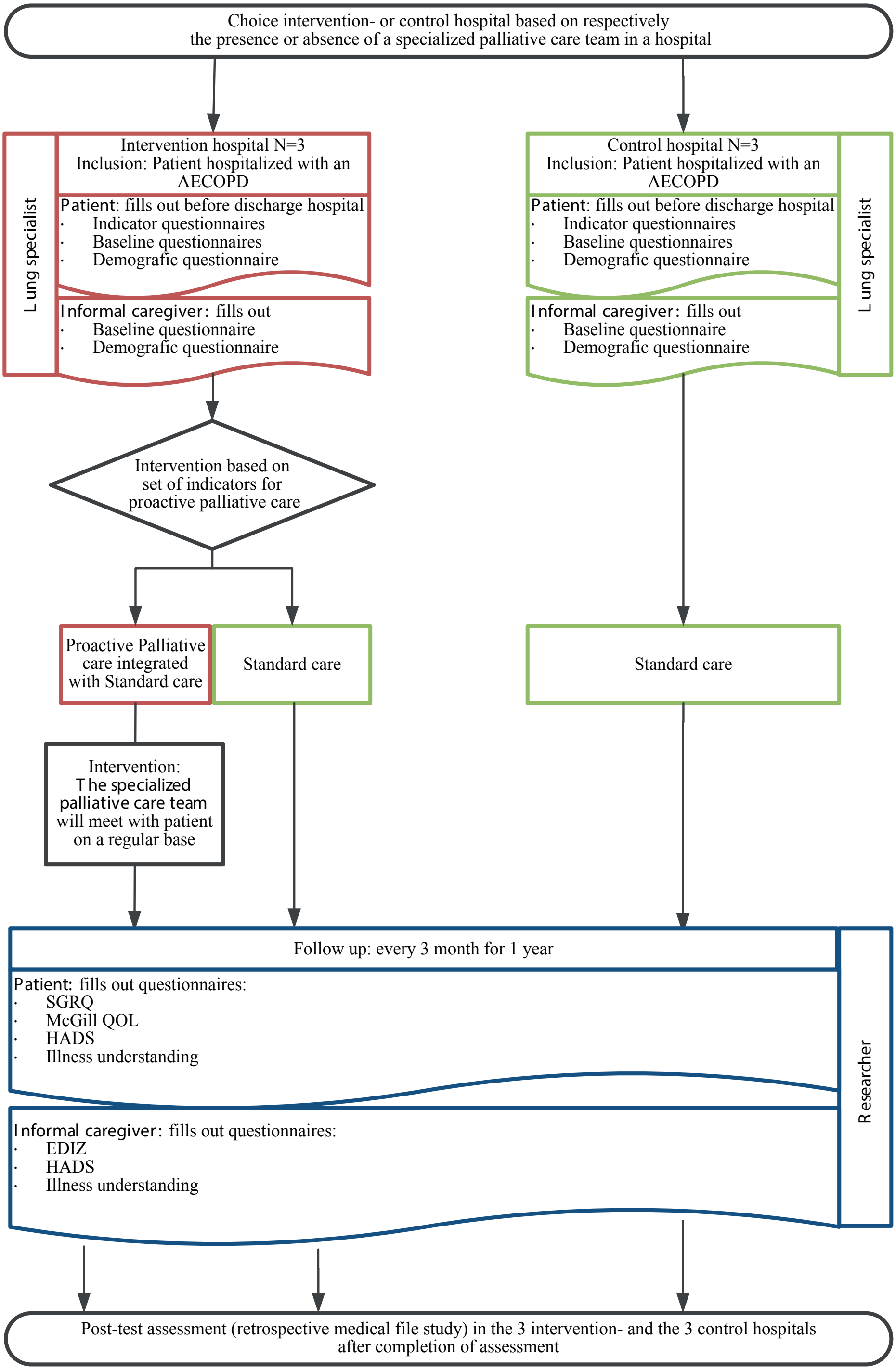


**Figure 2** Study schema of the controlled trial (assessment) and the post-test assessment for PROLONG.

*Informal caregiver*

During hospital stay, each eligible patient will identify a main informal caregiver, a relative or friend whom he or she relies upon most for help. By sharing the written information with the informal caregiver, the patient will provide the informal caregiver with information about the study. The informal caregiver can only participate if the patient is also participating. Once the informal caregiver has consented questionnaires will be distributed during hospital stay and every 3 month after hospital discharge of the patient. These questionnaires will be sent in the same envelop as the patient questionnaires.

*Lung specialist*

The treating lung specialist will provide standard care (usual care) to the patients hospitalized for an AECOPD. After the patient has filled out and returned the questionnaires the lung specialist in the control- and the intervention condition will fill out a case report form (CRF). The CRF consists of questions about the measurement results of each indicator of the set of indicators. The set of indicators is represented in Table 1. Only in the intervention condition the lung specialist will check if a patient meets two or more criteria of the set of indicators for proactive palliative care.

*Specialized palliative care team*

The specialized palliative care teams in the hospitals in the intervention condition consist of specially trained teams of professionals who provide care and support in inpatient and outpatient settings. A team consists of at least a physician who is specialized in palliative care, a nurse who is specialized in palliative care, and preferably a psychologist and a spiritual counselor.

**Table 1** Set of indicators for proactive palliative care

**A patient hospitalized for AECOPD is eligible for proactive palliative care when meeting two or more criteria of the following set of indicators**

1. Hypoxaemia (PaO2 < 8 kPa) or hypercapnia (PaCO2 > 6 kPa) at discharge
2. Treatment of the exacerbation with Non Invasive Ventilation (NIV)
3. Patient needs professional home care service for personal care after discharge
4. Negative answer to the surprise question:
   'Would I (as lung specialist) be surprised if this patient would have a subsequent readmission for AECOPD within 8 weeks and/or would die in the next year?
5. The diagnosis of a severe co-morbidity such as:
   a. Non-curable malignancy or
   b. Cor pulmonale (proven or non proven) or
   c. Proven Chronic Heart Failure (CHF) or
   d. Diabetes mellitus with neuropathy or
   e. Renal failure, clearance < 40 (GFR: in ml/min)
6. CCQ total, day version > 3
7. MRC dyspnea = 5
8. FEV1 (measured before AECOPD) < 30% of predicted
9. BMI < 21 or unplanned weight loss (> 10% in last 6 months or > 5% in last month)
10. Previous hospital admissions for AECOPD (last 2 years ≥ 2 and/or last year ≥ 1)
11. Age > 70 years

**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; BMI, body mass index; CCQ, Clinical COPD Questionnaire; FEV1, forced expiratory volume in 1 second; GRF, glomerular filtration rate; kPa, kilopascal; MRC dyspnea, Medical Research Council dyspnea questionnaire; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide.

### *Post-test assessment*

A post-test assessment will be performed in all participating hospitals. The medical files of all participating patients will be examined retrospectively regarding the assessment period on the following measures:

- Number and length of hospitalization of unexpected hospital admissions for AECOPD
- Number and length of hospitalization of unexpected ICU admissions for AECOPD
- Are the choices of Advance Care Planning (ACP) documented in the medical file? (when yes/when no)
- Place of death (ICU/hospital/hospice/nursing/home/at home)
- Is preferred place of death known? (when yes/when no)
- Has this wish come true? (when yes/when no)
- Length of survival after meeting conditions for proactive palliative care
- The primary and secondary measures of the indicator study

In order to take account of possible confounding variables, other parameters are: age, gender, marital status, type of admission, (acute or planned), condition of living (single, or living together), place of living (home, residential home, or nursing home), Gold stage, comorbidities, and date of diagnosis.

### Tools to help the clinical decision making

In order to help the clinical decision making, the specialized palliative care team will make use of two additional tools: 1) the Problems and Needs in Palliative Care questionnaire short version (PNPC-sv) and 2) the Proactive Palliative Care Planning Card (PPCPC).

The PNPC-sv patient is a concise, patient-centered tool that helps to identify the problems affecting the patient's quality of life and (unmet) needs for care. This self-report questionnaire is covering all dimensions of palliative care. The questionnaire consists of 36 items and is a reliable and valid tool.[40]

The PPCPC is a tool that can be used by members of the specialized palliative care team to structure the discussion with the patient and his/her informal caregiver. This tool is especially useful when exploring the actual en potential problems and needs of the patient.[41]

**Table 2** Overview of outcome measures per time point in the PROLONG study

| **Outcome Measures** | **B** | **3 m** | **6 m** | **9 m** | **12 m** | **R** |
|---|---|---|---|---|---|---|
| **Questionnaires** | | | | | | |
| Patient | | | | | | |
| CCQ | X | | | | | |
| MRC dyspnea | X | | | | | |
| SGRQ | X | X | X | X | X | |
| McGill QOL | X | X | X | X | X | |
| HADS | X | X | X | X | X | |
| Illness understanding | X | X | X | X | X | |
| Demographic questionnaire | X | | | | | |
| Informal caregiver | | | | | | |
| SPPIC | X | X | X | X | X | |
| HADS | X | X | X | X | X | |
| Illness understanding | X | X | X | X | X | |
| Demographic questionnaire | X | | | | | |
| Lung specialist | | | | | | |
| CRF | X | | | | | |
| **Medical files** | | | | | | |
| Number of hospitalizations of unexpected hospital admissions for AECOPD | | | | | | X |
| Number of days of unexpected hospital admissions for AECOPD | | | | | | X |
| Number of hospitalizations of unexpected ICU admissions for AECOPD | | | | | | X |
| Number of days of unexpected ICU admissions for AECOPD | | | | | | X |
| Are the choices of ACP documented in the medical file at baseline? (when yes/ when no) | | | | | | X |
| Are the choices of ACP documented in the medical file after one year or at time of death? (when yes/when no) | | | | | | X |
| Did the patient die within one year after inclusion? (when yes/when no) | | | | | | X |
| Date of death | | | | | | X |
| Place of death (ICU/hospital/hospice/nursing home/at home) | | | | | | X |
| Is preferred place of death known? (when yes/when no) | | | | | | X |
| Has this wish come true? (when yes/when no) | | | | | | X |
| Primary cause of death (pulmonary insufficiency/other cause) | | | | | | X |
| Secondary cause of death (pulmonary insufficiency/other cause) | | | | | | X |
| Did the patient have an unexpected hospital readmission for AECOPD within 8 weeks? (when yes/when no) | | | | | | X |
| Date of first unexpected hospital readmission for AECOPD. | | | | | | X |

**Abbreviations:** B= baseline; m= month; R=retrospectively

## Data collection

Data collection will take place by administration of questionnaires to the participating patients and their informal caregivers and by retrospectively collecting data from the medical files of the participating patients over the assessment period. The type of questionnaires for patients and informal caregivers, the frequency of their administration and the retrospectively collected data are detailed in Table 2.

## Instrument selection

### *Questionnaires used as indicator*

In order to be able to decide whether or not to start proactive palliative care, questionnaires used as indicator will be filled out by the patient .

We will use the CCQ day version to measure health status of patients. The CCQ is a questionnaire for self-administration specially developed to measure health status in patients with COPD and is valid, responsive, and reliable.[42, 43] The CCQ consists of 10 questions rated on a seven point Likert scale. Higher scores represent a worse health status. Questions are divided into three domains: symptoms (4 questions), functional status (4 questions), and mental state (2 questions).

The MRC dyspnea scale has been in use for many years for grading the effect of breathlessness on daily activities.[44] The MRC dyspnea scale consists of 5 questions and provides a simple and valid method of categorizing patients in terms of their disability due to COPD.[44] The patient's dyspnea is rated from 1-5 in terms of severity, with the higher the grade, the more severe the dyspnea. During the study MRC dyspnea will be measured by asking about the circumstances two weeks before hospital admission.

### *Questionnaires used as outcome measures*

*Patient questionnaires*

The SGRQ is a specific quality of life questionnaire for obstructive respiratory diseases.[36] It consists of 50 questions from which a total score is calculated. It is divided into three subscales: symptoms (8 items related to patients' recollection of their symptoms), activities (16 items on physical activities which are caused or limited by dyspnea), and impacts (26 items on the social and physiologic effects of the disease). The final score obtained ranges from zero to 100. A higher score indicates a lower quality of life. A score change of 4 points or more is considered significant in the quality of life of the patient.[45] The SGRQ is a reliable and valid measure of the quality of life in patients with COPD.[46]

The McGill QOL is designed to assess quality of life in patients with a life-threatening illness.[37] The questionnaire consists of 16 items with an 11-point scale (0-10) with appropriate anchors. It includes 5 domains: physical symptoms, physical well-being, psychological well-being, existential issues and support. The mean of all 5 domains is presented as McGill QOL total score. The acceptability, internal consistency, reliability and validity of the McGill QOL have been assessed in patients receiving palliative care.[47]

The HADS will be used to assess psychological wellbeing in patients. The HADS is a self-assessment 14-item questionnaire. It has two 7-item subscales assessing depression and anxiety in the preceding week. The format consists of four answering categories (0-3) that quantify the degree to which a particular emotion is experienced by the patient. The score on each subscale ranges from 0 to 21 and a score larger than 11 is considered to be consistent with definitive depression and anxiety. A score less than 7 is normal and a score of 8-10 is considered borderline for depression and anxiety.[38]

Patients with COPD tend to be poorly informed about the long-term prognosis of COPD and what to expect toward the end of life.[48] They may not realize that COPD is incurable and fatal. They also may not always attribute repeated exacerbations to advancing disease but instead seeing them as temporary setbacks caused by activities, environmental factors, faltering self-management, or infection. Toward the end of life this lack of understanding may impair quality of life.[2, 49] There are no validated tools to assess illness understanding in patients with COPD. Therefore, we adapted an illness understanding questionnaire used in studies of patients with advanced cancer.[50] The questionnaire consists of 4 self-report items which can be answered by yes or no.

Patients will be asked in a demographic questionnaire to indicate their sex, age, marital status, education, smoking history, living situation, name of main informal caregiver and kind of relationship with their main informal caregiver.

*Informal caregiver questionnaires*

The Self-Perceived Pressure from Informal Care questionnaire (SPPIC) is a non-disease specific instrument assessing the demands of the informal caregiver situation.[39] This instrument consists of nine statements that form a hierarchical scale that varies from less to more pressure. The statements are all related to the subjective perception of the informal caregiver. It is a validated and easy to use instrument since completing it takes less than 5 minutes.

The HADS (see patient questionnaires) will also be used in informal caregivers to assess psychological wellbeing. An adapted version of the illness understanding questionnaire for patients will be used for the informal caregivers as well. Finally, informal caregivers will be asked to indicate their sex, age and education in a demographic questionnaire.

## Sample size calculation

The primary outcome in the intervention study is the quality of life of the patients measured with the SGRQ. More specifically the change in SGRQ three month after inclusion is the variable of interest. Koff et all.,[51] published a difference in change of 9 between the two groups (standard care, standard care with proactive palliative care) with a common standard deviation of the change of 16. Then 64 patients would be needed in each group to obtain a power of 80% (two-sided t-test, alpha=0.05). To adjust for the clustering at hospital level (ICC=0.01, three hospitals per arm) and to allow for an additional loss to follow up of 10% a total of 86 patients are needed in each arm. This means that in each hospital 29 patients with an AECOPD are needed who have a poor prognosis according to our criteria. We expect to have to include between 60 and 90 patients with an AECOPD in each hospital to get sufficient patients that meet at least 2 criteria of the set of indicators.

## Statistical analysis

### *Study parameter(s) indicator study*

Non-continuous data will be reported as frequencies. Continuous variables normally distributed will be reported as mean ± standard deviation (SD). Not normally distributed data will be reported as median (interquartile range, IQR). The analytical plan consists of two steps. The first step will be to explore the discriminating power of meeting two or more criteria of the set of indicators for predicting death within one year and predicting unexpected hospital admission, respectively. The sensitivity and specificity for both death within one year and for unexpected admission to hospital will be presented. The second step will be to explore the discriminating power of individual indicators (or clusters) in predicting death within one year or unexpected admission to hospital. Univariable and multivariable logistic regression will be performed to examine which variables or cluster of variables are associated with death within one year (unexpected admission to hospital respectively). Variables will be eliminated one by one from the model based on likelihood ratio tests. Variables are eligible for inclusion into the final model if they are significantly associated with death within one year (unexpected admission to hospital respectively), with a p-value of < 0.10.

### *Study parameter(s) intervention study*

Frequencies, means and standard deviations will be used to describe the study variables. Differences between the study groups in baseline characteristics and clinical outcomes will be assessed and tested for statistical significance with the use of two-sided Fisher's exact tests and chi-square tests for categorical variables and independent-samples t-tests for continuous variables. The primary study outcome measure of the intervention study is the change in the score on the SGRQ from baseline to 3 months: a paired t-test will be used to test the difference between the groups for statistical significance. Linear mixed models, with adjustment for baseline scores, will be used to study the effect of proactive palliative care on SGRQ outcomes during the follow-up period. The analysis follows the principle of intention to treat. Survival time will be calculated from the date of enrollment to the date of death with the use of the Kaplan-Meier method. A Cox proportional-hazard model will be used to assess the effect of proactive palliative care on survival, with adjustment for demographic characteristics.

### Ethical considerations

Patients with COPD who participate in the study may be vulnerable but are certainly capacitated adults. Since this is a therapeutic research the participants, patients and informal caregivers, may even benefit from participation. The potential risks of this study are quite small. They relate to the burden of filling in questionnaires. This will take the patient about 20-30 minutes every three months. The potential benefits on the other hand are comparatively large. First, participating patients with severe COPD and their informal caregivers in the intervention condition will get, if indicated for it, extra proactive palliative care. Second, this study may lead to better understanding of the conditions to start and the effectiveness of proactive palliative care for patients with COPD. Third, there is a potentially benefit for society since results of this study may ultimately lead to different and improved clinical approaches to care of patients with severe COPD.

This Study has been approved by the Medical Ethics Committee (CMO) of the Radboud University Nijmegen Medical Centre (METC protocol number 2012/260).

## DISCUSSION

Research on the effectiveness of palliative care for the COPD patient is scarce and inconclusive.[52] The PROLONG study is the first prospective controlled trial evaluating the effectiveness of a multidisciplinary approach to palliative care in COPD disease. The outcomes of this study will give insight in the discriminating power of a set of indicators for proactive palliative care and the effectiveness of proactive palliative care for patients with COPD.

In the Netherlands, COPD is on the sixth place of causes of death for people older than 45 years. In 2011 6,535 patients died with COPD as primary cause of death while in 2010 the number of hospitalizations of patients with COPD as diagnosis was 22,5440. The prevalence of COPD in the Netherlands is high (361,800 in 2011) and will, with the aging of the population, further increase the coming years.[53] Up to now patients with COPD hardly receive palliative care. The above mentioned numbers reveal the social relevance of introducing palliative care for patients with COPD. Furthermore, introducing palliative care for patients with COPD can possibly be cost-saving since palliative care may lead to reduction of acute care.[33, 54, 55]

We have chosen a cluster controlled design for the PROLONG study to prevent cross-contamination of the intervention within a hospital. At the moment of recruitment of hospitals the minority of hospitals in the Netherlands had the availability of a specialized palliative care team. Therefore, it was not an option to perform a randomized cluster controlled trial. Hospitals are selected for the intervention condition based on the presence of a specialized palliative care team in the hospital. In order to be able to compare the hospitals in the control- and the intervention condition at baseline a pre-test assessment will be performed.

Recruitment for trials of patients with poor prognosis is often difficult. In order to ensure a sufficiently large sample for the PROLONG study broad inclusion criteria will be used. All patients hospitalized with an AECOPD over 17 years old can be screened for the study. This will facilitate lung specialists to include patients. Only after inclusion the distinction between patients with poor or better prognosis will be made in order to decide who is eligible for the intervention condition.

The PROLONG study may lead to better understanding of the conditions to start and the effectiveness of proactive palliative care for patients with COPD. The innovative aspects of the PROLONG study are: 1) the use of a set of indicators to identify patients hospitalized with an AECOPD who are in need of proactive palliative care, 2) the active involvement of a specialized palliative care team in the development and the implementation of proactive palliative care for patients with COPD and, 3) the use of a patient-tailored proactive palliative care plan in which lung specialist and a specialized palliative care team work together to optimize proactive palliative care for the COPD patient. This patient-tailored proactive palliative care plan is intended to meet and to adjust to the individual needs, wishes, possibilities and limitations of the patient and the informal caregiver.

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# Consistency of Medical Record Reporting of a Set of Indicators for Proactive Palliative Care in Patients with COPD: A Pilot Study

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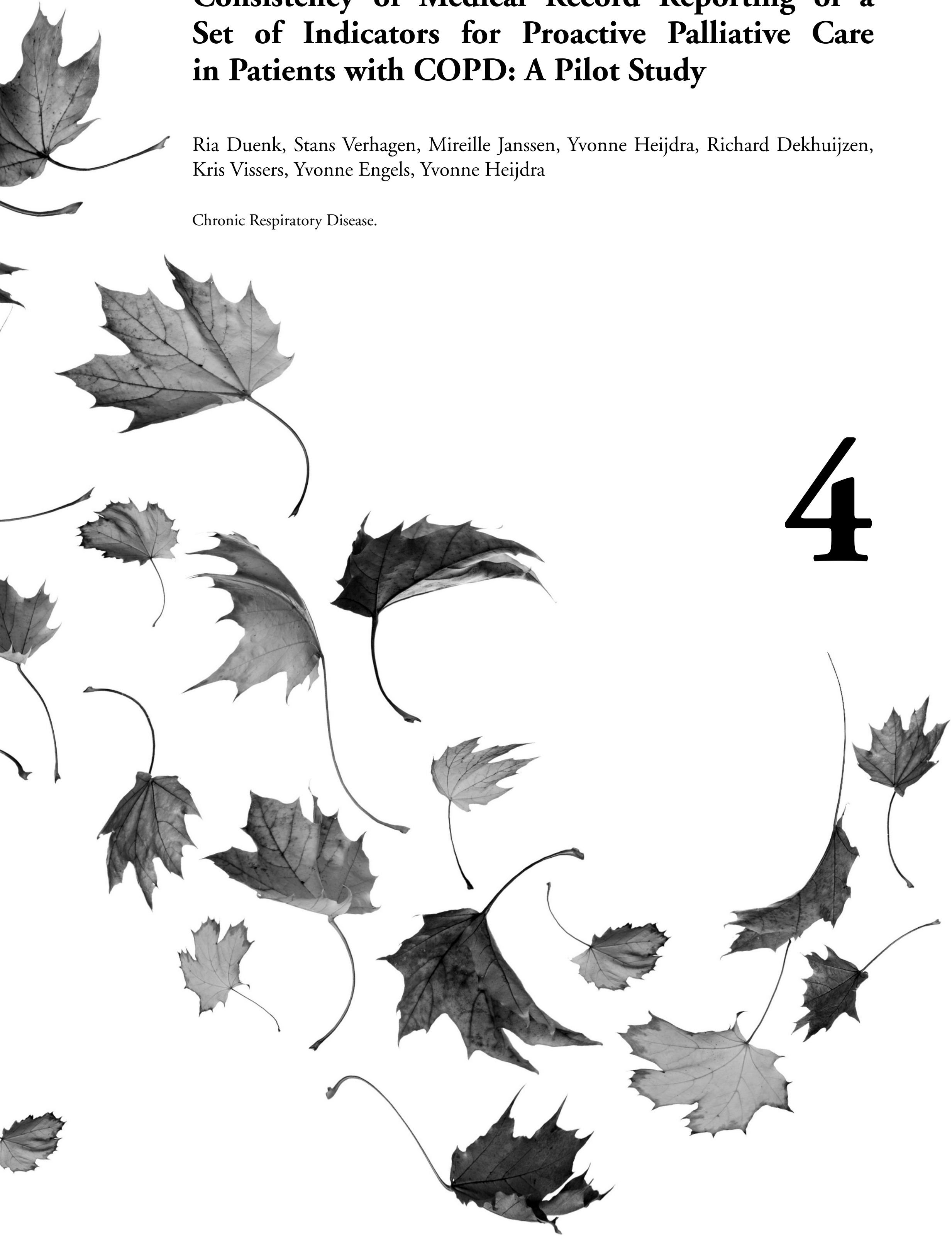
Chronic Respiratory Disease.

# 4



## ABSTRACT

**Objectiv**es: To identify patients hospitalized for an acute exacerbation COPD who have a poor prognosis and might benefit from proactive palliative care, a set of indicators had been developed from the literature. A patient is considered eligible for proactive palliative care when meeting ≥ 2 criteria of the proposed set of eleven indicators. In order to develop a doctor-friendly and patient-convenient tool our primary objective was to examine whether these indicators are documented consistently in the medical records. Besides, percentage of patients with a poor prognosis and prognostic value were explored.

**Method**s: We conducted a retrospective medical record review of 33 patients.

**Results:** Five indicators; NIV, comorbidity, BMI, previous admissions for AECOPD, and age were always documented. Three indicators, hypoxaemia and/or hypercapnia, professional home care, and actual FEV1% were documented in more than half of the records, while CCQ, MRC dyspnea, and the surprise question were never registered. Besides, 78.8% of the patients met ≥ 2 criteria and there was a significant association between meeting ≥ 2 criteria and mortality within 1 year (one-sided Fisher's Exact Test, p = .04).

**Conclusion**s: The set of indicators for proactive palliative care in patients with COPD appeared to be user-friendly and feasible.

**Keywords:** COPD, Exacerbation, Indicators, Prognosis, Proactive palliative care

## BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease with a high prevalence[1] and the third leading cause of death worldwide.[2] The symptoms that occur in the end stage of COPD are as severe as or even worse than in the final stage of lung cancer.[3, 4] However, patients with COPD are less likely than those with cancer to receive palliative care.[5, 6] This may be due to the fact that historically the initial focus of palliative care has been on oncology[7] but also to the different disease trajectory.[8] The unpredictable disease course of COPD can virtually paralyse lung specialists and prevent them from starting palliative care.[9] But, since patients with advanced COPD experience similar palliative care needs as patients with advanced cancer[10] they probably might also benefit from palliative care.

There is evidence that, for patients with cancer, provision of palliative care improved outcomes in the domain of pain and symptom control, and reduced hospital admissions.[11] Besides, early integration of palliative care improved quality of life, reduced depressive symptoms and even prolonged survival of patients with non-small-cell lung cancer.[12, 13] Recently, it has been demonstrated that early integration of palliative care improved breathlessness mastery for patients with diseases other than cancer, including COPD.[14] Further research specifically aimed at COPD is needed.[15] For this reason a prospective study has been set up to examine identification of patients with COPD with poor prognosis and implementation of proactive palliative care.[16]

Identification of patients with COPD for proactive palliative care is a challenge. In stable COPD population models of survival do exist but they are of limited value to predict survival for individual patients.[17] Therefore, a patient centered approach to palliative care has been proposed not based on prognosis but on palliative needs of the patient.[18] Although good palliative care indicators tools have been developed, such as the Supportive and Palliative Care Indicators Tool (SPICT), they are not specifically intended for patients with COPD, do not use criteria for the indicators and/or do not use a clear moment to be applied.[18, 19] Since COPD has a gradual decline that is punctuated by acute severe exacerbations, any one of which may be fatal.[8, 20], a hospitalization for an acute exacerbation COPD (AECOPD) might be such a clear moment to identify a need for palliative care.[21, 22] Not only is the patient during hospitalization literally present for the lung specialist, the patient is probably also more willing to address palliative issues. Several studies focused on the identification of predictive factors associated with poor prognosis for patients hospitalized for an AECOPD.[23] One of the conclusions in a recent review on this topic was that post-discharge mortality reflects the severity of COPD, as well as concomitant specific comorbidities while functional limitation and poor health-related quality of life influence the frequency of readmissions.[23] In accordance with these findings and based on existing literature[23-27] we developed a concept set of indicators for lung specialists to identify patients hospitalized for an AECOPD who have a poor prognosis. Poor prognosis was defined as having a hospital readmission for an AECOPD within 8 weeks or mortality within 1 year. We hypothesized that meeting $\geq$ 2 criteria of this set of indicators could be reason to start proactive palliative care.[28, 29] Since palliative care needs increase during the course of COPD, the prediction of poor prognosis will be used to ensure not to miss out patients with COPD hospitalized for an acute exacerbation who are in need of proactive palliative care. The final tool therefore should have a high sensitivity (near 100) and a high as possible specificity.

The use of this set of indicators was examined in this retrospective pilot study to get an indication of its applicability in our prospective study. Since we want to develop a doctor-friendly and patient-convenient tool that is easy to implement our primary objective was to examine whether these indicators are documented consistently in the medical records of patients hospitalized for an AECOPD. Secondary objectives were to get an indication of the percentage of patients hospitalized for an AECOPD that meet ≥ 2 criteria of the set of indicators and the prognostic value of meeting ≥ 2 criteria of the set of indicators regarding readmission within 8 weeks and/or mortality within 1 year.

## METHODS

### Study design

A retrospective medical record review was conducted in October 2013.

### Study population

All patients who were admitted to the Radboud University Medical Centre in Nijmegen, the Netherlands, with the clinical diagnosis COPD in the period January 2012 until March 2012 were considered. This period was chosen to ensure one year follow up data of each patient. A clinical diagnosis COPD was defined as chronic airway obstruction as determined by spirometry prior to hospitalization with an FEV1/FVC ratio < 70%. Next, only medical records of those patients hospitalized for an AECOPD were selected. An AECOPD was defined as ‘an acute worsening of the patient’s condition from the stable state, which is sustained and may warrant the patient to seek additional treatment [30]. Excluded from the analysis were medical records of patients who were not hospitalized and patients who came to the pulmonary rehabilitation centre of the Radboud University Medical Centre for current pulmonary rehabilitation.

This study was approved by the Medical Ethics Committee (CMO) of the Radboud University Nijmegen Medical Centre (METC registration number 2013/449). Informed consent was not obtained, since we only used data from an existing, clinical database, that was anonymized and de-identified prior to analysis.

**Table 1** Variables needed to explore the documentation of the set of indicators

| Indicator | Variable looked for in medical records |
|---|---|
| 1. Hypoxaemia at discharge | PaO2 (kPa), oxygen administration, and O2 saturation at admission and discharge |
| Hypercapnia at discharge | PaCO2 (kPa) at admission and discharge |
| 2. NIV | Noted as NIV or NPPV |
| 3. Professional home care | Existence of professional home care after admission |
| 4. Surprise question | Surprise question answered with 'yes'or 'no' |
| 5. Severe comorbidity | Existence of non-curable malignancy<br>Existence of cor pulmonale<br>Existence of proven CHF<br>Existence of diabetes mellitus with neuropathy<br>Renal failure, clearance (GFR: in ml/min) |
| 6. CCQ | CCQ total, day version (0-6) |
| 7. MRC dyspnea | MRC dyspnea (1-5) |
| 8. FEV1 | FEV1 % predicted |
| 9. BMI | BMI (kg/m$^2$), or length (m) and weight (kg) |
| Weight change | Weight loss in last 6 months (%) |
| 10. Previous hospital admissions | Previous hospital admissions AECOPD in last 2 years |
| 11. Age | Birth date and admission date |

**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; BMI, body mass index; CCQ, Clinical COPD Questionnaire; CHF, Chronic Heart Failure; FEV1, forced expiratory volume in 1 second; GRF, glomerular filtration rate; kPa, kilopascal; MRC dyspnea, Medical Research Council dyspnea questionnaire; NIV, non invasive ventilation; NPPV, non invasive positive pressure ventilation; PaCO2, partial pressure of carbon dioxide in arterial blood; PaO2, partial pressure of oxygen in arterial blood.

## Data collection

Data from the medical records were obtained from the Electronic Patient Record (EPR). We searched for the following variables: 1) demographic variables namely age, gender, marital status, condition of living and place of living; 2) COPD related variables namely GOLD stage and smoking history; 3) variables needed to explore the documentation of the set of indicators for proactive palliative care (see Table 1); and 4) date of first readmission for AECOPD and date of death if appropriate.

To explore the documentation of hypoxaemia and/or hypercapnia at discharge two methods were used, a strict and a clinical method. In the strict method only measurement documented at discharge were used, whereas in the clinical method also measurements documented at admission were considered. Hypoxaemia was defined as having oxygen administration, or a PaO2 $< 8$ kPa (without oxygen administration) or an O2 saturation $\leq 90\%$ (without oxygen administration)[31]. Hypercapnia was defined as having a PaCO2 $> 6$ kPa.

## Statistical analysis

Derived variables were calculated to see if ≥ 2 criteria of the set of indicators for proactive palliative care (see Table 2) were met. In order to decide if the criteria of the indicator hypoxaemia and/or hypercapnia at discharge were met the documentation according to the strict method was used.

**Table 2** Set of indicators with criteria for proactive palliative care

| | **A patient hospitalized for AECOPD is eligible for proactive palliative care when meeting two or more criteria of the following set of indicators** |
|---|---|
| 1. | Hypoxaemia (PaO2 < 8 kPa) or hypercapnia (PaCO2 > 6 kPa) at discharge |
| 2. | Treatment of the exacerbation with Non Invasive Ventilation (NIV) |
| 3. | Patient needs professional home care service for personal care after discharge |
| 4. | Negative answer to the surprise question:<br>'Would I (as lung specialist) be surprised if this patient would have a subsequent readmission for AECOPD within 8 weeks and/or would die in the next year? |
| 5. | The diagnosis of a severe co-morbidity such as:<br>a. Non-curable malignancy or<br>b. Cor pulmonale (proven or non proven) or<br>c. Proven Chronic Heart Failure (CHF) or<br>d. Diabetes mellitus with neuropathy or<br>e. Renal failure, clearance < 40 (GFR: in ml/min) |
| 6. | CCQ total, day version > 3 |
| 7. | MRC dyspnea = 5 |
| 8. | FEV1 (measured before AECOPD) < 30% of predicted |
| 9. | BMI < 21 or unplanned weight loss (> 10% in last 6 months or > 5% in last month) |
| 10. | Previous hospital admissions for AECOPD (last 2 years ≥ 2 and/or last year ≥ 1) |
| 11. | Age > 70 years |

**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; BMI, body mass index; CCQ, Clinical COPD Questionnaire; FEV1, forced expiratory volume in 1 second; GRF, glomerular filtration rate; kPa, kilopascal; MRC dyspnea, Medical Research Council dyspnea questionnaire; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide.

The statistical program SPSS version 20 was used to analyze the data. Non-continuous variables were reported as frequencies. Normally distributed continuous variables were reported as mean ± standard deviation (SD). Not normally distributed continuous variables were reported as median (interquartile range, IQR). In order to get an indication of the prognostic power of meeting ≥ 2 criteria of the set of indicators the differences between study groups in baseline characteristics and clinical outcomes were assessed and tested for statistical significance with the use of one-sided Fisher's exact tests for categorical variables and independent sample t-tests for continuous variables. Differences were considered significant with a p-value of < 0.05. If appropriate the sensitivity and the specificity for death within one year and unexpected hospital admission within 8 weeks were explored.

# RESULTS

## Study population

The medical records of 149 patients with the clinical diagnosis COPD were considered. Excluded from the analysis were 116 medical records of patients who were not hospitalized or who were included in a clinical pulmonary rehabilitation program. Finally, the medical records of 33 patients hospitalized for an AECOPD were examined. The characteristics of the study population are presented in Table 3.

**Table 3** Characteristics of the study population

| **Study population (N = 33)** | |
|---|---|
| | **Mean (+SD)** |
| Age | 72 (+10.4) |
| Duration of hospitalization | 11 (+7.6) |
| Pack years | 33.1 (+18.7) |
| | **N (%)** |
| *Sex* | |
| Male | 19 (58) |
| Female | 14 (42) |
| *Marital status* | |
| Married | 18 (55) |
| Unmarried | 3 (9) |
| Divorced | 3 (9) |
| Widow | 8 (24) |
| Unknown | 1 (3) |
| *Condition of living* | |
| Non single | 22 (67) |
| Single | 11 (33) |
| *Place of living* | |
| Home | 29 (88) |
| Residential home | 0 (0) |
| Nursing home | 4 (12) |
| *Gold stage* | |
| I | 0 (0) |
| II | 11 (33) |
| III | 7 (21) |
| IV | 14 (43) |
| Unknown | 1 (3) |
| *Smoking at admission* | |
| Yes | 9 (27) |
| No | 24 (73) |

**Abbreviations:** SD, standard deviation.

## Documentation of the set of indicators

Of the eleven indicators for proactive palliative care, five were always documented in the medical records (see Figure 1). These were NIV, comorbidity, BMI, previous admissions for AECOPD and age. According to the strict method hypoxaemia, hypercapnia, and hypoxaemia and/or hypercapnia at discharge were documented respectively in 85%, 36% and 85% of the cases. For the clinical method these numbers were respectively 100%, 97% and 100%. Having professional home care and actual FEV1% were recorded half of the time (respectively 57.5% and 54.5%). The surprise question, CCQ and MRC dyspnea were never documented (0%).

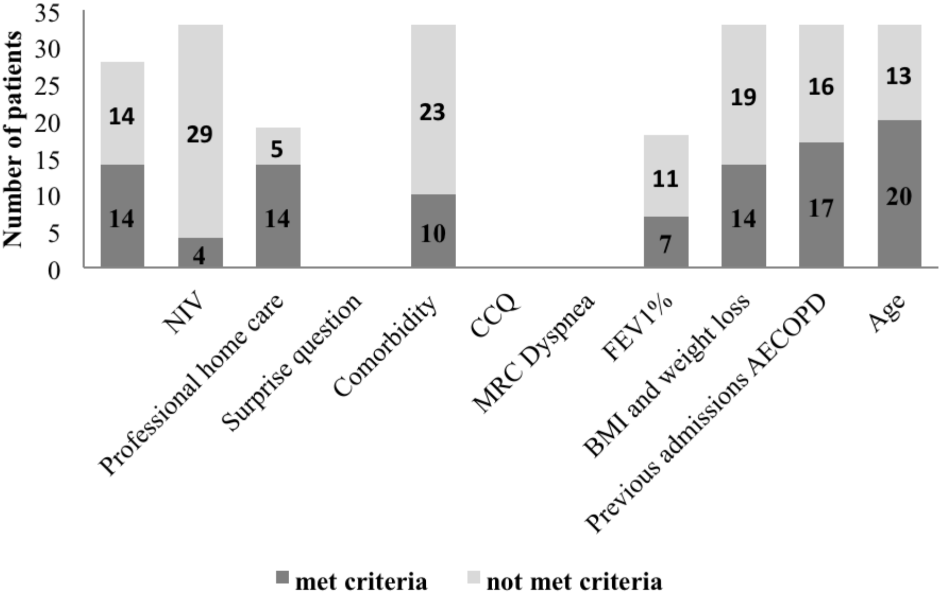


**Figure 1** Documentation of each indicator in the medical records and the number of patients that met or did not met the criterion of each indicator for proactive palliative care.

## Meeting ≥ 2 criteria of the set of indicators

Of the 33 patients hospitalized for AECOPD, 26 patients (78,8%) met ≥ 2 criteria of the set of indicators for proactive palliative care. The number of patients that met or did not met the criterion of each documented indicator is presented in Figure 1.

## Exploration of the prognostic value of the set of indicators

### *Deceased vs. Non deceased.*

There was a significant association between meeting the criteria for proactive palliative care and whether or not the patient died (one-sided Fisher's Exact Test, $p$ = .04). All patients who died within one year after admission (n = 11) met the criteria of the set of indicators for proactive palliative care (see Table 4) meaning that the sensitivity of the set of indicators in predicting death within one year was 100%. From the 22 patients who survived seven patients did not meet the criteria of the set of indicators for proactive palliative care meaning that the specificity of the set of indicators in predicting death in one year was 31.8%. Deceased patients met significantly more indicators (*M* = 4.27, *SE* = .24) than patients who survived (*M* = 2.41, *SE* = .36), *t*(31) = -3.47, *p* = .002+, *r* = .53.

### *Readmission vs. No readmission within 8 weeks.*

There was no association between meeting criteria for palliative care and whether or not the patient had a readmission for an AECOPD within 8 weeks (one-sided Fisher's Exact Test, p = .718). The contingency table is presented in Table 5.

**Table 4** Contingency table showing the number of patients deceased within 1 year in patients who meet or do not meet criteria for palliative care

| | ≥ 2 indicators | < 2 indicators | Total |
|---|---|---|---|
| Deceased | 11 (42.3%) | 0 (0%) | 11 (33.3%) |
| Non Deceased | 15 (57.7%) | 7 (100%) | 22 (66.7%) |
| Total | 26 (100%) | 7 (100%) | 33 (100%) |

**Table 5** Contingency table showing the number of patients with a readmission for an AECOPD within 8 weeks in patients who meet or do not meet criteria for palliative care

| | ≥ 2 indicators | < 2 indicators | Total |
|---|---|---|---|
| Readmission | 4 (15.4%) | 1 (14.3%) | 5 (15.2%) |
| No Readmission | 22 (84.6%) | 6 (85.7%) | 28 (84.8%) |
| Total | 26 (100%) | 7 (100%) | 33 (100%) |

## DISCUSSION

This study explored the use of a set indicators to get an indication of its applicability in a prospective study. This set of indicators has been developed from literature to identify patients hospitalized for an AECOPD who have a poor prognosis and might benefit from proactive palliative care.

### Documentation of indicators

Five of the eleven indicators were documented consistently in the medical records, three in more than half of the records, and three not at all. The consistent documentation of age and BMI was as expected, since this is basic patient information written down every time a patient visits the hospital. Previous admissions for AECOPD, NIV and comorbidity were also always documented when appropriate. The presence or absence of hypoxaemia and/or hypercapnia at discharge was documented in 85% of the cases. At admission the necessary measurements of arterial blood gas (ABG) were consistently documented. At discharge these measurements were sometimes missing (15% for hypoxaemia and 64% for hypercapnia). It is recommended to have ABG documented before hospital discharge for all patients with an AECOPD complicated by respiratory failure.[32] Taking into account this recommendation, the necessary ABG measurements of only one patient, who was admitted being hypercapnic, was not documented at discharge (3%). Hence, no ABG documented before hospital discharge in most cases meant that the patient was not hypoxaemic or hypercapnic at admission. Professional home care and actual FEV1% were documented half of the time. A possible explanation of these missing documentations is for professional home care that this is not documented if the patient is independent of such care and for actual FEV1% that if unknown at admission it cannot be assessed in an instable phase such as an AECOPD and therefore is not documented. An answer to the surprise question was never documented. Although widely known by palliative care specialists, no validation studies on the use of the surprise question to identify patients with COPD who can benefit from a palliative care approach have been published, which explains its absence in the medical record. Besides, up to now the surprise question has mainly be used in research. Also the CCQ and MRC dyspnea were never documented. This confirms the finding that these disease specific tools are mainly used in clinical trials or when selecting patients for treatment, but less often in usual care.[18]

Most indicators are fairly consistently documented in the medical records. This suggests that lung specialists already use these variables in clinical practice. With respect to these variables no extra measurements seem to be necessary to identify patients with COPD with poor prognosis. Only an answer to the surprise question, the CCQ and MRC dyspnea are variables never documented. For our prospective study this implies that these variables should be specifically asked for and measured. The surprise question, the CCQ and MRC dyspnea are short, easy to use questionnaires. We decided to include them into the concept set of indicators since they provide valuable information about respectively the view of the lung specialist, the severity of the dyspnea and the health status of the patient. The measurement of health status (CCQ) is important since functional limitation and poor health-related quality of life is recognized to influence the frequency of readmissions.[23] Beside anxiety, part of the mental state domain of the CCQ, is associated with mortality and may be a variable that influences early readmission rates.[25] Whether the surprise question, the CCQ and MRC dyspnea are also included into the final version of the set of indicators will depend on the outcome of the prospective study.

### Meeting ≥ 2 criteria

In this pilot, 78.8% of the patients hospitalized for an AECOPD met ≥ 2 criteria of the set of indicators. This suggests that 3 out of 4 patients hospitalized for an AECOPD could have a poor prognosis and may have an indication for proactive palliative care. Although it seems to be a high number it is in line with the recent tendency of reducing demand for unscheduled hospital admissions by admitting the more physically ill patients with an AECOPD and avoiding admissions for psychosocial reasons by optimizing care at home.[33]

### Prognostic exploration

Finally, we explored the prognostic value of meeting $\geq$ 2 criteria of the set of indicators for proactive palliative care. Meeting $\geq$ 2 criteria of the set of indicators was associated with risk of mortality within 1 year. The sensitivity of the set of indicators proved to be 100% in predicting mortality in this small sample. None of the patients who met less than two criteria of the set of indicators died within 1 year. The specificity of the set of indicators in predicting mortality proved to be 31.8%. So, meeting $\geq$ 2 criteria of the set of indicators did not always necessarily mean that the patient died within 1 year. However, in order to use this set of indicators in a prospective study to investigate the potential benefit of proactive palliative care, the risk of missing people in need of this care should be as minimal as possible. Of all the patients who were hospitalized for an AECOPD 33.3% died within 1 year stressing the risk for this specific population. This number is in line with the risk of death presented in a recent review on predictors of mortality in hospitalized patients with an AECOPD.[27] According to this review the risk of death was 3.6% for short-term mortality (not more than 90 days after exacerbation) and 31.0% for long-term mortality (between 90 days and 2 years after exacerbation). Meeting $\geq$ 2 criteria of the set of indicators was not associated with a risk of readmission for an AECOPD within 8 weeks. There is a considerable variability in exacerbation susceptibility between patients with COPD.[34] A history of COPD exacerbations showed to be the best predictor of future events independent of the severity of airflow limitation.[35] It has been assumed that some patients with a distinct and stable COPD phenotype are at high risk of recurrent exacerbations.[35] However, it seems that our set of indicators did not select this COPD phenotype and therefore was not able to make a distinction between patients with infrequent and frequent exacerbations. Nevertheless, in this small sample the majority of patients with early readmission seems also to be selected by our criteria.

### Strengths and limitations

This is the first time that the use of a set of indicators for proactive palliative care in COPD was examined in order to be used in a prospective study. Still, some considerations, concerning the external validity and the statistical power, need to be addressed. This pilot study was performed in an academic hospital. Mortality rates have shown to be higher in academic hospitals than in general hospitals.[36] We therefore expect that in general hospitals the percentage of patients hospitalized for an AECOPD who have a poor prognosis will be less and as a consequence the percentage of those patients who die within 1 year will be less too. Furthermore, in this pilot study a small sample size was used which may have resulted in less statistical power to detect an effect. However, this pilot study was performed to get an indication of the applicability in practice of a set of indicators in advance of a prospective study. The results of such a study will prove the actual characteristics and prognostic value of the set of indicators for proactive palliative care. Thereafter it will be decided which indicators have to be included into the final tool.

## CONCLUSIONS

In a prospective study, it seems feasible to use a set of indicators for proactive palliative care in patients with COPD in a prospective study. The three indicators that were not documented, being an answer to the surprise question, the CCQ and MRC dyspnea, are tools mainly used for clinical trials and less in usual care. They will specifically be requested in the prospective trial. Three out of four patients hospitalized for an AECOPD had a poor prognosis according to our set of indicators. Besides, meeting $\geq$ 2 criteria of the set of indicators was associated with risk of mortality within 1 year. The sensitivity of the set of indicators in predicting mortality within 1 year was 100% and the specificity 31.8%. For a prospective study this suggests that the risk of missing patients with COPD in need of proactive palliative care is small. Which indicators will be included into the final tool will depend on the outcomes of the prospective study.

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# Proactive Palliative Care for Patients with COPD (PROLONG): A Pragmatic Cluster Controlled Trial

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## ABSTRACT

**Background and aim:** Patients with advanced Chronic Obstructive Pulmonary Disease (COPD) have poor quality of life. We assessed the effects of proactive palliative care on the well-being of these patients.

**Trial registration:** This trial is registered with the Netherlands Trial Register, NTR4037.

**Patients and methods:** A pragmatic cluster controlled trial (quasi-experimental design) was performed with hospital as cluster (3 intervention, 3 control) and a pre-trial assessment. Hospitals were selected for the intervention condition based on the presence of a specialized palliative care team (SPCT). To control for confounders a pre-trial assessment was performed in which hospitals were compared on baseline characteristics. Patients with COPD with poor prognosis were recruited during hospitalization for acute exacerbation. All patients received usual care while patients in the intervention condition received additional proactive palliative care in monthly meetings with an SPCT. Our primary outcome was change in quality of life score after 3 months, which was measured using the St George Respiratory Questionnaire (SGRQ). Secondary outcomes were, among others, quality of life at 6, 9 and 12 months; readmissions; survival; and having made advance care planning (ACP) choices. All analyses were by intention-to-treat.

**Results:** During the year 2014, 228 patients were recruited (90 intervention, 138 control) and at 3 months, 163 patients (67 intervention, 96 control) completed the SGRQ. There was no significant difference in change scores of the SGRQ total at 3 months between groups (-0·79 [95% CI -4·61 to 3·34], p=0·70). However, patients who received proactive palliative care experienced less impact of their COPD (SGRQ impact subscale) at 6 month (-6·22 [-11·73 to -0·71], p=0·04), and had more often made ACP choices (adjusted odds ratio 3·26 [1·49 to 7·14], p=0·003). Other secondary outcomes were not significantly different.

**Conclusion:** Proactive palliative care did not improve overall quality of life of patients with COPD. However, patients more often made ACP choices which may lead to better quality of care towards the end of life.

**Keywords:** COPD, Proactive palliative care, Quality of life, Advance care planning, Readmission, Survival

# INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death worldwide and caused 3.1 million deaths (5.6% of total deaths) in 2012.[1,2] This progressive life-threatening lung disease has an unpredictable course characterized by episodes of gradual decline punctuated by acute severe exacerbations.[3] After the first hospitalization for an acute exacerbation of COPD (AECOPD), 50% of patients die within 3.6 years.[4] Patients with advanced COPD have a high symptom burden, including breathlessness, fatigue, cough, and anxiety.[5] Their quality of life is poor and often even worse than patients with lung cancer.[6]

Early or proactive palliative care can improve quality of life of patients with cancer,[7-9] and heart failure.[10,11] This kind of care is not restricted to end-of-life care but can be delivered earlier in the disease course by anticipating on wishes and needs of patients, in order to prevent and relief suffering from problems in the physical, psychosocial, and spiritual domain. [2] Patients with lung cancer receiving proactive palliative care even had longer survival while receiving less aggressive treatments.[8] Prolonged survival has also been observed in patients with refractory breathlessness (cancer, COPD, chronic heart failure, and interstitial lung disease).[12] In this study of Higginson et al, early introduction of a palliative breathlessness support service improved breathlessness mastery, a quality of life domain of the Chronic Respiratory Disease Questionnaire.[12] Although proactive palliative care has been shown to improve quality of life and prolong survival of patients with various life-threatening diseases, it is still not common for patients with COPD to receive this care.[13] Since little is known about the effects of proactive palliative care in COPD, research is needed to be able to improve care for this patient group.[13]

We report a pragmatic cluster controlled trial of proactive palliative care in patients with COPD. A cluster design was chosen to prevent contamination and to minimize ethical concerns of patients and clinicians with respect to randomization and gate keeping. We hypothesized that patients with COPD who received proactive palliative care integrated with usual care compared to patients who received usual care only would have better quality of life, lower levels of psychological distress, fewer and shorter hospital admissions for an AECOPD, prolonged survival, and that receiving proactive palliative care would increase the number of patients with whom advance care planning (ACP) choices were made.

# METHODS

## Study design

A pragmatic cluster controlled trial (quasi-experimental design) was performed in the Netherlands with general hospital as cluster (3 control, 3 intervention). Patients were recruited between Jan 6, 2014 - Jan 8, 2015, and each patient was followed for 1 year. Hospitals were selected for the intervention condition based on the presence of a specialized palliative care team (SPCT). A pre-trial assessment was performed to be able to control for confounders on hospital level. All outcome measures were on patient level.

## Participants

Patients with COPD, 18 years or older, who had a hospital admission for an AECOPD were considered for the PROLONG study.[14] Patients were excluded if they could not speak Dutch, had severe cognitive disorders or if they were being treated by an SPCT at the moment of inclusion. The attending pulmonologist selected and approached potential participants. Exclusion because of severe cognitive disorder was based on judgment of the pulmonologist. If the patient agreed to participate, an informed consent was signed. For the intervention study described here, only patients with poor prognosis were regarded. To identify these patients, the pulmonologist completed a standard checklist consisting of a set of 11 indicators derived from the literature.[14] If meeting two or more indicators the patient was considered to have a poor prognosis and eligible to participate in the study. The set of indicators of poor prognosis are presented in Table 1.[15,16]

The study protocol was approved by the Medical Ethics Committee (METC) of the Radboud University Medical Center, Nijmegen (METC protocol number 2012/260). Thereafter, research approval was received in all participating hospitals. Our protocol followed CONSORT recommendations,[14] but there were two protocol deviations. First, patients participating in other COPD-related studies were withdrawn from the intention-to-treat analysis from the moment they entered the other study. Second, patients who signed the informed consent but died in hospital during inclusion were also excluded as the pulmonologist was not able to complete the checklist because it consisted of indicators for post-hospital mortality. A comprehensive description of the methods is given in the published protocol.[14]

**Table 1** Set of indicators for proactive palliative care

| | **A patient hospitalized for AECOPD is eligible for proactive palliative care when meeting $\geq$2 of the following indicators:** |
|---|---|
| 1. | Hypoxaemia (PaO2 < 8 kPa) or hypercapnia (PaCO2 > 6 kPa) at discharge |
| 2. | Treatment of the exacerbation with Non Invasive Ventilation (NIV) |
| 3. | Patient needs professional home care service for personal care after discharge |
| 4. | Negative answer to the surprise question:<br>'Would I (as lung specialist) be surprised if this patient would have a subsequent readmission for AECOPD within 8 weeks and/or would die in the next year? |
| 5. | The diagnosis of a severe co-morbidity such as:<br>a. Non-curable malignancy or<br>b. Cor pulmonale (proven or non proven) or<br>c. Proven Chronic Heart Failure (CHF) or<br>d. Diabetes mellitus with neuropathy or<br>e. Renal failure, clearance < 40 (GFR: in ml/min) |
| 6. | CCQ total, day version > 3 |
| 7. | MRC dyspnea = 5 |
| 8. | FEV1 (measured before AECOPD) < 30% of predicted |
| 9. | BMI < 21 or unplanned weight loss (> 10% in last 6 months or > 5% in last month) |
| 10. | Previous hospital admissions for AECOPD (last 2 years $\geq$ 2 and/or last year $\geq$ 1) |
| 11. | Age > 70 years |

**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; BMI, body mass index; CCQ, Clinical COPD Questionnaire; FEV1, forced expiratory volume in 1 second; GRF, glomerular filtration rate; kPa, kilopascal; MRC dyspnea, Medical Research Council dyspnea questionnaire; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide.

## Randomization

A cluster design was chosen to prevent contamination and to minimize ethical concerns of patients and clinicians with respect to randomization and gate keeping. Contamination would certainly have taken place because our intervention involved a close cooperation between pulmonary team and SPCT. At the time of hospital recruitment, a minority of hospitals in the Netherlands had the availability of an SPCT. Since only four hospitals with an SPCT were willing to participate, it was not possible to create comparable groups through randomization in our trial. Instead we performed a pragmatic cluster controlled trial (quasi-experiment), in which three hospitals with an SPCT were selected for the intervention and three hospitals without an SPCT for the control condition. To control for confounders on hospital level a pre-trial assessment was performed in which hospitals were compared on baseline characteristics over the year before trial (number of hospitalizations and hospitalization days for AECOPD per patient, and percentage of patients hospitalized for an AECOPD who died in hospital). All outcome measures were on patient level and patients performed a pre and post intervention measurement.

The study was single-blinded. Clinicians were aware of treatment allocation, while patients were unaware of the existence of another group.

## Interventions

All patients received usual care. In the intervention condition patients received additional proactive palliative care from an SPCT. Patients had a first consultation with the SPCT during the initial hospitalization, or the latest within 1 week after hospital discharge. Thereafter, the SPCT had monthly meetings with the patient in the outpatient setting, preferably face to face but alternatively by telephone, for 1 year or until death.

Since delivering proactive palliative care for patients with COPD was not common for members of the SPCTs, they received a training, aimed at the specific problems in this patient group, which was provided by academic palliative care professionals of the Radboud University Medical Center, Nijmegen. Training was based on the specific guidelines for palliative care in COPD,[17] and consisted of two three-hour meetings. The first meeting took place in the month before trial and the second during the first month of trial. The training consisted of the following topics: how to communicate future care planning and end-of-life aspects with the patients and their families; how to create a patient-tailored proactive palliative care plan; how to proactively anticipate on illness- and death scenarios; how to organize transfer of care to the pulmonologist and general practitioner (GP); and how to perform a proactive palliative care plan in cooperation with the pulmonologist.

## Data collection

Data collection took place using questionnaires completed by the patients, and by retrospectively collecting data from their medical files over the trial period (see Table 2).[18-21]

ACP choices documented in medical files were defined as agreements about: Not To Be Resuscitated (NTBR) policy, Intensive Care Unit (ICU) admission, palliative dyspnea treatment, palliative sedation, treatment of future infections with antibiotics (AB), and preferred place of death. Those ACP choices were our objective outcome measures which served as a proxy for measuring whether ACP conversations had taken place.

### *Outcomes*

The primary outcome was change in quality of life from baseline after 3 months measured with the St George Respiratory Questionnaire (SGRQ). Secondary questionnaire outcomes were change of the SGRQ from baseline after respectively 6, 9, and 12 months and change of the McGill Quality of Life questionnaire (McGill) and the Hospital Anxiety and Depression Scale (HADS) from baseline after respectively 3, 6, 9, and 12 months. Secondary outcomes retrospectively retrieved from the medical files of the patients over the trial period are presented in Table 2.

**Table 2** Overview of data collection per time point

| Data collection | B | 3 m | 6 m | 9 m | 12 m | R |
|---|---|---|---|---|---|---|
| **Questionnaires:** | | | | | | |
| **Demographic questionnaire**<br>(age, pack years, sex, marital status, place and groups of living and education) | X | | | | | |
| **SGRQ** (COPD quality of life questionnaire)<br>(symptoms, activities and impacts subscales) | X | X | X | X | X | |
| **McGill** (palliative quality of life questionnaire)<br>(phys symptoms, phys and psych well-being, existential and support subscales) | X | X | X | X | X | |
| **HADS** (psych well-being questionnaire)<br>(anxiety and depression subscales) | X | X | X | X | X | |
| **Medical files (information over the 1 year trial period):** | | | | | | |
| Number of readmissions to hospital | | | | | | X |
| Number of readmissions to hospital for AECOPD | | | | | | X |
| Date of first readmission for AECOPD | | | | | | X |
| Number of days of readmission to hospital for AECOPD | | | | | | X |
| Choices of ACP documented in the medical file at baseline | | | | | | X |
| Choices of ACP documented in the medical file after one year or at death | | | | | | X |
| Did the patient die within one year after inclusion? | | | | | | X |
| Date of death | | | | | | X |

**Note:** X's indicate the times that that type of data was collected.

**Abbreviations:** ACP, advance care planning; AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; B, baseline; HADS, Hospital Anxiety and Depression Scale;[21] m, month; McGill, McGill quality of life questionnaire;[20] phys, physical; psych, psychological; R, retrospectively; SGRQ, St George Respiratory Questionnaire[18,19].

## Statistical analysis

Based on our primary outcome, change in quality of life measured with the SGRQ from baseline after 3 months, we estimated that 64 patients were needed in each arm to detect a mean difference of 9 (SD 16) with a p value of 0.05 at a power of 80%.[22] To adjust for clustering at hospital level (Intraclass Correlation Coefficient (ICC)=0.01, three hospitals per arm) and to allow for an additional loss to follow up of 10% a total of 86 patients were required in each arm.

We used the valid CASTOR data management system to ensure Good Clinical Practice.[23] Data were analyzed using R software, version 3.1.2. Frequencies, means and standard deviations were used to describe the study variables. Linear mixed models with a random intercept for hospitals to account for clustering were used to study the effects of proactive palliative care on the primary and secondary outcomes. The models contained an adjustment for baseline scores of which selection was based on theoretical background and differences between groups at baseline. The analysis followed the principle of intention-to-treat. Missing data were handled using available case analysis.

Survival was plotted using the Kaplan-Meier method. We calculated survival rates until 365 days from enrolment in both groups. A Cox proportional-hazard test was used to assess the effect of proactive palliative care on survival with adjustment for baseline characteristics. Again, mixed models with a random intercept for hospitals were used.

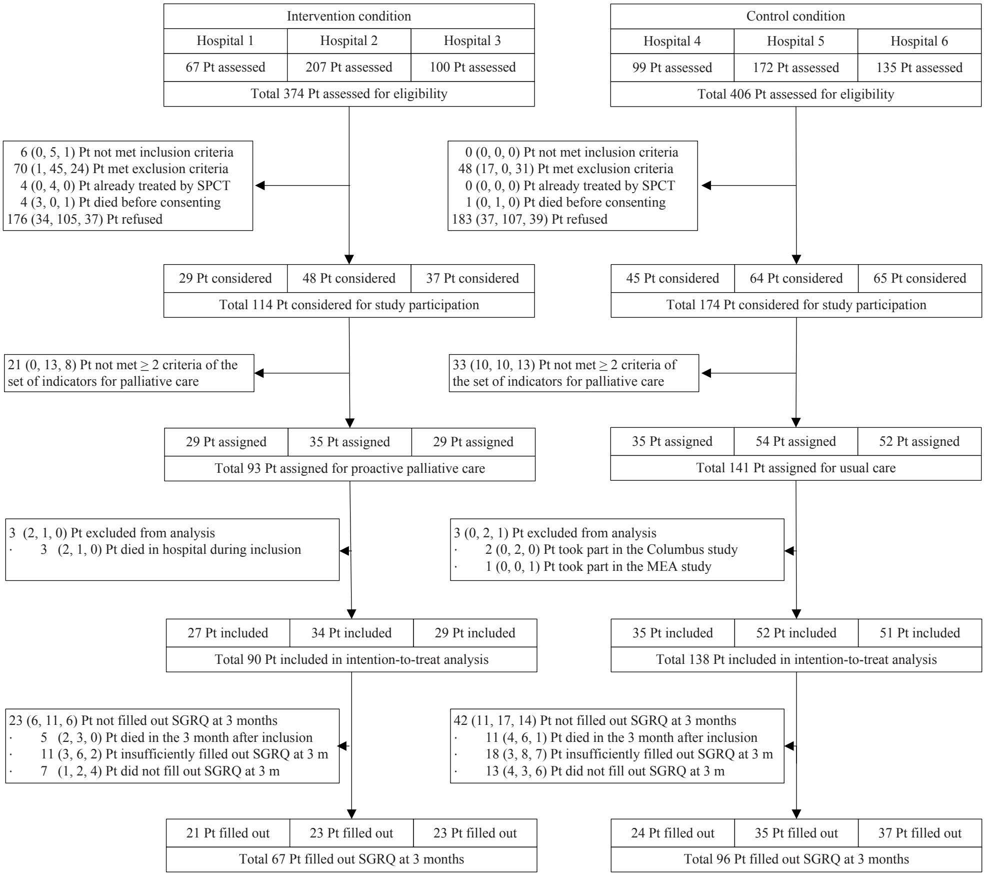


**Figure 1** Trial profile.

**Abbreviations:** m, months; Pt, patient; SGRQ, St George Respiratory Questionnaire; SPCT, specialized palliative care team.

## RESULTS

In six general hospitals, 780 patients were screened, of whom 228 (90 intervention, 138 control) were included in the intention-to-treat analysis (see Figure 1).

Baseline characteristics at hospital level over the year before trial (2013) are presented in Table 3. Tables 4 and 5 respectively show the demographics and baseline characteristics of the study population. In the intervention condition, compared to the control condition, more patients had severe dyspnea scores, were living alone, and were suffering from CHF. No substantial differences were seen between groups on baseline outcome measures.

Important change scores relative to baseline and the associated tests of effects between groups are presented in Table 6.[24] The outcomes of the McGill and HADS subscales are presented in the supplement. In the linear mixed models the baseline scores on patient level adjusted for were: baseline questionnaire score, sex, condition of living, level of education, packyears, MRC dyspnea score, forced expiratory volume in 1 second percentage of predicted value ($FEV_1$%), presence of comorbidity, number of indicators met, and number of admissions for AECOPD in the previous 2 years. To account for differences at baseline on hospital level we also adjusted for number of hospitalizations AECOPD per patient in the year before the trial (2013).

Incorrectly filled out questions were noticed at the McGill physical symptoms subscale. In an open text field, patients had to describe a troublesome physical symptom and indicate its seiousness on a visual analogue scale (VAS). This question proved to be subject to misinterpretation. Patients often listed not a physical symptom but a disease (eg diabetes), or a complaint of other origin (eg snoring partner). To prevent from too many missing values, we calculated the McGill total score by taking the mean of the remaining four of the five subscales.

**Table 3** Baseline characteristics at hospital level over the year before trial (2013)

| Characteristics | Intervention condition | | | | Control condition | | | |
|---|---|---|---|---|---|---|---|---|
| | Hospital 1 | Hospital 2 | Hospital 3 | Mean | Hospital 4 | Hospital 5 | Hospital 6 | Mean |
| Hospitalizations AECOPD per patient (n) | 1.32 | 1.60 | 1.24 | 1.39 | 1.23 | 1.51 | 1.21 | 1.32 |
| Hospitalization days for AECOPD per patient (n) | 9.21 | 10.58 | 10.15 | 9.98 | 9.30 | 12.32 | 10.43 | 10.68 |
| Patients with AECOPD who died in hospital (n) | 0.08 | 0.07 | 0.07 | 0.073 | 0.06 | 0.12 | 0.06 | 0.08 |

**Abbreviations:** AECOPD, acute exacerbation of Chronic Obstructive Pulmonary Disease.

**Table 4** Demographics of the intention-to-treat population

| **Demographics** | **Overall (n=228)** | **Intervention condition (n=90)** | **Control condition (n=138)** |
|---|---|---|---|
| **Age** | 68.54 (9.34) | 68.67 (9.08) | 68.45 (9.54) |
| **Pack years** | 40.00 (31.76) | 41.58 ((28.95) | 38.92 (33.62) |
| **Sex** | | | |
| Male | 110 (48.2%) | 46 (51.1%) | 64 (46.4%) |
| **Marital status** [a] | | | |
| Unmarried | 16 (7.0%) | 5 (5.6%) | 11 (8.0%) |
| Married | 145 (63.6%) | 51 (56.7%) | 94 (68.1%) |
| Divorced | 25 (11.0 %) | 12 (13.3%) | 13 (9.4%) |
| Widowed | 39 (17.1%) | 22 (24.4%) | 17 (12.3%) |
| **Living situation** [a] | | | |
| Single | 71 (31.1%) | 36 (40.0%) | 35 (25.4%) |
| Non single | 145 (63.6%) | 49 (54.4%) | 96 (69.6%) |
| **Place of living** [a] | | | |
| Home, independent of homecare | 144 (63.2%) | 60 (66.7%) | 84 (60.9%) |
| Home, dependent of homecare | 74 (32.5%) | 27 (30.0%) | 47 (34.1%) |
| Residential home | 3 (1.3%) | 1 (1.1%) | 2 (1.4%) |
| Nursing home | 1 (0.4%) | 1 (1.1%) | 0 (0%) |
| **Highest level of education** [a] | | | |
| No education | 2 (0.9%) | 1 (1.1%) | 1 (0.7%) |
| Elementary school | 38 (16.7%) | 16 (17.8%) | 22 (15.9%) |
| Secondary school | 57 (25.0%) | 18 (20.0%) | 39 (28.3%) |
| Primary education | 45 (19.7%) | 17 (18.9%) | 28 (20.3%) |
| Secondary education | 57 (25.0%) | 30 (33.3%) | 27 (19.6%) |
| Higher/University education | 23 (10.1%) | 8 (8.9%) | 15 (10.9%) |

**Notes:** Data are given as n (%) or mean (SD). [a] Because of missing values, some numbers do not add up to 100%.

The primary outcome of change scores in SGRQ total at 3 months did not differ significantly between groups (mean observed change score in intervention condition -1.84 (SD 12.20) vs control condition 0.20 (12.05), p=0.70.

There was a significant difference between groups in the change scores of the impact subscale of the SGRQ at 6 months (-5.73 (16.21) vs 0.86 (18.73), p=0.04). We also noted a significant difference between groups in number of patients that made ACP choices during the year of trial (76.7% vs 59.4%, adjusted OR 3.26 [95% CI 1.49 to 7.14], p=0.003). Of the 36.8% of patients (30.0% intervention, 41.3% control) who had not made ACP choices at baseline, 85.7% (100% intervention, 78.9% control) made ACP choices within the next year. Whereas, of the 63.2% of patients (70.0% intervention, 58.7% control) who had already made ACP choices at baseline, 54.9% (66.7% intervention, 45.7% control) made additional ACP choices within the next year. All other secondary outcome measures were not significantly different between groups. One year after enrolment 52 patients with poor prognosis (22.8%) had died. The Kaplan Meier curve is presented in Figure 2. The Cox proportional-hazard test showed that survival was not significantly different between groups (adjusted HR 0.74 [95% CI 0.34 to 1.62], p=0.45).

## DISCUSSION

This is the first study to explore the effects of proactive palliative care in a large group of patients with COPD with poor prognosis (n=228). We did not find an effect on our primary outcome: the change in quality of life measured using the SGRQ from baseline to 3 months was not different between groups. However, patients receiving proactive palliative care experienced less impact of their COPD (SGRQ impact subscale) at 6 months than patients receiving usual care. The change in symptoms and activity level (SGRQ symptoms and activity subscale) were not different between groups at 3, 6, 9, and 12 months. Moreover, there was a relevant difference in number of patients that made ACP choices during the year of trial, in favor of the intervention condition. We did not find a difference in other questionnaire outcomes, nor in number and length of hospital admissions or in survival between groups.

**Table 5** Baseline characteristics of the intention-to-treat population

| **Characteristics** | **Overall (n=228)** | **Intervention condition (n=90)** | **Control condition (n=138)** |
|---|---|---|---|
| **Clinical characteristics** | | | |
| FEV$_1$ (l) | 1.07 (0.49) | 1.05 (0.47) | 1.08 (0.50) |
| Predicted FEV$_1$ (%) | 42.51 (18.87) | 40.79 (16.09) | 43.70 (20.55) |
| VC (l) | 2.60 (0.82) | 2.63 (0.83) | 2.58 (0.82) |
| Predicted VC (%) | 79.84 (20.67) | 79.75 (21.90) | 79.90 (19.89) |
| **GOLD stage** [a] [b] | | | |
| 0 | 10 (4.4%) | 4 (4.4%) | 6 (4.3%) |
| I | 7 (3.1%) | 2 (2.2%) | 5 (3.6%) |
| II | 51 (22.4%) | 16 (17.8%) | 35 (25.4%) |
| III | 87 (38.2%) | 43 (47.8%) | 44 (31.9%) |
| IV | 63 (27.6%) | 24 (26.7%) | 39 (28.3%) |
| **Comorbidity** | | | |
| Non-curable Malignancy | 12 (5.3%) | 8 (8.9%) | 4 (2.9%) |
| Cor pulmonale | 12 (5.3%) | 3 (3.3%) | 9 (6.5%) |
| CHF | 16 (7.0%) | 11 (12.2%) | 5 (3.6%) |
| DM with neuropathy | 9 (3.9%) | 2 (2.2%) | 7 (5.1%) |
| Renal failure | 13 (5.7%) | 2 (2.2%) | 11 (8.0%) |
| Comorbidity total | 58 (25.4%) | 24 (26.7%) | 34 (24.6%) |
| **Hospitalization for AECOPD in previous 2 year (n)** | 1.95 (2.57) | 2.28 (3.1) | 1.73 (2.14) |
| **Indicators met (n)** | 4.35 (1.64) | 4.42 (1.51) | 4.30 (1.72) |
| **MRC dyspnea** [a] | | | |
| 0 | 4 (1.8%) | 3 (3.3%) | 1 (0.7%) |
| 1 | 6 (2.6%) | 3 (3.3%) | 3 (2.2%) |
| 2 | 6 (2.6%) | 1 (1.1%) | 5 (3.6%) |
| 3 | 31 (13.6%) | 5 (5.6%) | 26 (18.8%) |
| 4 | 44 (19.3%) | 15 ((16.7%) | 29 (21.0%) |
| 5 | 134 (58.8%) | 63 (70.0%) | 71 (51.5%) |
| **CCQ Total** | 3.45 (0.97) | 3.48 (0.88) | 3.44 (1.03) |
| **Outcome measures** | | | |
| **SGRQ total score** | 68.12 (14.43) | 69.00 (13.37) | 67.50 (15.15) |
| SGRQ symptoms score | 69.80 (17.39) | 70.93 (15.06) | 69.06 (18.78) |
| SGRQ activity score | 86.84 (13.65) | 87.38 (13.61) | 86.47 (13.72) |
| SGRQ impacts score | 57.57 (19.56) | 58.16 (18.77) | 57.16 ((20.13) |
| **McGill total score** | 5.16 (1.18) | 5.06 (0.98) | 5.25 (1.31) |
| McGill physical well-being | 4.03 (2.26) | 4.28 (2.28) | 3.87 (2.23) |
| McGill physical symptoms | 3.08 (1.84) | 2.91 (1.77) | 3.21 (1.89) |
| McGill psychological | 5.82 (2.61) | 5.92 (2.60) | 5.76 (2.63) |
| McGill existential | 5.55 (1.67) | 5.61 (1.47) | 5.51 (1.80) |
| McGill support | 7.39 (1.91) | 7.61 (1.63) | 7.24 (2.07) |
| **HADS total score** | 16.87 (7.80) | 16.48 (7.88) | 17.13 (7.78) |
| HADS anxiety | 8.78 (4.48) | 8.75 (4.53) | 8.80 (4.47) |
| HADS depression | 8.12 (4.29) | 7.74 (4.12) | 8.37 (4.40) |

**Notes:** Data are given as n (%) or mean (SD). [a] Because of missing values some numbers do not add up to 100%. [b] GOLD stage according to last known data in medical file; inclusion in study based on judgment pulmonologist.

**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; CCQ, Clinical COPD Questionnaire; CHF, Congestive Heart Failure; DM, Diabetes Mellitus; $FEV_1$, forced expiratory volume in 1 second; GOLD, Global initiative on Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Scale; MRC dyspnea, Medical Research Council dyspnea questionnaire; SGRQ, St George Respiratory Questionnaire; McGill, McGill quality of life questionnaire; VC, vital capacity.

There are several possible reasons at the level of identification, organization, patient, outcome measure, and disease course that may explain the failure to show an improvement of quality of life in patients with COPD by means of proactive palliative care in our study. First, 22.8% of patients identified as having a poor prognosis died; it is possible that our criteria for poor prognosis were too broad. Second, patients with advanced COPD are often homebound until they enter an acute phase with hospitalization.[25] Continuity of palliative care can therefore only be achieved with a coordinated, multidisciplinary care approach.[26] This requires collaboration between primary and secondary health care professionals. Although GPs were informed about the intervention and the SPCT was encouraged to collaborate with GPs, it is unknown to what extent this occured. Third, patients with COPD generally have a lower Social Economic Status (SES), i.e. on average a lower level of education and less financial means compared to other patient groups.[27] These aspects have an impact on COPD health outcomes.[27] Indeed, some patients in our study had difficulties understanding certain questions, which resulted in the return of incomplete questionnaires. Besides, some patients lacked financial means to afford transportation to the hospital, physical therapy, or even a walker. Fourth, for some patients with advanced COPD, filling in questionnaires may have been too demanding. Although all enrolled patients did consent to fill out questionnaires, about one out of five patients did not fully complete or return them. Incomplete data collection in advanced COPD has also been reported before.[28,29] Perhaps in this population the use of a qualitative instead of a quantitative approach is preferable for measuring changes in patient-reported outcomes.[28] Finally, there are differences in the palliative trajectory between patients with cancer and those with COPD. The palliative trajectory of COPD is less predictable since episodes of gradual decline are punctuated by acute severe exacerbations;[3] therefore, these acute exacerbations may have influenced findings defined at fixed time points.

Patients who received proactive palliative care experienced less impact of their COPD at 6 months. Although this may have been a chance finding, as it was a secondary outcome, merely an effect on the SGRQ impact subscale was also observed in the Glasgow supported self-management trial for patients with moderate to severe COPD.[29] Also Higginson and colleagues found no effect on quality of life from early introduction of a palliative breathlessness support service for patients with refractory breathlessness (including COPD), but they did find improved breathlessness mastery, a quality of life domain of the Chronic Respiratory Disease Questionnaire.[12] In contrast

**Table 6** Change scores relative to baseline of the primary outcome (SGRQ Total at 3 months) and secondary outcomes and associated tests of effects between groups

| **Outcomes** | **Descriptives Intervention** | | **Control** | | **Analysis of difference between groups for changes over time** [a] | | |
|---|---|---|---|---|---|---|---|
| | **n** | **Mean observed change from baseline (SD** | **n** | **Mean observed change from baseline (SD)** | **Estimated difference (95% CI)** | **Effect size** [b] | **p value** |
| **SGRQ Total** [f] | | | | | | | |
| 3 months | 62 | -1.84 (12.20) | 88 | 0.20 (12.05) | -0.79 (-4.61 to 3.34) | 0.17 | 0.70 |
| 6 months | 55 | -4.66 (12.09) | 70 | -1.64 (13.11) | -2.20 (-6.63 to 2.22) | 0.24 | 0.36 |
| 9 months | 53 | -3.94 (11.34) | 69 | 0.29 (11.90) | -4.26 (-8.55 to 0.03) | 0.36 | 0.07 |
| 12 months | 45 | -2.88 (13.14) | 63 | -0.50 (12.48) | -1.70 (-6.71 to 3.32) | 0.19 | 0.54 |
| **SGRQ Symptoms** [f] | | | | | | | |
| 3 months | 72 | -4.34 (15.79) | 109 | -6.78 (20.92) | 3.62 (-1.71 to 9.01) | -0.13 | 0.21 |
| 6 months | 65 | -6.17 (17.41) | 86 | -4.40 (19.77) | -0.54 (-6.27 to 5.20) | 0.09 | 0.86 |
| 9 months | 59 | -6.08 (19.88) | 85 | -6.37 (20.70) | -0.47 (-6.78 to 5.85) | -0.01 | 0.89 |
| 12 months | 53 | -5.55 (18.34) | 77 | -6.88 (20.90) | 3.77 (-4.72 to 12.25) | -0.07 | 0.49 |
| **SGRQ Activity** [f] | | | | | | | |
| 3 months | 63 | -1.74 (14.88) | 91 | -0.37 (10.92) | 0.31 (-3.40 to 4.01) | 0.11 | 0.87 |
| 6 months | 57 | -2.60 (12.67) | 77 | -1.78 (12.22) | 0.83 (-2.96 to 4.61) | 0.07 | 0.69 |
| 9 months | 57 | -2.03 (11.92) | 77 | 0.17 (11.25) | -0.70 (-4.34 to 2.95) | 0.19 | 0.72 |
| 12 months | 47 | -2.45 (12.45) | 70 | -0.44 (11.86) | -2.06 (-6.10 to 1.98) | 0.17 | 0.35 |
| **SGRQ Impact** [f] | | | | | | | |
| 3 months | 73 | -2.10 (15.94) | 107 | 0.10 (19.42) | -2.69 (-7.62 to 2.24) | 0.12 | 0.31 |
| 6 months | 63 | -5.73 (16.21) | 85 | 0.86 (18.73) | -6.22 (-11.73 to -0.71) | 0.37 | 0.04 |
| 9 months | 59 | -4.36 (14.58) | 81 | 1.24 (16.53) | -5.30 (-10.71 to 0.11) | 0.36 | 0.07 |
| 12 months | 51 | -1.27 (18.24) | 78 | 0.25 (20.74) | -2.78 (-9.49 to 3.93) | 0.08 | 0.45 |
| **McGill Total** [c g] | | | | | | | |
| 3 months | 60 | 0.08 (1.62) | 79 | 0.13 (1.73) | 0.26 (-0.30 to 0.83) | 0.03 | 0.43 |
| 6 months | 51 | -0.04 (1.50) | 70 | -0.10 (1.59) | 0.22 (-0.24 to 0.69) | -0.04 | 0.38 |
| 9 months | 44 | 0.05 (1.49) | 62 | -0.22 (1.56) | 0.14 (-0.45 to 0.73) | -0.18 | 0.71 |
| 12 months | 44 | -0.17 ((1.55) | 56 | -0.23 (1.65) | 0.30 (-0.40 to 1.00) | -0.04 | 0.44 |
| **HADS Total** [f] | | | | | | | |
| 3 months | 76 | 0.22 (6.81) | 112 | 0.27 (6.30) | -0.29 (-2.19 to 1.61) | 0.01 | 0.78 |
| 6 months | 66 | 0.46 (7.20) | 90 | 0.39 (6.43) | -0.28 (-2.39 to 1.83) | -0.01 | 0.81 |
| 9 months | 62 | -0.01 (7.20) | 87 | 0.33 (6.50) | -0.49 (-2.92 to 1.94) | 0.05 | 0.71 |
| 12 months | 55 | 0.85 (6.99) | 81 | 1.50 (6.62) | -1.01 (-3.52 to 1.51) | 0.10 | 0.46 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Readmissions for AECOPD (n)** | 90 | 1.72 (1.76) | 135 | 1.65 (2.00) | -0.08 (-0.39 to 0.23) [e] | 0.04 | 0.62 |
| **Days of readm for AECOPD (n)** | 62 | 20.27 (18.12) | 91 | 17.57 (14.27) | 0.07 (-0.25 to 0.39) [d] | 0.17 | 0.57 |
| | **n** | **No (%)** | **n** | **No (%)** | **Adjusted OR (95% CI)** | | **p value** |
| **Patients who made ACP choices** | 90 | 69/90 (76.7%) | 138 | 82/138 (59.4%) | 3.26 (1.49 to 7.14) | NA | 0.003 |
| | **n** | **No (%)** | **n** | **No (%)** | **Adjusted HR (95% CI)** | | **p value** |
| **Patients who died** | 90 | 20/90 (22.2%) | 138 | 32/138 (23.7%) | 0.74 (0.34 to 1.62) | NA | 0.45 |

**Notes:** Associated tests of effects between groups were estimated by linear mixed models, adjusted for baseline covariates. Analyses were by intention-to-treat. Missing data were handled using available case analysis. Descriptive data are mean (SD) unless otherwise stated. The ICC's of the questionnaire outcome measures were all very small near 0 or 0 and therefore not displayed. [a] Associated tests of effects between groups were estimated by linear mixed models, adjusted for baseline covariates. [b] Effect sizes are Cohen's d, 0.20 is small, 0.50 is moderate, and 0.80 is large.[24] [c] McGill Total score was calculated without the McGill physical symptoms subscale. [d] Because of skewness of distribution a logarithm of the variable 'number of days of readmission for AECOPD' was used. [e] Negative binomial regression analysis. [f] Change score interpretation: low score better. [g] Change score interpretation: high score better.

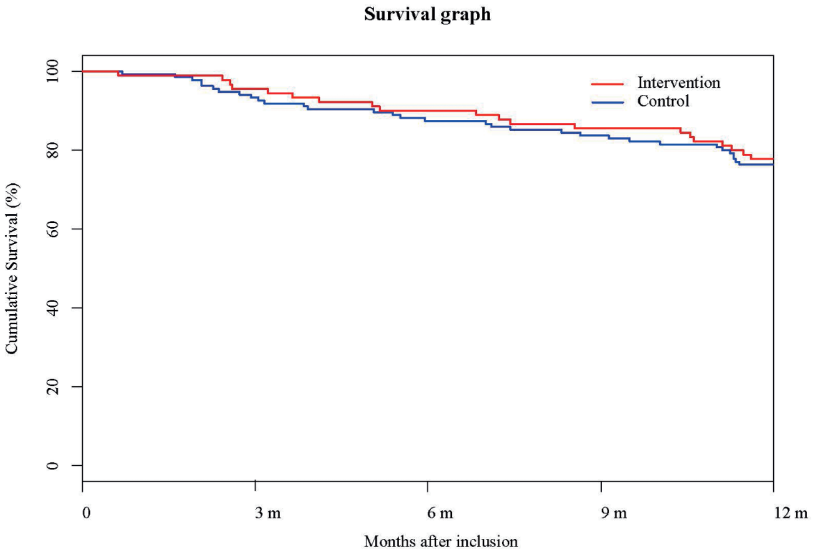
**Abbreviations:** ACP, advance care planning; AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; ICC, intraclass correlation coefficient; McGill, McGill quality of life questionnaire; OR, odds ratio; SD, standard deviation; SGRQ, St George Respiratory Questionnaire.

to patients with cancer in the palliative trajectory, for patients with advanced COPD in the palliative trajectory disease oriented care remains necessary until the last weeks of life. It is possible that resilience to improve overall quality of life (especially symptoms and activity) is exhausted in this patient group, but further research is needed to test this hypothesis.

We did not find a difference in number and length of hospital readmissions. Previous research has demonstrated that the frequency of readmissions for an AECOPD is associated with functional limitation and poor health-related quality of life.[30] The fact that there was no change in either of the conditions (SGRQ activity score and SGRQ total) between groups may explain our finding. Furthermore, post-discharge mortality is associated with COPD severity as well as specific comorbidities, especially cardiac disease.[30] More patients in the intervention compared to the control condition had severe dyspnea scores and CHF; however, we controlled for these confounders and found no difference in 1 year survival between groups.

During ACP conversations, patients are informed about their diagnosis, prognosis, their treatment options and treatment consequences. Besides, patients can express their values and preferences for life-sustaining treatments with the goal of improving the quality of their end-of-life care.[31] In our study more patients in the intervention condition made ACP choices and consequently had ACP conversations during the year. As follow up of patients was too short, we were not able to confirm earlier findings that those ACP conversations actually increased the quality of end-of-life care.[32,33] Further research is needed.

Our study has strengths and limitations. Although our pragmatic cluster controlled design completely ruled out contamination, this design was subject to selection bias at hospital level. However, by using outcomes of a pre-trial assessment we were able to control for confounders at hospital level. Besides, the small ICCs indicate that differences between hospitals not noteworthy contributed to the concerned study outcomes. Next, pulmonologists were aware of treatment allocation which may have caused bias. Our baseline data suggest that in the intervention condition pulmonologists may have included patients with more advanced COPD since those patients would profit from extra support whereas pulmonologists in the control condition may have included patients with less advanced COPD in order to not additionally burden more vulnerable patients. We used these differences in patients' baseline characteristics to control for confounders at patient level. However, it is unclear whether all important differences were taken into account and the true effect may therefore be underestimated in this study. Furthermore, attrition is common in long duration trials testing palliative interventions and does not necessarily reflect poor design or conduct.[34] The proportion of missing data typically increases with study duration;[34] however our proportion of missing data (28.5% at 3 months) was relatively low compared to the weighted estimate for missing data at primary endpoint of the palliative interventions (23.1% at 28 days, median time), reported in a systematic review.[34] Nevertheless, the width of 8 of the 95% CI of the primary outcome proved that, if present, our study had the power to detect the necessary minimal important difference (MID) of 4.[35] Since the attrition rates in both groups were comparable, the threat to compromise the internal validity was minimal.[34] We also have no reason to assume that the participating hospitals are not representative of other hospitals; consequently, our findings can be generalized to other general hospitals.



| Number at risk | 0 | 3 m | 6 m | 9 m | 12 m |
|---|---|---|---|---|---|
| Intervention | 90 | 86 | 81 | 77 | 70 |
| Control | 138 | 129 | 121 | 116 | 106 |

**Figure 2** Kaplan-Meier plot of survival according to study group.

**Note:** The Cox proportional-hazard test showed that survival was not significantly different between the intervention and control condition, adjusted HR 0.74 [95% CI 0.34 to 1.62], p=0.45.

**Abbreviations:** CI, confidence interval; HR, hazard ratio.

## CONCLUSION

In this study, proactive palliative care did not improve quality of life of patients with COPD at 3 months, as measured with the SGRQ. There are several possible reasons for this on identification, organization, patient, outcome measure, and disease course levels. Therefore, we recommend that future research on the effectiveness of proactive palliative care on quality of life in this patient group take our findings into account. However, this study did demonstrate that proactive palliative care increased the number of patients that made ACP choices, and we therefore suggest that proactive palliative care in COPD should place emphasis on supporting patients through ACP conversations to improve their quality of care towards the end of life.[32,33]

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# SUPPLEMENTARY MATERIAL

**Table 7** Change scores relative to baseline of McGill and HADS subscales and associated tests of effects between groups.

| **Outcomes** | **Descriptives Intervention** | | **Control** | | **Analysis of difference between groups for changes over time** [a] | | |
|---|---|---|---|---|---|---|---|
| | **n** | **Mean observed change from baseline (SD)** | **n** | **Mean observed change from baseline (SD)** | **Estimated difference (95% CI)** | **Effect size** [b] | **p value** |
| **McGill[c] physical well-being** | | | | | | | |
| 3 months | 61 | 0.15 (2.95) | 85 | 0.72 (2.87) | 0.15 (-0.64 to 0.95) | -0.21 | 0.72 |
| 6 months | 52 | -0.35 (2.60) | 73 | -0.37 (2.88) | 0.54 (-0·16 to 1.23) | 0.01 | 0.16 |
| 9 months | 47 | 0.43 (2.94) | 64 | -0.39 (2.75) | 0.69 (-0.13 to 1.51) | 0.29 | 0.13 |
| 12 months | 44 | -0.16 (2.82) | 59 | 0.08 (2.97) | -0.14 (-1.22 to 0.93) | -0.08 | 0.82 |
| **McGill[c] physical symptoms** | | | | | | | |
| 3 months | 34 | 0.65 (2.50) | 39 | -0.03 (2.32) | 0.66 (-0.37 to 1.68) | 0.28 | 0.27 |
| 6 months | 28 | 0.57 (2.20) | 37 | -0.03 (2.42) | 1.09 (0.08 to 2.11) | 0.26 | 0.12 |
| 9 months | 30 | 0.69 (2.91) | 37 | -0.41 (2.52) | 0.97 (-0.05 to 1.99) | 0.41 | 0.11 |
| 12 months | 24 | -0.19 (2.15) | 32 | -0.57 (2.46) | -0.13 (-1.20 to 0.82) | 0.16 | 0.85 |
| **McGill[c] psychological** | | | | | | | |
| 3 months | 73 | 0.21 (2·82) | 110 | 0.33 (2.67) | -0.01 (-0.79 to 0.76) | -0.04 | 0.97 |
| 6 months | 66 | 0.16 (2·97) | 91 | 0.23 (2.70) | 0.15 (-0.70 to 0.99) | -0.02 | 0.77 |
| 9 months | 61 | 0.38 (2·43) | 87 | 0.09 (2.64) | 0.35 (-0.49 to 1.20) | 0.11 | 0.44 |
| 12 months | 55 | 0.27 (2·18) | 80 | -0.17 (2.95) | 0.49 (-0.38 to 1.37) | 0.17 | 0.30 |
| **McGill[c] existential** | | | | | | | |
| 3 months | 75 | 0.37 (1.75) | 111 | 0.24 (2.29) | 0.36 (-0.22 to 0.95) | 0.06 | 0.27 |
| 6 months | 67 | 0.29 (1.61) | 92 | 0.38 (2.17) | -0.01 (-0.52 to 0.49) | -0.05 | 0.99 |
| 9 months | 63 | 0.08 (2.03) | 89 | 0.14 (2.18) | -0.26 (-0.96 to 0.45) | -0.03 | 0.58 |
| 12 months | 55 | 0.08 (2.18) | 82 | -0.01 (2.21) | 0.03 (-0.70 to 0.75) | 0.04 | 0.94 |
| **McGill[c] support** | | | | | | | |
| 3 months | 73 | -0.48 (1.96) | 104 | -0.63 (2.46) | 0.37 (-0.27 to 1.01) | 0.07 | 0.28 |
| 6 months | 65 | -0.93 (2.32) | 89 | -0.36 (2.17) | -0.34 (-1.01 to 0.32) | -0.26 | 0.39 |
| 9 months | 59 | -0.63 (1.97) | 86 | -0.98 (2.29) | 0.21(-0.50 to 0.93) | 0.16 | 0.58 |
| 12 months | 53 | -0.66 (2.25) | 78 | -0.99 (2.10) | 0.52 (-0.25 to 1.28) | 0.15 | 0.21 |
| **HADS[d] anxiety** | | | | | | | |
| 3 months | 76 | -0.29 (4.03) | 111 | -0.27 (3.77) | -0.12 (-1.21 to 0.97) | -0.01 | 0.83 |
| 6 months | 66 | -0.46 (4.35) | 90 | -0.52 (3.75) | 0.02 (-1.26 to 1.29) | 0.01 | 0.98 |
| 9 months | 62 | -1.23(4.29) | 87 | -0.26 (3.79) | -0.65 (-2.11 to 0.81) | -0.24 | 0.41 |
| 12 months | 55 | -0.38 (4.34) | 81 | 0.17 (3.82) | -0.12 (-1.55 to 1.32) | -0.14 | 0.88 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **HADS[d] depression** | | | | | | | |
| 3 months | 76 | 0.51 (3.65) | 111 | 0.53 (3.59) | -0.25 (-1.33 to 0.83) | -0.01 | 0.66 |
| 6 months | 66 | 0.91 (3.83) | 89 | 0.90 (3.67) | -0.30 (-1.43 to 0.82) | 0.00 | 0.61 |
| 9 months | 62 | 1.20 (3.91) | 87 | 0.59 (3.55) | 0.15 (-1.11 to 1.41) | 0.16 | 0.82 |
| 12 months | 55 | 1.21 (3.88) | 80 | 1.20 (3.79) | -0.78 (-2.30 to 0.74) | 0.00 | 0.42 |

**Notes:** Associated tests of effects between groups were estimated by linear mixed models, adjusted for baseline covariates. Analyses were by intention-to-treat. Missing data were handled using available case analysis. Descriptive data are mean (SD) unless otherwise stated. The ICC's of the questionnaire outcome measures were all very small near 0 or 0 and therefore not displayed. [a] Associated tests of effect between groups were estimated by linear mixed models, adjusted for baseline covariates. [b] Effect sizes are Cohen's d, 0·20 is small, 0·50 is moderate, and 0·80 is large. [c] Change score interpretation high score better. [d] Change score interpretation: low score better.

**Abbreviations:** CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; ICC, intraclass correlation coefficient; McGill, McGill Quality of Life Questionnaire; SD, standard deviation.

# Development of the ProPal-COPD Tool to Identify Patients with COPD for Proactive Palliative Care

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# 6

## ABSTRACT

**Background:** Our objective was to develop a tool to identify patients with COPD for proactive palliative care. Since palliative care needs increase during the disease course of COPD, the prediction of mortality within 1 year, measured during hospitalizations for acute exacerbation COPD (AECOPD), was used as a proxy for need of proactive palliative care.

**Patients and methods:** Patients were recruited in three general hospitals in the Netherlands in 2014. Data of 11 potential predictors, a priori selected based on literature, were collected during hospitalization for AECOPD. After 1 year the medical files were explored for date of death. An optimal prediction model was assessed by Lasso logistic regression, with 20-fold cross validation for optimal shrinkage. Missing data were handled using complete case analysis.

**Results:** Of 174 patients 155 patients were included; of those 30 (19·4%) died within 1 year. The optimal prediction model was internally validated and had good discriminating power (AUC = 0·82, 95% CI 0·81 to 0·82). This model relied on seven predictors: the surprise question, Medical Research Council dyspnea questionnaire (MRC dyspnea), Clinical COPD Questionnaire (CCQ), $FEV_1$% of predicted value, Body Mass Index (BMI), previous hospitalizations for AECOPD, and specific co-morbidities. To ensure minimal miss out of patients in need of proactive palliative care we proposed a cut-off in the model that prioritized sensitivity over specificity (respectively 0·90 over 0·73). Our model (ProPal-COPD tool) was a stronger predictor of mortality within 1 year than the CODEX (comorbidity, age, obstruction, dyspnea and previous exacerbations) index.

**Conclusion:** The ProPal-COPD tool is a promising multivariable prediction tool to identify patients with COPD for proactive palliative care.

**Keywords:** COPD, Exacerbation, Proactive palliative care, Prognosis, Mortality

# INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive life threatening lung disease.[1] During the disease course the need for disease-oriented care remains unchanged while the need for proactive palliative care increases for patients with COPD.[2] Proactive palliative care which includes Advance Care Planning (ACP) conversations is intended to improve quality of life and quality of care.[3,4] However, for patients with COPD such care is not yet common.[2,5] An important barrier is the identification of patients with COPD who might benefit from proactive palliative care.[2]

Identification for proactive palliative care is complicated by the unpredictable disease course of COPD.[6] Stable phases in the disease course are interrupted by acute exacerbations; any one of which may be fatal.[6] Although, general tools to identify patients for palliative care exist, they are not specifically intended or validated for identification of patients with COPD.[7,8] In addition, models of survival in stable COPD have been developed to be able to adjust and optimize care.[9,10] Unfortunately, these population models are of limited value to predict survival for individual patients.[11] This prognostic difficulty has led to a discussion among clinicians whether or not a transition point for the initiation of proactive palliative care exists.[12-15] Some clinicians argue that more specific criteria of end stage COPD need to be explored.[13] Others argue that, since such criteria may not exist, searching further may lead to prognostic paralysis.[14,15] Instead, they promote early integration of palliative care according to needs.[15] The focus in this discussion has been on whether or not we can accurately predict mortality instead of the intended objective; identifying patients with COPD in need of proactive palliative care. Since palliative care needs increase during the disease course of COPD,[2] the prediction of mortality can be used as a proxy for the need of palliative care. To ensure minimal miss out of patients in need of such care, this tool should have a sensitivity near 100 with a high as possible specificity.

Hospitalizations for an acute exacerbation COPD (AECOPD) are associated with significant mortality and therefore create an opportunity to identify patients with poor prognosis in need of palliative care [16]. Recently potential relevant variables have been identified to predict post-hospital mortality in patients hospitalized for an AECOPD.[16,17] This is the first prospective study to incorporated these variables with the objective to develop a multivariable prediction tool (the ProPal-COPD tool) to identify patients with COPD in need of proactive palliative care. Our objective was to assess the discriminating power of a set of indicators for proactive palliative care in predicting death for any cause within 1 year. This outcome was used as a proxy for the potential need of proactive palliative care in patients with COPD.

## PATIENTS AND METHODS

### Source of data

Data for prognostic accuracy testing in patients hospitalized for an AECOPD were obtained from the PROLONG study.[18] This prospective pragmatic cluster controlled trial was performed in six general hospitals in the Netherlands of which three were in the intervention and three in the control condition. All recruited patients hospitalized for an AECOPD received usual care while only patients in the intervention condition with poor prognosis additionally received proactive palliative care. In this trial poor prognosis was defined as meeting two or more predictors of a set of 11 predictors of poor prognosis. For the prognostic accuracy study, described in this study, we only used data of those patients recruited in the three hospitals in the control condition.

### Participants

We screened for potential participants in three general hospitals in the Netherlands from Jan 14, 2014 to Dec 29, 2014. All patients with the clinical diagnosis COPD, hospitalized for an AECOPD who were 18 years or older were eligible. An AECOPD was defined as 'an acute worsening of the patient's condition from the stable state, which is sustained and may warrant the patient to seek additional treatment'.[19] Since the severity of airway obstruction and spectrum of pathogens in pneumonic and non-pneumonic exacerbations are similar,[20] patients with COPD who had been hospitalized for an acute pneumonia accompanied by increased sputum and dyspnea, were also included. Patients who did not speak Dutch or had a severe cognitive disorder were excluded from participation. All patients received usual care for an AECOPD and the period thereafter.

The study was approved by the Medical Ethics Committee (METC) of the Radboud University Medical Center, Nijmegen (METC protocol number 2012/260). Thereafter we requested and received research approval in all three participating hospitals. All participants gave written informed consent before enrolment.

### Outcome

The outcome measure was death for any cause within 1 year. This outcome measure was used as a proxy for the potential need of proactive palliative care. To ensure minimal miss out of patients in need of such care, we were looking for a tool with a sensitivity near 100% and an as high as possible specificity.

### Predictors

All 11 predictors are presented in Table 1. Each of them is a categorical variable indicating whether or not the participant meets the specific criteria for this predictor. References with the rationale to include the predictor in the multivariable prediction model are also presented in Table 1. Patients filled out demographics, the Medical Research Council dyspnea questionnaire (MRC dyspnea) and the Clinical COPD Questionnaire (CCQ) on the sixth day of hospital stay or in case the patient was discharged earlier on the day before leaving the hospital. The MRC dyspnea is a questionnaire used for grading the effect of breathlessness on daily activities.[27] The patient's dyspnea score is rated from 1 to 5, and higher scores represent a more severe dyspnea. The patient was asked to rate the dyspnea severity as it was two weeks before hospital admission. The CCQ day version was used to measure health status of patients.[28] The CCQ consists of 10 questions covering three domains (symptoms, functional status and mental state). The maximum total CCQ score is 6 and higher scores represent a worse health status. The treating pulmonologist thereafter filled out a checklist consisting of the remaining nine predictors. A year after the last patient was included the medical files of all participants were explored. Variables looked for were: if applicable, date of death and missing scores of predictors on the checklist. In case of uncertainty about death and/or date of death we contacted the general practitioner (GP) of the patient for information.

## Sample size

In this prospective study we included all eligible patients willing to participate during the year 2014 to maximize the power and generalizability of the results.

**Table 1** Set of 11 predictors of poor prognosis for patients hospitalized for an AECOPD and the references with the rational to include them in the prediction model

| Predictors of poor prognosis | References |
|---|---|
| 1. Hypoxaemia ($PaO2 < 8$ kPa) or hypercapnia ($PaCO2 > 6$ kPa) at discharge | 16,17 |
| 2. Treatment of the exacerbation with Non Invasive Ventilation (NIV) | 21 |
| 3. Patient needs professional home care service for personal care after discharge | 22 |
| 4. Negative answer to the surprise question:<br>'Would I (as pulmonologist) be surprised if this patient would die in the next year? | 23 |
| 5. The diagnosis of a severe co-morbidity such as: | |
| a. Non-curable malignancy or | 17,24 |
| b. Cor pulmonale (proven or non proven) or | 16 |
| c. Proven CHF or | 16,17 |
| d. Diabetes mellitus with neuropathy or | 16,17 |
| e. Renal failure, clearance < 40 (GFR: in ml/min) | 16,17 |
| 6. CCQ total, day version > 3 | 25 |
| 7. MRC dyspnea = 5 | 16,26 |
| 8. FEV1 (measured before AECOPD) < 30% of predicted | 16,17 |
| 9. BMI < 21 or unplanned weight loss (> 10% in last 6 months or > 5% in last month) | 16,17 |
| 10. Previous hospital admissions for AECOPD (last 2 years $\geq$ 2 and/or last year $\geq$ 1) | 16 |
| 11. Age > 70 years | 16,17 |

**Notes:** PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen.

**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; BMI, body mass index; CCQ, Clinical COPD Questionnaire; CHF, Chronic Heart Failure, FEV1, forced expiratory volume in 1 second; GRF, glomerular filtration rate; MRC dyspnea, Medical Research Council dyspnea questionnaire; NIV, non invasive ventilation.

### Missing data

Missing data were handled using complete-case analysis. Participant data were excluded from the analysis if a participant had missing information on any of the potential predictors. Possible reasons for missing data were a not or incomplete filled out questionnaire by the patient and/or an incomplete filled out checklist by the pulmonologist.

### Statistical analyses

Baseline characteristics were described using frequencies for non-continuous data, means with standard deviation (SD) for continuous variables normally distributed and median with interquartile range (IQR) for continuous variables not normally distributed. The analysis plan consisted of two steps. The first step had a descriptive nature and was aimed at exploring the discriminating power of individual predictors in predicting death for any cause within 1 year. For all eleven predictors the area under the curve (AUC), sensitivity and specificity were calculated. The goal of the second step was to build an optimal prediction model and to assess its predictive performance using internal validation. The model was build using a Least absolute shrinkage and selection operator (Lasso) logistic regression model, with 20-fold cross validation for optimal shrinkage.[29,30] By using the Lasso method, the risk of over-fitting was reduced, and at the same time a relatively simple prediction model was obtained. Because the performance of our optimal prediction model was validated in the same population used to construct it, its predictive performance was overestimated (“optimism”). To estimate this optimism, the procedure proposed by Steyerberg was followed.[30] In short, using bootstrapping 500 new populations were created, and a prediction model was built for each population in a completely analogous way. The predictive performance of the model, as expressed by the AUC in both the bootstrapped population as well as in the original population was calculated. The mean difference between these two AUC values is an estimate of the optimism of our prediction model.

### Risk groups

No risk groups were created.

## RESULTS

### Participants

The participant flow diagram is presented in Figure 1. Of all 174 participants , 155 participants were included in the analyses. The characteristics of the study populations are presented in Table 2.

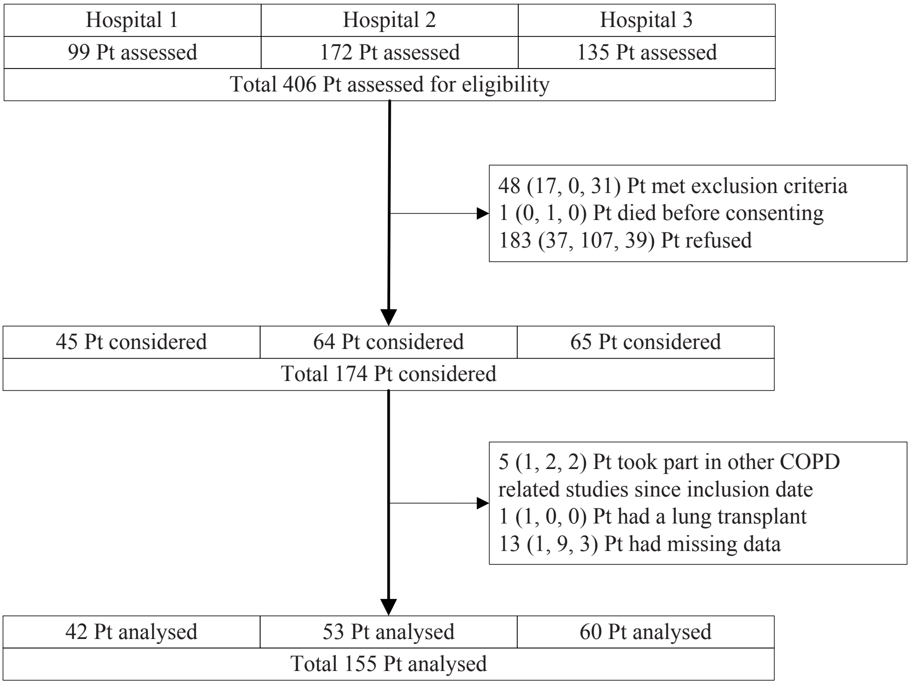

**Figure 1** Participant flow diagram.
**Abbreviation:** Pt, patient.

## Model development

The numbers of participants that met the criteria of each predictor are presented in Table 2. In the study population 19.4% of the participants (30 of 155) died within 1 year.

The discriminating power of individual predictors in predicting death within 1 year is presented in Table 3.

## Model specification and performance

The optimal prediction model, build using the Lasso method, and its predictive performance is presented in Table 4. This logistic regression model includes an intercept and the weighted sum of the value of each predictor. The weights are the regression coefficients (*B*). The value of each predictor is 1 when present and 0 when absent.

A patient can be considered as in need of proactive palliative care when the total sum of the logistic regression models exceeds a certain cut-off point of the model. The choice of this cut-off is essentially a trade-off between sensitivity and specificity. A popular choice is to choose the cut-off that considers sensitivity and specificity to be of equal importance, so maximizing the sum of sensitivity and specificity. In the setting of this study a cut-off that prioritizes sensitivity above specificity does make sense. Therefore, we also present the cut-off that maximizes the sum of specificity and 1.5 times the sensitivity. Possible cut-offs for both choices are presented in Table 5.

The receiver operating characteristic (ROC) curve for prediction of death within 1 year with the optimal cut-offs considering different trade-offs between sensitivity and specificity are presented in Figure 2.

**Table 2** Characteristics of the study population

| **Study population (N = 155)** | | |
|---|---|---|
| **Characteristics** | **Mean** | **(±SD)** |
| **Age** | 67.5 | (±9.6) |
| **Pack years** (N = 148) | 36.4 | (±32.8) |
| | **N** | **(%)** |
| **Sex** | | |
| Male | 68 | (43.9) |
| **Marital status*** | | |
| Married | 110 | (71.0) |
| Unmarried | 11 | (7.1) |
| Divorced | 13 | (8.4) |
| Widow | 18 | (11.6) |
| **Condition of living*** | | |
| Single | 34 | (21.9) |
| Non single | 111 | (71.6) |
| **Place of living*** | | |
| Home, independent of homecare | 103 | (66.5) |
| Home, dependent of homecare | 45 | (29.0) |
| Residential home | 2 | (1.3) |
| **Highest level of education*** | | |
| No education | 1 | (0.6) |
| Elementary school | 21 | (13.5) |
| Secondary school | 47 | (30.3) |
| Primary education | 35 | (22.6) |
| Secondary education | 29 | (18.7) |
| Higher/University education | 15 | (9.7) |
| **Gold stage*●** | | |
| 0 | 8 | (5.2) |
| I | 10 | (6.5) |
| II | 41 | (26.5) |
| III | 52 | (33.5) |
| IV | 36 | (23.2) |

| | | |
|---|---|---|
| **Predictors** | | |
| Hypoxaemia or hypercapnia | 62 | (40.0) |
| NIV | 11 | (7.1) |
| Professional home care | 50 | (32.3) |
| Negative answer SQ | 76 | (49.0) |
| Co-morbidity | 31 | (20.0) |
| CCQ total, day version > 3 | 96 | (61.9) |
| MRC dyspnea = 5 | 71 | (45.8) |
| FEV1 < 30% of predicted | 45 | (29.0) |
| BMI < 21 or weight loss | 26 | (16.8) |
| Prev. hosp. AECOPD | 62 | (40.0) |
| Age > 70 years | 62 | (40.0) |

**Notes:** *Because of missing values some numbers do not add up to 100%. •GOLD stage according to last known data in medical file; inclusion in the study was based on the judgment by pulmonologist.

**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; BMI, body mass index; CCQ, Clinical COPD Questionnaire; FEV1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC dyspnea, Medical Research Council dyspnea questionnaire; NIV, non invasive ventilation; Prev. hosp., previous hospitalization; SQ, surprise question.

## DISCUSSION

This study shows that we were able to develop a promising multivariable prediction tool to identify patients with COPD in need of proactive palliative care, the ProPal-COPD tool. Since palliative care needs increase during the disease course,[2] and hospitalizations for AECOPD are associated with significant mortality risk,[16] these hospitalizations create an opportunity for identification. This is why the prediction of death was used as a proxy for identification of patients in need of palliative care. In our study population 19.4% of participants died within 1 year. This number is in line with the 1 year mortality rate in other studies investigating patients hospitalized for AECOPD.[31,32] Our optimal prediction model of death within 1 year had good discriminating power; the true AUC was 0.82 (95% CI 0.81 to 0.82), and the estimated optimism of 0.05 indicated good internal validity. To ensure minimal miss out of patients in need of palliative care we propose a cut-off in the prediction model that prioritizes sensitivity above specificity. This optimal cut-off was -1.36, with a sensitivity of 0.90 and a specificity of 0.73. This implies that, when used, only 10% of patients in need of palliative care would be missed out and that of all patients identified for such care 84% would die within 1 year.

**Table 3** The discriminating power of individual predictors in predicting death within 1 year

| **Predictor** | **Se** | **Sp** | **AUC** |
|---|---|---|---|
| Hypoxaemia or hypercapnia | 0.53 | 0.63 | 0.583 |
| NIV | 0.93 | 0.07 | 0.503 |
| Professional home care | 0.47 | 0.71 | 0.589 |
| Negative answer SQ | 0.80 | 0.58 | 0.692 |
| Co-morbidity | 0.43 | 0.86 | 0.645 |
| CCQ total, day version > 3 | 0.83 | 0.43 | 0.633 |
| MRC dyspnea = 5 | 0.80 | 0.62 | 0.712 |
| FEV1 < 30% of predicted | 0.43 | 0.64 | 0.589 |
| BMI < 21 or weight loss | 0.33 | 0.87 | 0.603 |
| Prev. hosp. AECOPD | 0.60 | 0.65 | 0.624 |
| Age > 70 years | 0.43 | 0.61 | 0.521 |

**Note:** Study population (N=155).

**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease; AUC, area under the curve; BMI, body mass index; CCQ, Clinical COPD Questionnaire; FEV1, forced expiratory volume in 1 second; MRC dyspnea, Medical Research Council dyspnea questionnaire; NIV, non invasive ventilation; Prev. hosp., previous hospitalization; Se., sensitivity; Sp., specificity; SQ, surprise question.

The ProPal-COPD tool is the first which is using specific predictors of mortality during AECOPD requiring hospitalizations. This tool relies on seven predictors: the surprise question (a general predictor), five markers of COPD severity, and the presence of specific co-morbidities proven to independently predict post-hospital mortality in AECOPD.[24] Through the surprise question the tool incorporates clinical judgment of severity. The surprise question has shown to be a proven predictor of mortality in patients with advanced chronic diseases,[33] and is recommended to be used in combination with other disease-specific predictors as screening tool for proactive palliative care.[23] Those disease-specific predictors in the ProPal-COPD tool are five markers of COPD severity being; the CCQ (health status), MRC dyspnea, $FEV_1$% of predicted value, BMI, and previous hospitalizations for an AECOPD. The presence of either one of the following co-morbidities, non-curable malignancy, cor pulmonale, Chronic Heart Failure (CHF), diabetes mellitus with neuropathy or renal failure, is also incorporated in our tool. These co-morbidities, except non-curable malignancy, are conditions liable to acute decompensation especially during AECOPD, which may explain their association with an increased mortality risk.[16]

**Table 4** Optimal prediction model and its predictive performance of death within 1 year

| **Predictors in model** | ***B*** | **AUC** | **True AUC** | **95%CI** |
|---|---|---|---|---|
| (Intercept) | -3.901 | 0.870 | 0.818 | 0.813 – 0.824 |
| Hypoxaemia or hypercapnia | / | | | |
| NIV | / | | | |
| Professional home care | / | | | |
| Negative answer SQ | 0.959 | | | |
| Co-morbidity | 1.479 | | | |
| CCQ total, day version > 3 | 0.257 | | | |
| MRC dyspnea = 5 | 1.475 | | | |
| FEV1 < 30% of predicted | 0.565 | | | |
| BMI < 21 or weight loss | 1.005 | | | |
| Prev. Hosp. AECOPD | 0.102 | | | |
| Age > 70 years | / | | | |

**Notes:** Study population (N=155). *B*, weight in the model;/ , not incorporated in the optimal prediction model.
**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease, AUC, area under the curve; BMI, body mass index; CCQ, Clinical COPD Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 second; MRC dyspnea, Medical Research Council dyspnea questionnaire; NIV, noninvasive ventilation; Prev. hosp., previous hospitalization; SQ, surprise question.

**Table 5** Possible cut-offs considering different trade-offs between sensitivity and specificity of the optimal prediction model

| **Cut-off** | **Sensitivity** | **Specificity** | **Se + Sp** | **1.5 Se + Sp** |
|---|---|---|---|---|
| -1.105 | 0.800 | 0.840 | 1.640 | 2.040 |
| -2.896 | 0.967 | 0.328 | 1.295 | 1.778 |
| -2.169 | 0.933 | 0.504 | 1.437 | 1.904 |
| -1.362 | 0.900 | 0.728 | 1.628 | 2.078 |

**Abbreviations:** Se, sensitivity; Sp, specificity.

Most predictors of the ProPal-COPD tool are variables already used in clinical practice and do not need extra measurement.[34] Only the surprise question, the CCQ and MRC dyspnea, which are short easy to use questionnaires, are often not documented and need to be specifically asked for.[34] Besides, each predictor in our tool has an own weight (*B*). Those weights take into account the correlation with other predictors of the tool and therefore should not be interpreted as the individual importance of each predictor in the tool. Moreover, the Lasso method used for model development is looking for the most efficient model.[30] In the trade-off between efficiency and effectiveness four predictors (hypoxaemia or hypercapnia, NIV, professional home care and age) were excluded from our optimal prediction model. This does not mean that those predictors were not predictive of death within 1 year. If we look at the predictor NIV, for example, it was noticeable that only 11 patients met the criteria of this predictor. Besides, NIV as an individual predictor had high sensitivity (0.93) and low specificity (0.07), meaning that almost all patients who were treated with NIV died within 1 year but patient who were not treated with NIV also had a considerable risk of dying. The exclusion of the predictor NIV can therefore be explained by the limited number of patients involved and the high correlation with predictors incorporated in our optimal prediction model. The other three predictors, hypoxaemia or hypercapnia, professional home care and age, were merely excluded because of correlation.

The ProPal-COPD tool shows promise for identification of patient with COPD in need of proactive palliative care. The ROC analysis suggests that it has good prognostic performance with a prognostic capacity superior to the CODEX index (co-morbidity, age, obstruction, dyspnea and previous exacerbations). [35] The CODEX index has an AUC of 0.68 in predicting death within 1 year and is the only other multivariable model developed to evaluate post-hospital prognosis in patients with an AECOPD.[35] However, the main objective of both tools is different. Our tool was developed to identify patients in need of proactive palliative care whereas the CODEX was developed to predict mortality and/or readmissions. In addition there are several substantive differences. First, our tool incorporates disease specific predictors of mortality in AECOPD requiring hospitalization, whereas the CODEX index was developed using disease specific predictors of mortality in stable COPD. Second, our tool contains specific co-morbidities proven to independently predict post-hospital mortality in AECOPD, whereas the evidence of the Charlson index (co-morbidity burden) used in the CODEX index in predicting post-hospital mortality in AECOPD is less consistent.[16] Finally, each predictor in our tool has an own weight (*B*) in contrast to the predictors in the CODEX index. Those weights do not represent the individual importance of each predictor since they take into account the correlation with other predictors in the tool. Still, the own contribution of each predictor is better represented in our tool. It is possible that the above mentioned substantive differences between the ProPal tool and the CODEX index have contributed to the better prognostic performance of our tool.

Our study had several limitations that should be acknowledged. First, predicting post hospital mortality for patients with COPD is complex and this is reflected by the number of potential predictors incorporated in the original set of predictors. We only used already known predictors in this set and it is uncertain if all possible predictors were accounted for. In addition it is possible that certain predictors were underrepresented in the set of potential predictors. Anxiety and depression for example were represented as a subscale of the predictor CCQ. Second, to facilitate implementation in clinical practice we used dichotomized variables. Each potential predictor was given a clinical cut-off value based on literature. Such dichotomization of continuous predictors may lead to loss of information and reduction of power.[36] Third. the use of the ProPal-COPD tool may require collection of data that are not always captured routinely (surprise question, CCQ, MRC dyspnea). Fourth, the ProPal-COPD tool was developed in the Netherlands.

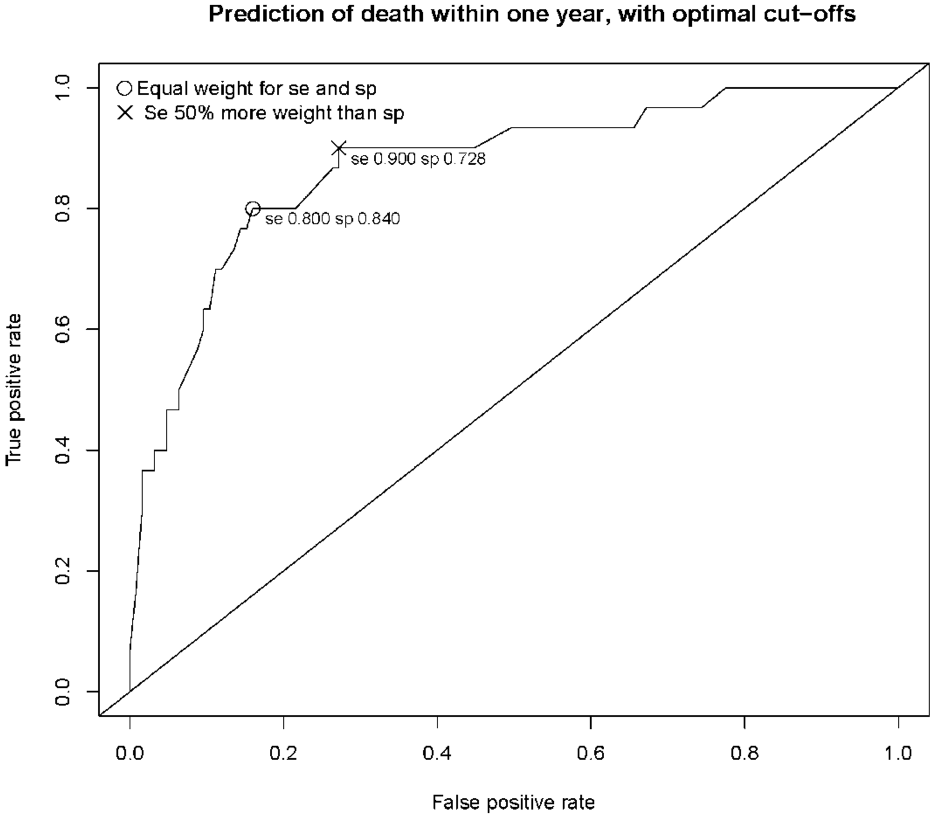

**Figure 2** The ROC curve for prediction of death within 1 year with the optimal cut-offs considering different trade-offs between sensitivity and specificity.

**Abbreviations:** ROC, receiver operating characteristic; se, sensitivity; sp, specificity.

International differences in hospital admission policy for patients with an AECOPD may affect the usefulness in other countries. Fifth, it is unknown whether the ProPal-COPD tool is also applicable in academic hospitals since it was developed using a population of patients in general hospitals. Finally, the ProPal-COPD tool was developed in a single population without validation in a different one. The external validity of our findings is therefore unknown and needs to be addressed in further research. Hence, other participant data need to be collected in a new prospective study performed in general and/or academic hospitals to evaluate the performance of the ProPal-COPD tool.

## CONCLUSION

The ProPal-COPD tool is a promising tool to identify patients with COPD for proactive palliative care with good discriminating power (AUC = 0.82). It relies on seven predictors; the surprise question (a general predictor), five markers of COPD severity, and the presence of specific co-morbidities. The prediction of death within 1 year was used as a proxy for the potential need of proactive palliative care. To ensure minimal miss out of patients in need of proactive palliative care we propose a cut-off in the prediction model that prioritizes sensitivity over specificity. This optimal cut-off has a sensitivity of 0.90 and a specificity of 0.73. Each predictor in the tool has an own weight and only when the total sum of the model exceeds the specific cut-off point the patient can be considered in need of proactive palliative care. This prognostic equation can be easily integrated in the Electronic Patient Record (EPR) system. However, before clinical use of the ProPal-COPD tool the external validity should be addressed in further research.

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# Letter to the Editor Regarding: "Development of the ProPal-COPD Tool to Identify Patients with COPD for Proactive Palliative Care"

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## Dear Editor

We read with interest the recent article of Duenk et al. entitled "Development of the ProPal-COPD tool to identify patients with COPD for proactive palliative care" recently published in the International Journal of COPD.[1] We fully agree with the authors on the capital importance of proactive palliative care (PPC) in COPD, as well as its underutilization. Any article that contributes to bettering knowledge of PCC and its use with COPD patients who can benefit from it is to be celebrated. We also agree with the authors on the unpredictability of prognosis in COPD, especially the uncertain evolution of severe exacerbations and the impact of comorbidities. We believe that the article deserves some considerations. First and most important, in our opinion PPC should not be limited to the terminal phase of chronic diseases such as COPD; it can be delivered alongside standard therapies, according to the needs and preferences of patients regardless of the risk of death in the short or medium term. Obviously, this does not mean that prognostic prediction scales are not useful in prognosis prediction. Nevertheless, its exclusive use may exclude many patients who could benefit from PPC.[2] For instance, in the model proposed by Duenk et al. seven dichotomic predictor variables were suggested to consider PPC based on their relationship with 1-year mortality. However, it seems clear that a COPD patient with severe airflow obstruction, disabling dyspnea and several previous hospitalizations, although strictly not meeting all the recommended criteria, is a candidate for PPC. In this patient PCC includes advanced care planning conversations, with their perspectives in case of a poor evolution in future exacerbations and preferences concerning the ceiling of treatment such as cardiopulmonary resuscitation, admission to the intensive care unit and invasive mechanical ventilation. Additionally, pharmacological and non-pharmacological measures for dyspnea or others symptom treatment should be considered and discussed with the patient. In this example, the onset of these measures should be independent of other predictor variables and of foreseeable life expectancy. Of note, PPC measures by themselves do not shorten life, but may be associated with increased survival.[3]

Second, from a strictly methodological point of view, we cannot forget that the model is built from just 30 positive patients. Even by using most sophisticated statistical procedures we still having little information about the general behavior of this population and this is a strong limitation moreover due to the relevance of the topic and the final decisions taken. Additionally, all prognosis models must be validated in a different external cohort, to avoid the risk of overestimation inherent in development cohorts. In the present study only internal validation was performed. Finally, the exclusive use of the ROC curves and AUC for 1-year mortality limits consideration to the vital status of the patient 1 year after discharge, regardless of the time of death, and clearly survival time is relevant in this population. Cox regression analysis and Kaplan-Meier curves comparing patients with and without criteria would be of help to further clarify the results.

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## Dear Editor

We thank Dr Almagro and Dr Martinez Camblor for their letter to the editor in response to our manuscript entitled "Development of the ProPal-COPD tool to identify patients with COPD for proactive palliative care".[1] We are pleased that both authors agree with us on the importance of proactive palliative care (PPC) in COPD as well as its underutilization in this patient group. We also fully support their view that PPC should not be limited to the terminal phase of chronic diseases such as COPD, but that it can be delivered alongside standard therapies, according to the needs and preferences of patients.

The authors' main concern with respect to our recent article was about the exclusive use of prognosis prediction of mortality for the start of PPC in COPD. They worried that patients in need of PCC would be missed out, because a recent review showed that existing prognostic criteria were not sufficiently reliable.[2] However, as mentioned in our manuscript, prediction of mortality or identification of the terminal phase was never our objective. Our actual objective was to develop a tool as additional aid to identify patients with COPD in need of PPC. Since palliative care needs increase during the disease course of COPD,[3] we merely used the prediction of one year mortality as a proxy for the need of PPC. Moreover, to ensure minimal miss out of patients in need of PCC we looked for and also managed to develop a tool with a high sensitivity (0.90) and a high as possible specificity (0.73), while ensuring good discriminating power (AUC = 0·82, 95% CI 0·81 to 0·82).

Not all seven dichotomic criteria of the ProPal-COPD tool need to be fulfilled to be eligible for PPC, as suggested by the authors. Each criterion has an own weight and when the total sum of the model exceeds the specific cut-off point the patient can be considered in need of PPC. This means that different combinations of a few or more criteria may be indicative for the need of PPC. Of course, as also mentioned in our manuscript, before clinical use of the ProPal-COPD tool the external validity should be addressed in further research. This will be done in a nation-wide project in the Netherlands.

PPC in COPD, which includes advance care planning (ACP) conversations, still hardly takes place although the need for PPC in this patient group has been recognized. This is not only due to the unpredictable disease course but also to the fact that both patients and physicians encounter barriers to initiate such conversations.[4] A recent study examining the quality of ACP conversations in patients with advanced chronic organ failure suggests that facilitation of initiation of ACP conversations is the key to improve PPC. It seems that otherwise, even when the disease progresses, needs and preferences of patients are hardly being explored.[4] Therefore, we believe that the development of the ProPal-COPD tool, for initiation of PPC in COPD, responds to the need of patients and physicians.[5]

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# General Discussion

# 7

Patients with advanced COPD have a high symptom burden and poor quality of life.[1,2] Towards the end of their lives most of them prefer a treatment with an emphasis on comfort rather than life prolongation but this kind of care is not common practice.[3] Research even showed that referrals to palliative care were less likely for patients with COPD (20%) than for patients with cancer (60%), dementia (37%) or heart failure (34%).[4] However, in the past decade the need for palliative care in this patient group has been recognized.[5] Although the benefits of a proactive approach to palliative care on symptom burden and quality of life have been proven in other diseases,[6-10] little research has been performed to demonstrate its benefits in COPD.[11]

The disease trajectory of COPD is unpredictable with a gradual functional decline punctuated by acute severe exacerbations any one of which may be fatal.[12-14] This unpredictable course hinders the timely identification of patients with COPD requiring palliative care, and compromises the continuity of palliative care because of the different healthcare professionals involved during the acute and stable phases of the disease.[5,15,16] Timely identification of patients requiring palliative care not only enables a proactive approach but also facilitates initiation of advance care planning (ACP) conversations as well as promotes communication between healthcare professionals necessary to ensure the continuity of proactive palliative care delivery.[5,17] Nevertheless, it has not yet been determined how to identify patients with COPD in need of proactive palliative care and how to organize such a coordinated healthcare plan.[18,19] Since pulmonologists have a central role in COPD management their view on this subject is important.[20] Therefore, the objectives of this thesis were: to explore the views, needs, and wishes of pulmonologists concerning proactive palliative care for patients with COPD; to examine the effectiveness of proactive palliative care on the wellbeing of patients with COPD; and to examine the identification of patients with COPD for proactive palliative care.

In this chapter the main findings and methodological considerations of these studies are discussed and put into a broader perspective. I will also present recommendations for clinical practice, education and research in order to move towards the use of proactive palliative care for patients with COPD.

## THE VIEW OF PULMONOLOGISTS

A survey study (**Chapter 2**) was performed to gain insights into the view of pulmonologists in the Netherlands regarding: 1) palliative care for patients with COPD in general; 2) the identification of patients with COPD for palliative care; 3) important aspects of palliative care for patients with COPD; and 4) the organization of palliative care for patients with COPD.

Almost all pulmonologists considered palliative care for patients with COPD to be desirable. In 2010, the Lung Alliance Netherland (LAN), the Dutch society for chronic lung diseases, developed a clinical guideline on palliative care for people with COPD, to ensure that the best available evidence would be translated into everyday clinical practice.[21] About half of the pulmonologists did not use this guideline, most often because they were unaware of its existence. This is cause for concern since limited awareness and the resulting low adherence to clinical guidelines may result in potential suboptimal healthcare.[22] In general, adherence to COPD guidelines is sub-optimal and barriers have been identified.[22] Understanding these barriers may help with the optimization of strategies to ensure the better use of the clinical guideline on palliative care for people with COPD.

COPD is a chronic progressive life-threatening disease. Patients experience a gradual functional decline punctuated by acute severe exacerbations during which disease-oriented care remains necessary and the need for palliative care gradually increases.[11,12] A clearly marked transition from disease-oriented care to palliative care is not present in COPD, leading some clinicians to argue that a palliative phase may not exist for this disease.[23,24] Nevertheless, the majority of pulmonologists in our study (92.2%) indicated that they do distinguish a palliative phase in the COPD trajectory.

At the time we performed our survey, validated evidence-based criteria to determine the prognosis in advanced COPD were not available.[5,25] In order to facilitate timely identification of patients with COPD requiring palliative care, several criteria and tools had been proposed.[5,25-28] The formulated 14 identification criteria in our survey were selected on the basis of this literature. All pulmonologists reported using several criteria, the combinations of which were different for each pulmonologist. Four criteria were mentioned by about three quarters of the pulmonologists: repeated hospital admissions for an acute exacerbation of COPD (AECOPD); feeling /experience of the pulmonologist that palliative care is needed; wish of the patient; and severe comorbidity. All other formulated criteria were mentioned by about one third of the pulmonologists while some pulmonologists also mentioned the additional aspects 'no treatment options left' and 'a negative answer to the surprise question' (would I, as pulmonologist, be surprised if my patient would die in the next year?). The fact that criteria of prognosis as well as curability and palliative needs were chosen by the pulmonologists reflected the absence of consensus about the way of identification of patients with COPD requiring palliative care.[29]

The pulmonologists also indicated which aspects of palliative care for patients with COPD they considered important and which aspects should be improved. Aspects described as important by over three-quarters of the pulmonologists were: Advance Care Planning (ACP) conversations, communication between pulmonologists and GPs, and the identification of patients for palliative care. For improvement only one aspect, the identification of patients for palliative care, was mentioned by almost three quarters of the pulmonologists. The aspects thereafter mentioned for improvement by about two fifth of the pulmonologists were: ACP conversations, the organization of palliative care, communication between pulmonologists and GPs, and defining the coordinating role. These findings reveal that pulmonologists not only consider the identification of patients for palliative care vital, but also highlighted it as the most important aspect for improvement.

An integrated coordinated multidisciplinary model of palliative care, in which healthcare professionals of primary and secondary care work together to address the palliative care needs of patients with COPD, is increasingly recommended as best practice in the literature.[11,18,19] Almost three quarters of the pulmonologists answered in agreement of this, preferring a multidisciplinary cooperation between pulmonologists, GPs, and respiratory nurse specialists in the ambulatory setting. When asked who should organize palliative care for patients with COPD during hospitalization, more than half of the pulmonologists felt they themselves should be responsible. About three-tenth of the pulmonologists preferred to organize this in cooperation with a specialized palliative care team (SPCT) while about one-tenth mentioned that specialized pulmonologists should take part in SPCTs. The idea that SPCTs should hold the primary responsibility for care was almost never suggested, which is in line with the fact that, in practice, the input of an SPCT often is demanded for more complex disease trajectories.[30] These findings show, that during hospitalization of patients with COPD, pulmonologists want to be involved in the organization of their palliative care, while there is also room for the involvement of an SPCT.

Aside from differences in ideas about best practice, variations in palliative care delivery may also be influenced by factors such as the availability of facilities, access, and reimbursement issues.[5,19] In any case, as best practice, most pulmonologists preferred a model of integrated care, achieved through the collaboration of primary and secondary healthcare professionals. To successfully share the care of patients in need of proactive palliative care, good communication between the relevant healthcare professionals is essential.[31] There is increasing consensus that respiratory nurse specialists would be best placed to fulfill a coordinating role to ensure the continuity of care across different settings.[1,18] In addition, practical applications are proposed. In a recent study, the use of a Key Information Summary (KIS), a shared electronic medical record that captures the key points of proactive care plans, was explored, and was found not only to improve communication between healthcare professionals, but also to achieve earlier identification of patients (including patients with COPD) for palliative care.[32] Currently, shared palliative care initiatives are being pilot-tested in several regions in the Netherlands.

## Methodological considerations

The questionnaire we used in our survey was not validated. Therefore, it is possible that certain questions were not totally unambiguous and may not always have been interpreted in the same way. Although comparable with other survey studies that investigate views of pulmonologists,[33,34] the overall response rate of 32% was low, raising concerns about whether the results can be generalized to the Dutch population of pulmonologists. Those pulmonologists who participated may have been more interested in palliative care in patients with COPD than the non-responders, and may have provided a more favorable view. For this reason, the low response rate will not have influenced our findings that the identification of patients with COPD for palliative care and the organization of such care need improvement.

## EFFECTIVENESS OF PROACTIVE PALLIATIVE CARE FOR PATIENTS WITH COPD

We were the first to examine the effectiveness of proactive palliative care on the wellbeing of patients with COPD (**Chapter 5**) by performing a pragmatic cluster controlled trial (quasi-experimental design) with hospital as cluster (3 intervention, 3 control). Patients with poor prognosis were recruited during hospitalization for AECOPD. Poor prognosis was defined as meeting two or more indicators of a checklist of 11 indicators of poor prognosis. All patients received usual care while patients in the intervention condition received additional proactive palliative care in monthly meetings with an SPCT. Our primary outcome was change score in quality of life after 3 months using the St George Respiratory Questionnaire (SGRQ). Secondary outcomes were change in quality of life (SGRQ and McGill) after 3, 6, 9, and 12 months; change in psychological wellbeing (HADS) after 3, 6, 9, and 12 months; number and length of readmissions for an AECOPD; survival; and whether patients had made ACP choices during the one-year trial period.

In total, 228 patients were recruited (90 intervention, 138 control) and at 3 months, 163 patients (67 intervention, 96 control) completed the SGRQ. We did not find an effect on our primary outcome, as the change in quality of life after 3 months using the SGRQ did not differ between groups. After six months however, patients receiving proactive palliative care experienced less impact of their COPD (SGRQ impact subscale) than patients receiving usual care. Moreover, there was a relevant difference in the number of patients who made ACP choices during the year of trial, in favor of the intervention group. The change in symptoms and activity level (SGRQ symptoms and activity subscale) were not different between groups at any of the time points. We did not find a difference in the other questionnaire outcomes, nor in the number and length of hospital admissions, or in survival between groups.

Several possible reasons related to our study plan, the characteristics of the COPD patient, the COPD disease course and/or palliative care interventions in general may have contributed to the failure to demonstrate an improvement of quality of life in patients with COPD by means of proactive palliative care in our study:

*Study plan*

The study plan related reasons are at the level of identification, organization and outcome measure. First, only 22.8% of patients identified as having a poor prognosis died within one year; therefore, it seems that our criteria for poor prognosis were too broad. Second, patients with advanced COPD are often homebound until they enter an acute phase requiring hospitalization.[35] Continuity of palliative care can therefore only be achieved with a coordinated, multidisciplinary care approach in which primary and secondary health care professionals collaborate.[36] Although GPs were informed about the intervention and the SPCT was encouraged to collaborate with GPs, we did not control for this aspect and it is unknown to what extent this occurred. Third, for some patients with advanced COPD, filling in questionnaires appeared to be too demanding. Although all enrolled patients did consent to fill out questionnaires, about one in five patients did not fully understand, complete, or return them. Incomplete data collection in advanced COPD has also been reported before.[37,38] Perhaps in this population the use of a qualitative approach instead of or in addition to a quantitative approach is preferable for measuring changes in patient-reported outcomes.[38]

*Characteristics of the COPD patient*

Patients with COPD generally have a lower socioeconomic status (SES), i.e. on average a lower level of education and less financial means than other patient groups.[39] These aspects have an impact on COPD health outcomes.[39] Indeed, some patients in our study had difficulties understanding certain questions, which resulted in the return of incomplete questionnaires or obvious mistakes in answering questions. Additionally, some patients lacked the financial means to afford transportation to the hospital, physical therapy, or even a walker.

*Characteristics of the COPD disease course*

There are differences in the palliative trajectories of patients with cancer and those with COPD. First, the palliative trajectory of COPD is less predictable because episodes of gradual decline are punctuated by acute severe exacerbations.[12] As a consequence, the quality of life will also fluctuate over time; therefore, these acute exacerbations may have influenced our findings, which were defined at fixed time points. Second, for patients with cancer, palliative care often starts when cure is no longer possible. Initially, the discontinuation of aggressive curative care, such as chemotherapy, may result in an improvement of the patients' quality of life followed by a period of gradual decline. However, for patients with severe COPD in the palliative trajectory, 'curative care' to manage the symptoms of COPD remains necessary until the last weeks of life. In our study, patients with COPD who received proactive palliative care for six months experienced less impact from their disease. Although this may have been a chance finding, as it was a secondary outcome, merely an effect on a quality of life subscale was also observed in the Glasgow supported self-management trial for patients with moderate to severe COPD.[37] Also Higginson and colleagues found no effect on quality of life from early introduction of a palliative breathlessness support service for patients with refractory breathlessness (including COPD), but these authors did find improved breathlessness mastery, a quality of life domain of the Chronic Respiratory Disease Questionnaire.[40] As mentioned before, in contrast to patients with cancer in the palliative trajectory, disease-oriented care remains necessary for patients with advanced COPD in the palliative trajectory until the last weeks of life. Therefore, it is possible that resilience to improve overall quality of life (especially symptoms and activity) is exhausted in this patient group.

*Characteristics of palliative care interventions in general*

Palliative care is a personalized intervention in which patients receive treatment according to their needs, which can be in the physical, psychological, social, and/or spiritual domains of quality of life. In this patient-centered approach some patients have, for instance, only physical problems, while other patients suffer from distressing conditions in the social and spiritual domain. Despite these different needs and the consequent personalized treatment of patients, the overall quality of life questionnaire, which includes all domains, is used as an outcome measure in palliative trials. It is therefore possible that, in palliative trials in general, the real but difficult-to-measure effect of palliative care on quality of life is being underestimated.[41]

In a recent systematic review and meta-analysis, the association between palliative care and different outcomes in patients with advanced incurable illness was determined.[42] The meta-analysis showed that palliative care was associated with improvements in quality of life. However, these trials mainly targeted patients with cancer (69.7%) and none of them focused on patients with COPD. One of the conclusions of this analysis was that additional studies are needed to examine the effects of palliative care in chronic nonmalignant diseases, such as COPD. Moreover, as in our study, no association was found between palliative care and survival.[42] This is important because there is an unfounded belief among some clinicians and members of the lay public that palliative care may actually shorten survival.[43,44] In addition, also in line with our study, the narrative synthesis demonstrated an association between palliative care and improved ACP conversations.[42]

During ACP conversations, patients are informed about their diagnosis, prognosis, treatment options, and treatment consequences. Patients can also express their values and preferences for life-sustaining treatments with the goal of improving the quality of their end-of-life care.[17] In our study, more patients with COPD in the intervention condition made ACP choices and consequently had ACP conversations during the year of the study. As the follow up period of patients was too short, we were not able to confirm earlier findings that those ACP conversations improved the quality of end-of-life care;[45,46] and further research is needed.

## Methodological considerations

For our intervention study, a cluster design was chosen to prevent contamination and to facilitate recruitment by minimizing the ethical concerns of patients and clinicians with respect to randomization and gate keeping.[47,48] At the time of hospital recruitment, a minority of hospitals in the Netherlands had an available SPCT. Since only four hospitals with an SPCT were willing to participate, it was not possible to create comparable groups through cluster randomization in our trial. Instead, we performed a pragmatic cluster controlled trial (quasi-experimental design) in which three hospitals with an SPCT were selected for the intervention and three hospitals without an SPCT for the control condition. To control for confounding variables at hospital level, a pre-trial assessment was performed, in which hospitals were compared on baseline characteristics over the year before trial. All outcome measures were taken at patient level and patients performed a pre- and post-intervention measurement.

Although our pragmatic cluster controlled design completely ruled out contamination, this design was subject to selection bias at hospital level. However, using the outcomes of a pre-trial assessment we were able to control for hospital level confounders. Next, pulmonologists were aware of the treatment allocation, which may have caused bias. Our baseline data suggest that in the intervention condition pulmonologists included patients with more advanced COPD since those patients would profit from extra support, whereas pulmonologists in the control condition included patients with less advanced COPD, so as not to additionally burden more vulnerable patients. We used these differences in the patients' baseline characteristics to control for confounders at patient level. However, it is unclear whether all important differences were taken into account and the true effect may therefore be underestimated in this study. Furthermore, attrition is common in long trials testing palliative interventions and does not necessarily reflect poor design or conduct.[49] The proportion of missing data typically increases with study duration.[49] However, our proportion of missing data (28.5% at 3 months) was relatively low compared to the weighted estimate for missing data at primary endpoint of the palliative interventions (23.1% at 28 days, median time), reported in a systematic review.[49] Nevertheless, the width of 8 of the 95% CI of the primary outcome indicated that, if present, our study had the power to detect the necessary minimal important difference (MID) of 4.[50] Since the attrition rates in both conditions were comparable, the threat to compromise the internal validity was minimal.[49] We also have no reason to assume that the participating hospitals are not representative of other hospitals; consequently, our findings can be generalized to other general hospitals.

## IDENTIFICATION OF PATIENTS WITH COPD FOR PROACTIVE PALLIATIVE CARE

The identification of patients for proactive palliative care is complicated by the unpredictable disease course of COPD.[51] Although general tools to identify patients for palliative care exist, they are not specifically intended or validated for use with patients with COPD.[29,52] Despite the development of models of survival in stable COPD to enable the adjustment and optimization of care,[53,54] these population models are unfortunately of limited value for the prediction of the survival of individual patients.[25] A discussion has begun among clinicians about whether or not a transition point for the initiation of proactive palliative care exists.[24,55-57] Some clinicians argued that more specific criteria of end stage COPD need to be explored,[56] while others argued that, since such criteria may not exist, this search may result in prognostic paralysis, and instead promoted the early integration of palliative care according to patient needs,[24,57] The focus of this discussion has been whether or not it is possible to accurately predict mortality instead of the intended objective; identifying patients with COPD in need of proactive palliative care. Since palliative care needs increase during the disease course of COPD,[11] we used the prediction of mortality as a proxy for the need of proactive palliative care. To ensure minimal miss out of patients in need of such care, a potential identification tool should have a sensitivity near 100 with as high a specificity as possible.

Hospitalizations for an AECOPD are associated with significant mortality and therefore create an opportunity to identify patients with poor prognosis in need of palliative care.[26] Recently potentially relevant variables were identified to predict post-hospital mortality in patients hospitalized for an AECOPD.[5,26,27,58-62] We incorporated these variables in our study with the objective of developing a multivariable prediction tool to identify patients with COPD in need of proactive palliative care (**Chapter 6**). Our objective was to assess the discriminating power of a set of indicators for proactive palliative care in predicting death by any cause within one year. This outcome was used as a proxy for the potential need for proactive palliative care in patients with COPD.

We first performed a pilot study to examine whether the 11 potentially relevant variables were documented consistently in the medical records (**Chapter 4**). In a retrospective medical record review of 33 patients, we found that five variables, noninvasive ventilation (NIV), comorbidity, body mass index (BMI), previous admissions for AECOPD, and age were always documented. Three variables, hypoxaemia and/or hypercapnia, professional home care, and actual FEV1% were documented in more than half of the records, while answers to the Clinical COPD Questionnaire (CCQ),[63,64] the Medical Research Council dyspnea questionnaire (MRC dyspnea),[65] and the surprise question[59] were never registered. Most variables were therefore fairly consistently documented in the medical records suggesting that pulmonologists already used these variables in clinical practice. Only an answer to the surprise question, the CCQ and the MRC dyspnea were variables never documented. For our prospective study this would imply that these variables should be specifically asked for and measured. However, the surprise question, the CCQ and the MRC dyspnea are short, easy-to-use questionnaires. In addition, these questionnaires provide valuable information about, respectively, the view of the pulmonologist, the severity of dyspnea and the health status of the patient. Therefore, we decided to include them in the concept set of indicators used in our prospective pragmatic controlled trial.

Data for prognostic accuracy testing in patients hospitalized for an AECOPD were obtained from the three hospitals in the control condition of our prospective pragmatic cluster controlled trial (**Chapter 6**). An optimal prediction model was assessed using Lasso logistic regression,[66,67] with 20-fold cross validation for optimal shrinkage. Missing data were handled using complete case analysis.

We were the first to develop a promising multivariable prediction tool to identify patients with COPD in need of proactive palliative care, the ProPal-COPD tool (Table 1). Our optimal prediction model of death within one year has good discriminating power; the true AUC was 0.82 (95% CI 0.81 to 0.82), and the estimated optimism of 0.05 indicates good internal validity. To ensure minimal miss out of patients in need of palliative care we proposed a cut-off in the prediction model that prioritizes sensitivity 1.5 times above specificity. This optimal cut-off is -1.36, with a sensitivity of 0.90 and a specificity of 0.73. This implies that, when used, only 10% of patients in need of palliative care would be missed out and that of all patients identified for such care, 84% would die within one year. However, before clinical use of the ProPal-COPD tool, the external validity should be addressed in further research.

The ProPal-COPD tool relies on seven predictors: the surprise question (a general predictor), five markers of COPD severity, and the presence of specific co-morbidities proven to independently predict post-hospital mortality in AECOPD.[60] Through the surprise question, the tool incorporates clinical judgment of severity. The surprise question has been shown to be a reasonable predictor of mortality in patients with advanced chronic diseases, and its use has been recommended in combination with other disease-specific predictors as a screening tool for proactive palliative care.[59,68,69] Those disease-specific predictors in the ProPal-COPD tool are five markers of COPD severity: the CCQ (health status), MRC dyspnea, FEV1% of predicted value, BMI, and previous hospitalizations for an AECOPD. The presence of the following co-morbidities is also incorporated in our tool: non-curable malignancy, cor pulmonale, Chronic Heart Failure (CHF), diabetes mellitus with neuropathy and/or renal failure. These co-morbidities, except non-curable malignancy, are conditions liable to acute decompensation especially during AECOPD, which may explain their association with an increased mortality risk.[26]

**Table 1** The ProPal-COPD tool with its predictors, predictive performance, and optimal cut-off

| Predictors in model | *B* | AUC | True AUC | 95%CI | Optimal cut-off | Se | Sp |
|---|---|---|---|---|---|---|---|
| (Intercept) | -3.901 | 0.870 | 0.818 | 0.813 – 0.824 | -1.365 | 0.900 | 0.728 |
| Negative answer SQ | 0.959 | | | | | | |
| Co-morbidity | 1.479 | | | | | | |
| CCQ total, day version > 3 | 0.257 | | | | | | |
| MRC dyspnea = 5 | 1.475 | | | | | | |
| FEV1 < 30% of predicted | 0.565 | | | | | | |
| BMI < 21 or weight loss | 1.005 | | | | | | |
| Prev. hosp. AECOPD | 0.102 | | | | | | |

**Notes:** *B*, weight in the model.

**Abbreviations:** AECOPD, acute exacerbation Chronic Obstructive Pulmonary Disease, AUC, area under the curve; BMI, body mass index; CCQ, Clinical COPD Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 second; MRC dyspnea, Medical Research Council dyspnea questionnaire; Prev. hosp, previous hospitalization; Se, sensitivity; Sp, specificity; SQ, surprise question.

Each dichotomic predictor in our tool has its own weight (*B*), and only when the total sum of the model exceeds the specific cut-off point can the patient be considered in need of proactive palliative care. This means that not all predictors need to be fulfilled and that different numbers and combinations of predictors may be indicative of the need of proactive palliative care. Besides, the weights take into account correlation with other predictors in the tool and therefore should not be interpreted as the individual importance of each particular predictor. Moreover, the Lasso method used for model development identifies the most efficient model.[67] In the trade-off between efficiency and effectiveness, four predictors were excluded from our optimal prediction model. However, this does not mean that these predictors were not predictive of death within one year. The exclusion of these predictors can be explained by the limited number of patients involved (NIV) and/or the high correlation with predictors incorporated into our optimal prediction model (hypoxaemia or hypercapnia, NIV, professional home care and age).

Some researchers worried that patients with COPD in need of proactive palliative care would be missed out by use of the ProPal-COPD tool (**Chapter 6**). Their concern was based on a recent review on prognosis in COPD, which showed that existing prognostic criteria of mortality were not sufficiently reliable.[70] Instead these authors promoted the delivery of proactive palliative care according to the needs and preferences of the patient. However, we believe that the ProPal-COPD tool is suited to and needed for the identification of patients with COPD who require proactive palliative care because the tool has good prognostic performance, ensures minimal miss out of patients in need of proactive palliative care, and facilitates the initiation of ACP conversations:

*Good prognostic performance*

The prognostic performance of the ProPal-COPD tool seems good and is superior to criteria and tools incorporated in the review. The better prognostic performance may be explained by substantive differences. First, the ProPal-COPD tool incorporates disease-specific predictors of mortality in AECOPD requiring hospitalization, whereas the tools examined in the review incorporate disease-specific predictors of mortality in stable COPD. Second, each predictor in the ProPal-COPD tool has an own weight ($B$), in contrast to the tools examined in the review. Although those weights do not represent the individual importance of each predictor, the own contribution of each predictor may be better represented in our tool.

*Minimal miss out of patients in need of proactive palliative care*

The objective of our tool was not to predict mortality but to identify patients with COPD in need of proactive palliative care. Since palliative care needs increase during the disease course of COPD,[11] we merely used the prediction of mortality as a proxy of the need for palliative care. Our main concern was to ensure minimal miss out of patients in need of proactive palliative care. Therefore, we looked for and managed to develop a tool with high sensitivity (0.90) and specificity as high as possible (0.73), while ensuring good discriminating power.

*Facilitation of the initiation of ACP conversations*

Proactive palliative care in COPD, which includes ACP conversations, still hardly takes place despite the recognized need for such care in this patient group.[5] This results not only from the unpredictable disease course, but also from the fact that both patients and physicians encounter barriers to initiating ACP conversations.[71] A recent study examining the quality of ACP conversations in patients with advanced chronic organ failure suggested that facilitation of initiation of ACP conversations is the key to improving proactive palliative care.[72] It seems that otherwise, even when the disease progresses, the needs and preferences of patients are hardly explored.[72] We therefore believe that the development of the ProPal-COPD tool responds to the need of patients and physicians.

## Methodological considerations

This study had several limitations. First, predicting post-hospital mortality for patients with COPD is complex, which is reflected by the number of potential predictors incorporated in the original set of predictors. We only used known predictors in this set, and it is therefore uncertain whether all possible predictors were accounted for. In addition, it is possible that certain predictors were underrepresented in the set of potential predictors; for example, anxiety and depression were represented as a subscale of the predictor CCQ. Second, to facilitate implementation in clinical practice we used dichotomized variables. Each potential predictor was given a clinical cut-off value based on literature. Such dichotomization of continuous predictors may lead to loss of information and reduction of power.[73] Third, the use of the ProPal-COPD tool may require collection of data that are not always captured routinely (surprise question, CCQ, MRC dyspnea). Fourth, the ProPal-COPD tool was developed in the Netherlands, so international differences in hospital admission policies for patients with an AECOPD may affect its usefulness in other countries. Fifth, it is unknown whether the ProPal-COPD tool can also be applied in academic hospitals, since it was developed using a population of patients in general hospitals. Finally, the ProPal-COPD tool was developed in a single population without validation in a different one. The external validity of our findings is therefore unknown and will be addressed in further research.

## RECOMMENDATIONS

### Recommendations for clinical practice

To accomplish a proactive approach to palliative care for patients with COPD, I have the following recommendations for clinical practice:

1. The LAN is urged to take the “barriers to guideline adherence in COPD” into account to optimize strategies and ensure the effective implementation of the clinical guideline on palliative care for patients with COPD.
2. Clinicians involved in the care of patients with COPD should read and use this clinical guideline “palliative care for patients with COPD” to optimize palliative care delivery in this patient group.
3. The ProPal-COPD tool should be used by pulmonologists as an additional aid in the identification of patients with COPD who require proactive palliative care.
4. The implementation of an integrated multidisciplinary approach to proactive palliative care is strongly advised for patients with COPD. This could be accomplished by shared care through cooperation and good communication of relevant healthcare professionals in the different settings involved.
5. Respiratory nurse specialists should fulfill a coordinating role in the organization of proactive palliative care in COPD to ensure continuity of care across these different settings involved.
6. To improve the delivery of proactive palliative care in COPD during hospitalization pulmonologists should improve their palliative care skills and members of the SPCT should be better informed about the management of COPD.

### Recommendations for education and training

For education and training I have the following recommendations:

1. More attention should be paid to palliative care in general in the educational program of all medical and nursing students. This will enable each medical professional to develop basic knowledge about proactive palliative care.
2. During the educational program to become a medical specialist, the elaboration of the specifics of the early identification of palliative patients and proactive palliative care planning for malignant as well as nonmalignant life-threatening diseases is strongly advised.

3. Based on the input of pulmonologists, it is recommended to emphasize the following aspects of palliative care in COPD in education and training: organization of palliative care, communication between pulmonologists and GPs, definition of the coordinating role, and initiation and performance of ACP conversations.
4. ACP conversations encompass more than just communicating bad news. In order to initiate and take part in these conversations, clinicians should develop skills in anticipatory care and shared decision-making. Since the development of these skills is not yet part of the medical curriculum, this should be incorporated into the educational program of medical students.

## Recommendation for research

Based on the results presented in this thesis, I have the following recommendations for research:

1. Before the clinical use of the ProPal-COPD tool, its external validity should be addressed in further research. This research is planned to be carried out in a current nationwide project in the Netherlands, led by the LAN, Leiden University Medical Center, and Radboud University Medical Center.
2. It is possible that, for patients with advanced COPD, filling in the SGRQ or questionnaires in general is too demanding. I therefore recommend the development and evaluation of a shorter, easier to use quality of life questionnaire specifically for patients with advanced COPD and/or the use of a qualitative approach for measuring changes in quality of life of this patient group. By using (additional) qualitative research, one might explore whether and how proactive palliative care affects patients with COPD.
3. It is possible that resilience to improve overall quality of life (especially symptoms and activity) is exhausted in patients with advanced COPD. Future research should therefore explore the effects of proactive palliative care in COPD on the different individual aspects of quality of life, such as the physical, emotional, social, and/or spiritual wellbeing of patients.
4. Proactive palliative care is a complex intervention composed of several components. The delivery of proactive palliative care is patient centered according to their needs, and patients may benefit from pharmacological and/or non-pharmacological components, such as rehabilitation, or social support. However, it is still unknown which components are most useful and for whom. I therefore recommend that future research focuses on identification of the key components of proactive palliative care in COPD that are most effective and those patients most likely to benefit.

## SOCIETAL DISCUSSION

Since the World Health Organization (WHO) introduced a new definition of palliative care in 2002, the clinical use of a proactive approach to palliative care has been promoted for all patients with a life-threatening illness. However, at the start of my PhD study “proactive palliative care for patients with COPD”, palliative care was still often associated with terminal care only, was mainly limited to a reactive approach and was mainly restricted to patients diagnosed with cancer. Although the guideline ‘palliative care for patients with COPD’ had been published, no tools were given to identify patients in need of palliative care. In practice patients with COPD rarely received palliative care. That is why the most important goals of my graduate studies were to raise awareness of the need for proactive palliative care in patients with COPD and to promote this kind of support. Therefore, we explored the views of pulmonologists, we developed an identification tool and we examined the effectiveness of proactive palliative care in patients with COPD. In the meantime, there have been several developments in the fields of palliative care, COPD, and healthcare in general that needs to be discussed to give an impression of the context of our research.

Palliative care is often associated with terminal care only.[44] Research showed that a name change from palliative care to supportive care was associated with more inpatient referrals and earlier referrals in the outpatient setting.[74] Hence, the stigma associated with the term palliative care can be an impediment for a proactive approach to palliative care and may deprive patients of the full benefits of palliative care.[74] As a consequence, a discussion has started whether a name change should be considered.[44,75] However, it is not yet decided if a name change or a change in social view on palliative care is required.[75]

The traditional Global initiative of Chronic Obstructive Lung Disease (GOLD) classification of COPD severity is based on the degree of airflow limitation.[76] However, several studies have shown that the severity of symptoms, functional impairment and quality of life are poorly related to the degree of airflow limitation.[77-79] That is why, recently, different COPD assessments have been developed to understand the impact of the disease on an individual patient.[80-82] These different COPD assessment tools are: the Nijmegen Clinical Screening Instrument (NCSI), the Assessment of Burden of COPD (ABC) scale, and the GOLD 2017 ABCD assessment tool, which all assess the integrated health status of the patient with COPD in order to guide treatment.[80-82] However, it is not yet decided when during these assessments the focus should include proactive palliative needs of patients, in which the patient and professional caregiver plan ahead on future needs and ACP conversations take place. The LAN, who was involved in the development of the ABC scale, has just started a four-year nationwide project in the Netherlands with the objective to make palliative care as usual available care for patients with COPD. During this project, which has been made possible thanks to financial support of ZonMW, the external validity of the ProPal-COPD tool will also be aassessed.

Assessments of the integrated health status of the patient with COPD fits into the recent shift in healthcare from a doctor-centered to a patient-centered approach. Within a patient-centered approach, patients are well informed about their health status, establish their own treatment goals, and collaborate with healthcare providers.[83] This patient empowerment with the emphasis on communication, health promotion, and partnership has become necessary because of the aging of the population. In this manner, the quality of care can be improved while at the same time the cost for healthcare can be reduced. The recent shift to patient-centered care links in with the new perception of health, as the ability to adapt and self manage in the face of social, physical, and emotional challenges, instead of the old WHO definition of health as complete wellbeing.[84]

Within the concept of patient centered care the patients' capability of self management is vital.[83] If patients are to participate fully in their care and in the management of a long-term condition, such as COPD, good communication is essential.[85] However, it is likely that in the population of patients with COPD, the proportion of people with low health literacy is relatively high, as they are an older population with a lower average SES.[86] Increased awareness of low health literacy in COPD is necessary to assist clinicians to improve patients' knowledge of their disease and adherence to healthcare recommendations.[87] In addition, I advise to examine to which level patients with COPD, especially those with low health literacy, are capable of self management of their disease.

Modern medicine has made major breakthroughs. However, there is a reverse side to the improvement of the possibilities to cure diseases and to extend lives. Certain treatments are very radical, cause serious side effects and even have damaging consequences. In my opinion, the discussion regarding treatment in the final phase of life should therefore certainly include the consequences of treatment on quality of life and quality of dying. This way patients can make choices that are congruent with their wishes and values. Thankfully, small steps in the societal discussion concerning this subject have recently been made through a report titled 'not everything that is possible needs to be done', which promotes appropriate care for patients in their final phase of life.[88]

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# Summary
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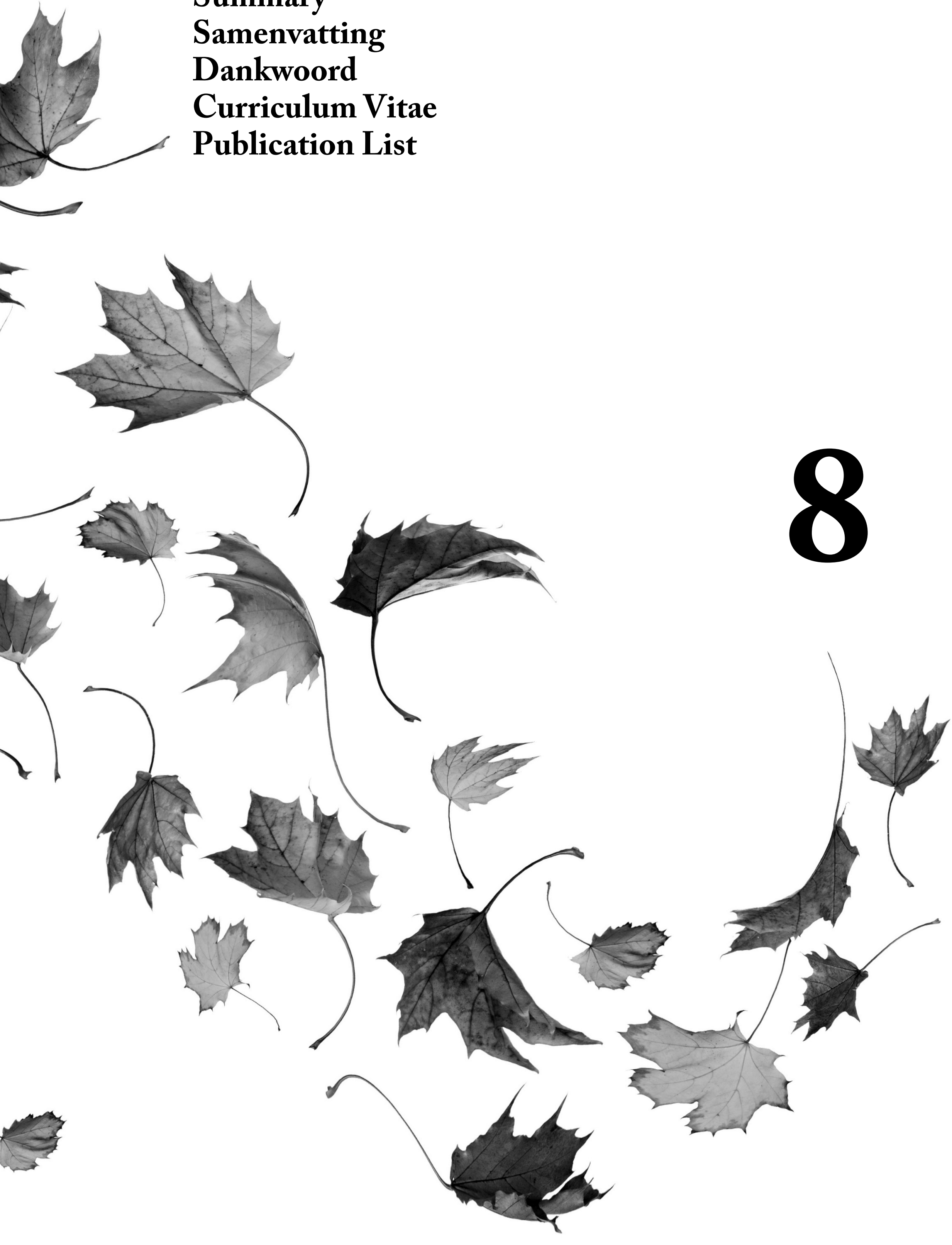
# 8



## SUMMARY

Chronic Obstructive Pulmonary Disease (COPD) is a progressive life-threatening lung disease. Patients with advanced COPD have a high symptom burden and poor quality of life. Their quality of life is equally or sometimes even worse than that of patients with lung cancer. Research has shown that early or proactive palliative care can improve the quality of life of patients in the palliative phase. Up till now, this kind of care has been reserved mostly for patients with cancer and is not very common for patients with COPD. But the World Health Organization (WHO) states in its 2002 definition that palliative care should be available for all patients with a life-threatening disease. So, also patients with COPD may profit of such care. However, because of a difference in disease trajectory patients with COPD require another approach to palliative care compared to patients with cancer. The disease trajectory of COPD is less predictable with a gradual functional decline, often punctuated by acute severe exacerbations any one of which may be fatal. This unpredictable disease trajectory not only complicates timely identification of patients who may profit of palliative care but also compromises continuity of palliative care delivery, since during stable phases of the disease often different healthcare professionals are involved than during the acute phases. The lack of a valid prognostic tool to identify patients for proactive palliative care may hinders adequate care, communication and organization in the palliative phase. Whereas, at this point, a well-coordinated, multidisciplinary approach is needed to guarantee continuity of palliative care. However, it has not been determined how this coordinated care should be successfully organized. Since pulmonologist have a central role in COPD management, they seem to be the appropriate professionals to take the lead in organizing this coordinated, multidisciplinary approach to palliative care. Therefore, the objectives of this thesis were to explore the view, needs and wishes of pulmonologists concerning proactive palliative care for patients with COPD, to examine identification of patients with COPD for proactive palliative care and to examine the effectiveness of proactive palliative care on the well-being of patients with COPD (**Chapter 1**).

Since pulmonologists have a central role in COPD management, their view on palliative care for patients with COPD is important. In **Chapter 2** we describe the results of a survey study performed by members (pulmonologists) of the Netherlands Association of Physicians for Lung Diseases and Tuberculosis. (NVALT). The 256 respondents (32%) covered 85.9% of the hospital organizations in the Netherlands. Almost all pulmonologists indicated that palliative care for patients with COPD is desirable. However, about half of the pulmonologists mentioned not to use the clinical guideline on palliative care for patients with COPD, most often because they were not aware of its existence. We therefore recommend that more attention should be paid to the implementation of this guideline. Most pulmonologists (92.2%) indicated to distinguish a palliative phase in the COPD trajectory, but there was no consensus about the different criteria used for its identification. All pulmonologists mentioned using several criteria, the combinations

of which were different for each pulmonologist. These were different criteria concerning prognosis, curability and palliative needs to mark the start of palliative care in COPD. We also asked the pulmonologists about the content of palliative care for patients with COPD. Aspects considered most important were: advance care planning (ACP) conversations (82%), communication between pulmonologist and general practitioner (77%), and identification of the palliative phase (75.8%), while the latter was considered the most important aspect for improvement (67.6%). We therefore recommended to conduct further research into more specific criteria to timely initiate the palliative trajectory. With respect to the organization of care, pulmonologists indicated to prefer organizing palliative care for hospitalized patients with COPD themselves (55.5%), while 30.9% indicated to prefer cooperation with a Specialized Palliative Care Team (SPCT). Since palliative care in COPD is not common practice, we recommended pulmonologists to improve their skills of palliative care and members of the SPCT to be better informed about the management of COPD. In the ambulatory setting a multidisciplinary cooperation between pulmonologist, general practitioner and a respiratory nurse specialist was preferred (71.1%). Because pulmonologist also indicated ACP conversations and communication between pulmonologist and GP as important improvement aspects (respectively 46.5% and 40.6%), we recommended to emphasize these aspects in training for professionals involved in palliative care for this group of patients.

In **Chapter 3** the study protocol of a pragmatic cluster controlled trial (quasi-experimental design) was provided in which the background and the methodology of our study were explained. The main objectives of the study were: 1) to assess the discriminating power of a set of indicators for poor prognosis in order to identify patients with COPD for proactive palliative care (indicator study), and 2) to assess the effects of proactive palliative care for qualifying patients with COPD on the wellbeing of these patients (intervention study). A cluster design was chosen to prevent contamination and to minimize ethical concerns of patients and clinicians with respect to randomization and gate keeping. At the time of hospital recruitment, a minority of hospitals in the Netherlands had the availability of an SPCT and randomization of these hospitals was not possible. Therefore, hospitals were selected for the intervention condition based on the presence of an SPCT. In total, six general hospitals participated, three hospitals in the control and three in the intervention condition. In order to control for confounders on hospital level, a pre-trial assessment was performed in which hospitals were compared on baseline characteristics over the year before trial. All outcome measures were on patient level and patients performed a pre and post intervention measurement.

The planned study population consisted of patients with COPD. Patients would be included during hospitalization for an acute exacerbation COPD (AECOPD). All patients in the study would receive usual care, while only patients in the intervention condition who had a poor prognosis according to our set of indicators additionally would receive proactive palliative care provided by an SPCT. Poor prognosis was defined as meeting two or more indicators of a checklist of 11 indicators of poor prognosis. This set of indicators were, a priori, selected based on literature. For data analysis of the indicator study we planned to use all the data collected in the hospitals in the control condition. In the intervention study we planned to compare the data of patients with COPD with poor prognosis between the hospitals in the intervention and the control condition. Innovative aspects of the study were: the use of a set of indicators for proactive palliative care, the active involvement of an SPCT, and the use of a patient-tailored proactive palliative care plan.

Before starting a prospective study, we performed a pilot study to get an indication of the applicability of the set of 11 indicators in our prospective study (**Chapter 4**). Since we wanted to develop a doctor-friendly and patient-convenient tool that is easy to implement, our objective was to examine whether these indicators were documented consistently in the medical records of patients hospitalized for an AECOPD. A retrospective medical record review showed that five indicators, namely non invasive ventilation (NIV), comorbidity, body mass index (BMI), previous admissions for AECOPD and age were always documented. The presence or absence of hypoxaemia and/or hypercapnia at discharge was documented in 85% of the records. No documentation in most cases meant that the patient was not hypoxaemic or hypercapnic at admission. Professional home care and actual FEV1% of predicted value were documented half of the time. A possible explanation of lack of documentation about the need for professional home care might be that this is not documented if the patient does not have such care. An explanation of the absence of actual FEV1% might be that if unknown at admission it cannot be assessed truthful in an instable phase such as an AECOPD. Only an answer to the surprise question, the Clinical COPD Questionnaire (CCQ) and MRC dyspnea were never documented and should be specifically asked for. However, these three questionnaires are short and easy to use. Therefore, we concluded that in our prospective study the use of the set of concept indicators for proactive palliative care appeared to be user-friendly and feasible.

**Chapter 5** describes the results of the intervention study of our pragmatic cluster controlled trial. Although, in general, research of patients in the palliative phase has difficulties with recruitment, we were able to include the necessary number of patients with advanced COPD. We did not find, though, an effect of proactive palliative care on our primary outcome: the change in quality of life measured with the St George Respiratory Questionnaire (SGRQ) from baseline to 3 months was not different between groups. This result may be explained by several possible reasons on identification, organization, patient, outcome measure, and disease course level. First, it is possible that our criteria for poor prognosis were too broad. Second, it is unknown to what extend collaboration between GPs and the SPCT, necessary to ensure continuity of palliative care, was implemented. Third, the in general, lower Social Economic Status (SES) of patients with COPD may have affected study outcomes, since some patients in our study had difficulties understanding the questionnaires and /or lacked the financial means to afford necessary additional support. Fourth, for some patients with advanced COPD filling in questionnaires may have been too demanding. Finally, outcomes of measurements in COPD are influenced by acute exacerbations and this may have influenced findings in our study defined on fixed time points.

However, patients receiving proactive palliative care experienced less impact of their COPD (SGRQ impact subscale) at 6 months than patients receiving usual care. In contrast to patients with cancer in the palliative trajectory, for patients with advanced COPD who receive palliative care disease oriented care remains necessary until the last weeks of life. We concluded that it is possible that resilience to improve overall quality of life (especially symptoms and activity) is exhausted in this patient group and that further research is needed to test this hypothesis. Moreover, there was a relevant difference in number of patients that made ACP choices during the year of trial, in favor of the intervention group. Since research has shown that such choices increase the quality of end-of-life care, we suggested that proactive palliative care in COPD should place emphasis on supporting patients through ACP conversations. Finally, other questionnaire outcomes, number and length of hospital admissions nor in survival were not different between groups.

In **Chapter 6** we report the development of the ProPal-COPD tool to identify patients with COPD for proactive palliative care. Data of 11 potential predictors of poor prognosis, a priori selected based on literature, were collected during hospitalization for an acute exacerbation COPD (AECOPD). Since palliative care needs increase during the disease course of COPD, the prediction of mortality within one year was used as a proxy for need of proactive palliative care. After one year the medical files were, if applicable, explored for date of death. An optimal prediction model was assessed by a Lasso logistic regression, with 20-fold cross validation for optimal shrinkage. The optimal prediction model was internally validated and had good discriminating power (AUC = 0·82, 95% CI 0·81 to 0·82). This model relied on seven predictors: the surprise question, MRC dyspnea, Clinical COPD Questionnaire (CCQ), FEV1% of predicted value, Body Mass Index (BMI), previous hospitalizations for AECOPD, and specific co-morbidities. To ensure minimal miss out of patients in need of proactive palliative care we proposed a cut-off in the model that prioritized sensitivity over specificity (respectively 0·90 over 0·73). Our model (ProPal-COPD tool) was a stronger predictor of mortality within one year than the CODEX index (AUC = 0.68). Each predictor in the tool has an own weight and only when the total sum of the model exceeds the specific cut-off point the patient can be considered in need of proactive palliative care. This prognostic equation can be easily integrated in the Electronic Patient Record (EPR) system. However, before clinical use of the ProPal-COPD tool we recommended to address the external validity in further research.

In response to our paper, some authors wrote a letter to the editor, in which they expressed their worries that patients with COPD in need of proactive palliative care would be missed out by use of the ProPal-COPD tool. Their concern was based on a recent review on prognosis in COPD, which showed that existing prognostic criteria of mortality were not sufficiently reliable. Instead these authors promoted the delivery of proactive palliative care according to the needs and preferences of the patient. Ideally, this should be the case, but in practice there are patient and doctor centered barriers to start ACP conversations, implying that many patients don’t receive palliative care at all. Therefore, we believe that the ProPal-COPD tool is suited and needed for the identification of patients with COPD who require proactive palliative care because the tool: has good prognostic performance, ensures minimal miss out of patients in need of proactive palliative care, and on top of that facilitates the initiation of ACP conversations.

In **Chapter 7**, the final chapter of this thesis, the main findings and strengths and weaknesses of the studies are discussed and placed in a wider perspective. Next, recommendations are given for clinical practice, education and training, and research. This chapter ends with a societal discussion on the topic of our thesis “Proactive palliative care for patients with COPD”.

# SAMENVATTING

Chronic Obstructive Pulmonary Disease (COPD) is een progressieve levensbedreigende longziekte. In een gevorderd stadium van deze ziekte, hebben patiënten vaak een hoge symptoomlast en een slechte kwaliteit van leven. Hun kwaliteit van leven is gelijk aan, of soms zelfs slechter dan, die van patiënten met longkanker. Onderzoek heeft aangetoond dat vroege of proactieve palliatieve zorg de kwaliteit van leven kan verbeteren van patiënten in de palliatieve fase. Tot nu toe is deze zorg vooral toegepast bij patiënten met kanker en is niet erg gebruikelijk voor patiënten met COPD. De Wereldgezondheidsorganisatie (World Health Organization, WHO) verklaart echter in de definitie van palliatieve zorg (2002) dat deze zorg beschikbaar moeten zijn voor alle patiënten met een levensbedreigende ziekte. Dit betekent dat patiënten met COPD ook baat zouden kunnen hebben bij deze zorg. Vanwege een verschil in ziekteverloop, hebben patiënten met COPD echter een andere aanpak van palliatieve zorg nodig dan patiënten met kanker. Het ziekteverloop van COPD is minder voorspelbaar met een geleidelijke functionele afname onderbroken door ernstige acute longaanvallen (exacerbaties), die ieder fataal kunnen zijn. Dit onvoorspelbare ziekteverloop bemoeilijkt niet alleen tijdige identificatie van patiënten die baat kunnen hebben bij palliatieve zorg maar brengt ook de continuïteit van de palliatieve zorgvoorziening in gevaar. Immers, tijdens de stabiele fase van de ziekte zijn vaak andere gezondheidszorg professionals betrokken dan in de acute fase. Het gebrek aan een valide, prognostisch instrument ter identificatie van patiënten met COPD voor proactieve palliatieve zorg belemmert mogelijk adequate zorg, communicatie en organisatie in de palliatieve fase. Terwijl een goed gecoördineerde, multidisciplinaire aanpak nu juist nodig is om de continuïteit van palliatieve zorg te kunnen waarborgen. Het is echter nog niet duidelijk hoe deze gecoördineerde zorg zou moeten worden georganiseerd. Aangezien longartsen een centrale rol hebben in COPD management, lijken zij de geëigende professional te zijn om een leidende rol op zich te nemen in de organisatie van deze gecoördineerde, multidisciplinaire aanpak van palliatieve zorg. Vandaar dat de doelstellingen van dit proefschrift waren: het exploreren van de zienswijzen, de behoeften, en de wensen van longartsen betreffende proactieve palliatieve zorg voor patiënten met COPD, het ontwikkelen van een instrument ter identificatie van patiënten met COPD voor proactieve palliatieve zorg, en het onderzoeken van de effectiviteit van proactieve palliatieve zorg op het welzijn van patiënten met COPD (**Hoofdstuk 1**).

Aangezien longartsen een centrale rol hebben in COPD management, wilden we weten hoe zij aankijken tegen palliatieve zorg bij COPD. In **Hoofdstuk 2** beschrijven we de resultaten van een vragenlijstonderzoek uitgevoerd bij leden (longartsen) van de Vereniging van Artsen voor Longziekten en Tuberculose (NVALT). De 256 respondenten (32%) omvatten 85,9% van de ziekenhuisorganisaties in Nederland. Bijna alle longartsen gaven aan dat palliatieve zorg voor patiënten met COPD wenselijk is. Ongeveer de helft van de longartsen gaf echter aan dat zij de klinische richtlijn palliatieve zorg voor patiënten met COPD niet gebruikten, veelal omdat zij niet van het bestaan afwisten. We raadden daarom aan om meer aandacht te schenken aan de implementatie van deze richtlijn. De meeste longartsen gaven aan dat zij een palliatieve fase onderscheiden in het COPD traject, maar er was geen consensus over de verschillende criteria die gebruikt werden voor de identificatie van deze fase. Alle longartsen gaven aan meerdere criteria te gebruiken maar iedere longarts noemde een andere combinatie van criteria. Dit waren criteria met betrekking tot prognose, behandelbaarheid en palliatieve behoefte om de start van de palliatieve fase te markeren. We hebben de longartsen ook gevraagd naar de inhoud van palliatieve zorg bij COPD. Aspecten die het belangrijkste gevonden werden waren: gesprekken met de patiënt over voorkeuren ten aanzien van levensverlengende behandelingen (82%), communicatie tussen longarts en huisarts (77%), en identificatie van de palliatieve fase (75,8%), terwijl het laatste werd beschouwd als het belangrijkste aspect voor verbetering (67,6%). We raadden daarom aan om verder onderzoek te verrichten naar meer specifieke criteria voor een tijdige start van de palliatieve fase. Met betrekking tot de organisatie van zorg gaven de meeste longartsen aan zelf verantwoordelijk te willen zijn voor palliatieve zorgverlening bij patiënten met COPD die zijn opgenomen in het ziekenhuis (55,5%), terwijl 30,9% aangaf de voorkeur te geven aan samenwerking met een consultteam palliatieve zorg. Aangezien palliatieve zorg bij COPD niet gebruikelijk is, raadden we longartsen aan hun palliatieve zorg vaardigheden te verbeteren en leden van het consultteam palliatieve zorg om beter geïnformeerd te zijn over de behandeling van COPD. In de ambulante setting werd de voorkeur gegeven aan een multidisciplinaire samenwerking tussen longarts, huisarts en de verpleegkundig specialist longgeneeskunde (71,1%). Omdat longartsen als aspecten voor verbetering ook aangaven: gesprekken met de patiënt over voorkeuren ten aanzien van levensverlengende behandelingen (46,5%), en communicatie tussen longarts en huisarts (40,6%), raadden wij aan deze aspecten te benadrukken tijdens trainingen voor zorgprofessionals die te maken hebben met palliatieve zorg in deze patiëntengroep.

In **Hoofdstuk 3** is het studieprotocol beschreven van de pragmatische cluster gecontroleerde studie (quasi-experimenteel design) waarin de achtergrond en de methodologie van dit onderzoek zijn uiteengezet. De belangrijkste doelstellingen van het onderzoek waren: 1) het vaststellen van het discriminerend vermogen van een set van indicatoren voor slechte prognose ter identificatie van patiënten met COPD voor proactieve palliatieve zorg (indicatorenstudie), en 2) het vaststellen van de effectiviteit van proactieve palliatieve zorg bij daarvoor in aanmerking komende patiënten met COPD, op het welzijn van deze patiënten (interventiestudie). Er was gekozen voor een cluster design om contaminatie te voorkomen en om ethische bezwaren te beperken van patiënten en clinici met betrekking tot randomisatie en selectie. Aangezien op het moment van werving van de ziekenhuizen (2013) slechts enkele ziekenhuizen in Nederland de beschikking hadden over een consultteam palliatieve zorg was randomisatie van deze ziekenhuizen niet mogelijk. Vandaar dat ziekenhuizen werden toegewezen aan de interventieconditie op basis van de aanwezigheid van een consultteam palliatieve zorg. In totaal namen zes algemene ziekenhuizen deel, drie in de controle- en drie in de interventieconditie. Om te controleren voor

verstorende factoren (confounders) op ziekenhuisniveau werd een voormeting uitgevoerd waarbij ziekenhuizen werden vergeleken op baseline karakteristieken over het jaar voorafgaande aan de studie. Alle uitkomsten waren op patiëntniveau en patiënten voerden eenzelfde meting voor en na de interventie uit.
De geplande studiepopulatie bestond uit patiënten met COPD, die geïncludeerd zouden worden tijdens een ziekenhuisopname voor een acute exacerbatie COPD (AECOPD). Alle patiënten in het onderzoek zouden gebruikelijke zorg ontvangen, terwijl uitsluitend patiënten in de interventieconditie die volgens onze set van indicatoren een slechte prognose hadden, extra proactieve palliatieve zorg zouden ontvangen van een consultteam palliatieve zorg. Een slechte prognose werd gedefinieerd als het voldoen aan twee of meer indicatoren van een set van 11 indicatoren voor slechte prognose. Deze set van indicatoren waren, voorafgaande aan de studie, geselecteerd op basis van de literatuur. Voor data-analyse van de indicatorenstudie planden we alle data te gebruiken die we hadden verzameld in de ziekenhuizen in de controleconditie. In de interventiestudie planden we om de data van alle patiënten met een slechte prognose in de interventie- en de controleconditie met elkaar te vergelijken. Innovatieve aspecten van de studie waren: het gebruik van een set van indicatoren voor proactieve palliatieve zorg, de actieve betrokkenheid van een consultteam palliatieve zorg, en het gebruik van een persoonlijk op de patiënt toegesneden proactief palliatief zorgplan.

Voorafgaande aan de start van de prospectieve studie, voerden we een pilot studie uit om een indicatie te krijgen van de toepasbaarheid van de set van 11 indicatoren in onze prospectieve studie (**Hoofdstuk 4**). Aangezien we een instrument wilden ontwikkelen dat zowel voor de arts als de patiënt gebruikersvriendelijk is en daardoor makkelijk te implementeren, was ons doel te onderzoeken of deze indicatoren consequent gedocumenteerd waren in de medische dossiers van de patiënten die opgenomen waren in het ziekenhuis voor een AECOPD. Een retrospectief medisch dossier onderzoek liet zien dat vijf indicatoren, te weten noninvasieve ventilatie (NIV), comorbiditeit, body mass index (BMI), eerdere opnames voor AECOPD en leeftijd altijd waren gedocumenteerd. De aan- of afwezigheid van hypoxaemia en/of hypercapnia bij ontslag was in 85% van de dossiers gedocumenteerd. Geen documentatie betekende in de meeste gevallen dat tijdens opname de patiënt niet hypoxaemisch of hypercapnisch was. Professionele thuiszorg en actuele FEV1% van voorspelde waarde waren in de helft van de dossiers gedocumenteerd. Een mogelijke verklaring voor de afwezigheid van documentatie betreffende de behoefte aan professionele thuiszorg is dat dit niet gedocumenteerd wordt als de patiënt deze zorg niet nodig heeft. Een mogelijke verklaring voor de afwezigheid van FEV1% van voorspelde waarde is dat indien dit onbekend is bij opname het niet nauwkeurig gemeten kan worden tijdens een instabiele fase zoals een AECOPD. Alleen een antwoord op de surprise question, de Clinical COPD Questionnaire (CCQ) en de MRC dyspnea waren nooit gedocumenteerd en zouden extra afgenomen moeten worden. Deze drie vragenlijsten zijn echter kort en makkelijk in gebruik. Vandaar dat we concludeerden dat in onze prospectieve studie het gebruik van de set van concept indicatoren voor proactieve palliatieve zorg gebruikersvriendelijk en haalbaar lijkt.

**Hoofdstuk 5** beschrijft de resultaten van de interventiestudie van onze pragmatische cluster gecontroleerde studie. Hoewel onderzoek van patiënten in de palliatieve fase over het algemeen te maken heeft met wervingsproblemen, is het ons gelukt het noodzakelijke aantal patiënten met gevorderd COPD in een jaar tijd te includeren in de studie. We vonden geen effect van proactieve palliatieve zorg op de primaire uitkomstmaat: de verandering in kwaliteit van leven gemeten met de St George Respiratory Questionnaire (SGRQ) van baseline tot 3 maanden was niet verschillend tussen de beide groepen. Factoren op identificatie-, organisatie-, patiënt-, uitkomstmaat-, en ziekteverloopniveau zouden aan dit uitblijven van effect kunnen hebben bijgedragen. Ten eerste is het mogelijk dat onze inclusiecriteria wat betreft 'slechte prognose' te ruim waren. Ten tweede is het onduidelijk in welke mate de beoogde samenwerking tussen de huisartsen en het consultteam palliatieve zorg daadwerkelijk heeft plaatsgevonden. Deze samenwerking was nodig om continuïteit van palliatieve zorg te waarborgen. Ten derde is het mogelijk dat de, over het algemeen, lage sociaal economische status (SES) van patiënten met COPD de uitkomsten van de studie heeft beïnvloed, aangezien sommige patiënten in onze studie de vragen van de vragenlijsten niet begrepen en/of niet de financiële middelen hadden om zich de noodzakelijke extra ondersteuning te kunnen permitteren. Ten vierde is het invullen van vragenlijsten voor sommige patiënten met gevorderd COPD mogelijk te veeleisend geweest. Tenslotte beïnvloeden acute exacerbaties de uitkomsten van metingen bij COPD. Omdat de metingen in onze studie plaatvonden op vooraf vastgestelde momenten, kan dit zeker onze studie hebben beïnvloed.

Patiënten die proactieve palliatieve zorg ontvingen, ervoeren echter wel minder impact van hun COPD (SGRQ impact subschaal) na 6 maanden dan patiënten die gebruikelijke zorg ontvingen. In tegenstelling tot palliatieve patiënten met kanker, blijft voor patiënten met gevorderd COPD ziektegerichte zorg noodzakelijk tot de laatste weken van hun leven. Vandaar dat we concludeerden dat in deze patiëntengroep mogelijk de veerkracht ontbreekt om de overall kwaliteit van leven (in het bijzonder, symptomen en activiteiten) te verbeteren en dat vervolgonderzoek nodig is om deze hypothese te testen. Bovendien was er een relevant verschil in het aantal patiënten dat ACP keuzes maakten in het jaar van de studie, in het voordeel van de interventiegroep. Omdat onderzoek heeft aangetoond dat dergelijke keuzes de kwaliteit van eindleven zorg kan verbeteren, raadden we in de palliatieve fase aan patiënten met COPD te ondersteunen door ACP gesprekken te voeren. Tenslotte vonden we geen verschillen tussen beide groepen in de uitkomsten van andere vragenlijsten, aantal en duur van de ziekenhuisopnames en in overleving.

In **Hoofdstuk 6** rapporteren we de ontwikkeling van het ProPal-COPD instrument ter identificatie van patiënten met COPD voor proactieve palliatieve zorg. Data van 11 potentiële predictoren van slechte prognose, vooraf geselecteerd op basis van literatuur, werden verzameld

tijdens ziekenhuisopname voor een AECOPD. Aangezien palliatieve zorgbehoeften toenemen tijdens het ziektetraject van COPD werd de voorspelling van sterfte binnen één jaar gebruikt als afgeleide (proxy) van de behoefte aan proactieve palliatieve zorg. Na één jaar werden, indien van toepassing, de medische dossiers onderzocht op datum van sterfte. Een optimaal predictie model werd verkregen door een Lasso logistieke regressie, met 20-voudige cross validatie voor optimale krimping. Het optimale predictie model was intern gevalideerd en had een goed discriminerend vermogen (AUC = 0,82, 95% CI 0,81 to 0,82). Het model bestond uit zeven predictoren: de surprise question, MRC dyspnea, CCQ, FEV1% van voorspelde waarde, BMI, eerdere ziekenhuisopnamen voor AECOPD, en specifieke comorbiditeiten. Om ervoor te zorgen dat zo min mogelijk patiënten die proactieve palliatieve zorg nodig hebben gemist worden, stelden we een afkappunt in het model voor waarbij meer waarde wordt gehecht aan sensitiviteit dan specificiteit (respectievelijk 0,90 en 0,73). Ons model (het ProPal-COPD instrument) was een betere voorspeller van sterfte binnen één jaar dan de CODEX index (AUC = 0,68). Iedere predictor van dit instrument heeft een eigen gewicht en alleen als de totale som van het model hoger is dan het specifieke afkappunt kan de patiënt beschouwd worden als behoeftig aan proactieve palliatieve zorg. Deze prognostische optelsom kan gemakkelijk worden geïntegreerd in het Elektronische Patiënten Dossier (EPD). Echter, voor klinisch gebruik van het ProPal-COPD instrument raden we aan om eerst de externe validiteit te bepalen in vervolgonderzoek.
In antwoord op ons artikel hebben een aantal auteurs een brief aan de editor geschreven waarin zij hun zorgen uitten over het mogelijk missen van patiënten met COPD die proactieve palliatieve zorg nodig hebben bij gebruik van het ProPal-COPD instrument. Hun bezorgdheid was gebaseerd op een recente review over prognose in COPD, die aantoonde dat bestaande prognostische criteria van sterfte niet voldoende betrouwbaar waren. In plaats daarvan promootten deze auteurs het aanbieden van proactieve palliatieve zorg die afgestemd is op de behoefte en voorkeur van de patiënt. Idealiter, zou dit natuurlijk het geval moeten zijn, maar in werkelijkheid spelen er zowel bij iedere patiënt als bij de behandelaar allerlei barrières om het ACP gesprek aan te gaan, waardoor dit bij een flink deel van de patiënten tot op heden in het geheel niet plaatsvindt. Wij geloven daarom dat het ProPal-COPD instrument geschikt en van belang is ter identificatie van patiënten met COPD voor proactieve palliatieve zorg aangezien het instrument: een goed prognostisch vermogen heeft, ontwikkeld is om zo min mogelijk patiënten die proactieve palliatieve zorg nodig hebben te missen, en bovendien de initiatie van ACP gesprekken faciliteert.

In **Hoofdstuk 7**, het laatste hoofdstuk van dit proefschrift, worden de belangrijkste bevindingen en de sterke en zwakke kanten van de studies besproken en in een breder perspectief geplaatst. Vervolgens worden aanbevelingen gegeven voor de klinische praktijk, onderwijs en training, en wetenschappelijk onderzoek. Dit hoofdstuk eindigt met een maatschappelijke discussie over het onderwerp van mijn proefschrift “Proactieve palliatieve zorg voor patiënten met COPD”.

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# CURRICULUM VITAE

Ria G. Duenk werd geboren op 14 augustus 1960 in Hengelo (O). In 1978 behaalde ze haar VWO diploma aan het Ichthus College in Enschede. Na twee keer te zijn uitgeloot voor de studie Geneeskunde is zij gestart met de studie Fysiotherapie aan de Twentse Academie voor Fysiotherapie in Enschede. In 1984 behaalde ze haar diploma en vertrok zij naar het buitenland (Zwitserland, Egypte en de Filippijnen) waar ze in totaal 15 jaar als fysiotherapeut gewerkt heeft in zowel ziekenhuizen als particuliere praktijken.

In 1999 keerde zij met haar gezin terug naar Nederland en vond zij een baan als fysiotherapeut in gezondheidscentrum de Kroonsteen in Malden. Tijdens haar werkzaamheden ondervond ze dat gedragsverandering bij cliënten de sleutel was tot lange termijn therapiesucces. Om cliënten beter te kunnen begeleiden in het proces van gedragsverandering heeft ze zich gespecialiseerd als psychosomatisch fysiotherapeut.

Sindsdien nam haar interesse in “wat mensen beweegt” alleen maar toe. Uiteindelijk heeft ze in 2006 de knoop doorgehakt en is Psychologie gaan studeren aan de Radboud Universiteit in Nijmegen. Tijdens deze studie, die ze in 2010 cum laude afrondde, ontwikkelde ze een passie voor mensgebonden toepassingsgericht wetenschappelijk onderzoek.

Vandaar dat ze allereerst als waarnemend onderzoekscoördinator werkzaam is geweest bij het IRAS van de Universiteit Utrecht alvorens een PhD positie te aanvaarden. In 2012 is zij gestart met haar promotieonderzoek naar proactieve palliatieve zorg bij patiënten met COPD op de afdeling Anesthesiologie, Pijn en Palliatieve Geneeskunde van het Radboud Universitair Medisch Centrum in Nijmegen.

Ria is getrouwd met Joop Hageman. Samen hebben zij drie kinderen Jart (1992), Koen (1994) en Hidde (1996).

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