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Patient-reported outcome measures in early palliative care for end-stage chronic obstructive pulmonary disease (COPD): from research to applicability into clinical practice

-HABILITATION THESIS-

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2021

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ABBREVIATION LIST

AD autonomic dysfunction
AI aerodigestive impairment
BDI-baseline dyspnea index
BMI-body mass index
BODE index
BPOC-bronhopneumopatia obstructiva cronica,
BUD/FOR: budesonide/formoterol
COPD- chronic obstructive pulmonary disease
CAT-COPD Assessment Test
CCQ-Clinical COPD Questionnaire
CCQ-S CCQ domain for symptoms
CCQ-F CCQ domain for functioning
CCQ-M CCQ domain for mental status
CRF-chronic respiratory failure
CRQ-Chronic Respiratory Disease Questionnaire
EHD-early hospital discharge
ESAS-Edmonton Symptom Assessment Scale
EuroQol-5D-EuroQol five dimensions
FACIT- F- Functional Assessment of Chronic Illness Therapy for fatigue scale
FACIT-PWB-physical domain of FACIT-F scale
FACIT-EWB emotional domain of FACIT-F scale
FACIT-FACIT-FWB functional of FACIT-F scale
FACIT-SWB social domain of FACIT-F scale
FACIT-T total score of FACIT-F scale
FEV1-forced expiratory volume in the first second
FVC- forced vital capacity
FF/ UME/VI: furoate/umeclidinium/vilanterol
GOLD- Global Initiative on Obstructive Lung Disease
HR-hazard ratio
HRQoL-health-related quality of life
HS-health status
KPSS- Karnofsky Performance Status Scale
LABA- long-acting beta2 agonist
LAMAs- long-acting antimuscarinic agents
LE- loss of energy
LHD-late hospital discharge
LoS-length of hospital stay
LTOT long-term oxygen therapy

mMRC- modified Medical Research Council dyspnea scale
MRC study-Medical Research Council Study
MRF-26 Maugeri Respiratory Failure Questionnaire 26 items
NOTT- Nocturnal Oxygen Therapy Trial study
OLIN-Obstructive Lung Disease in Northern Sweden
P- placebo
paO2-partial pressure of oxygen in arterial blood
PI-poor intake
PRO-patient reported outcome
QALYs-quality-adjusted life years
SF-36- Medical Outcome Study Questionnaire Short Form 36
SF-PCS Physical Component Summary of the SF-36
SF-MCS Mental Component Summary of the SF-36
SGRQ- Saint George Respiratory Questionnaire
SpO2-oxygen saturation by pulse oxymetry
T-tiotropium
TNF-α tumour necrosis factor alpha
VAS-visual analogue scale
VO2max- peak oxygen uptake
WHO Five Well Being Index(WHO-5)

ABSTRACT OF THE THESIS

For an academic clinician the continuous professional development is a key approach for a competitive professional performance. This development must be multilateral because this role involves teaching students and in training physicians, caring from patients and doing clinical research. Therefore it is necessary that didactic, research and clinical activities are continuously improved and updated and new topics of interest are added in order to fulfill the own expectations, the promotion requirements and in order to contribute to the increase in visibility and prestige of the university where such a professional works.

I am a Pulmonary Disease consultant physician as a clinical background but my "real" career started as an Assistant Lecturer in Pulmonary Disease at the University of Medicine and Pharmacy Grigore T Popa in Iasi, Romania and this academic setting opened new professional horizons and triggered the development of many of the skills acquired subsequently. Most notably during this professional step I had the opportunity to train and perform quality clinical research abroad and this helped me to further expand this professional field when back home. As a Clinical Research fellow I focused on patient-reported outcomes and mostly on the study of quality of life/health-related—quality of life/health status. Based on this initial experience I have been constantly involved in doing research projects with students and with colleagues from the university the result being a number of very well received (and cited) papers and most recently the recognition of the research visibility with the inclusion in the last edition (2020) of the top 2% authors cited worldwide list prepared by the experts from Stanford University (Updated science-wide author databases of standardized citation indicators). Subsequently, my academic career switched to palliative care and this not only did not prevented me but further motivated to also expand my research interests still focusing on quality of life which is one of the key outcomes in this field, and further considering outcome measures which could be appropriate in palliative care as applied to end-stage respiratory disease. Thus throughout my career I built on previous experiences at teaching, clinical and research level. As far as the latter domain of career development is concerned the habilitation thesis thereby presented tries to describe the continuum of the research from a past focus on health status in pulmonary disease(mainly on COPD) to the current and future interests in documenting the appropriateness of and in identifying new patient-reported outcome measures in end-stage COPD. The habilitation thesis hereby presented is structured into three main sections, based on the criteria recommended by the National Council for Attestation of Academic Titles, Diplomas and Certificates (CNATDCU).

The first section starts with an introductory part in which my professional profile and pathways are presented. This section also includes three chapters which respectively approach the following topics:

1. Health status/health-related quality of life/quality of life in chronic obstructive pulmonary disease
2. Emerging relevance of extrarespiratory symptoms in COPD
3. Outcome measures in palliative care for end-stage COPD

The first chapter is an elaborated overview on the main issues related to health status as a patient reported outcome measure in COPD. In my thesis I use this term health-status and I argument this choice with the need to reflect in a more clear manner that I am referring to disease-specific (impairment of the) quality of life. As mentioned above health status/quality of life was my initial topic of research in patients with chronic respiratory failure due to various underlying conditions. I did my PhD thesis on the subset of patients with chronic respiratory failure due to COPD and I retained this interest afterwards by doing for example health status evaluation in patients with hospitalisations (severe exacerbations) of COPD and by publishing several papers regarding health status assessment in this disease.

The second chapter discusses the emerging relevance of extra-respiratory symptoms in COPD. Among them fatigue is the most studied one. I also studied it in relationship to its association with other markers of disease severity, considering that this symptom is more common in more advanced COPD. I then considered other extra-respiratory symptoms and more specifically their association in patients with COPD hospitalisations and demonstrated that the more they are detected concomitantly in the same patient, the bigger their impact on health status respectively on functional status was.

In the last chapter of the first section I review the outcome measures which are relevant for assessing the need for palliative care in COPD patients. If in oncology palliative care is very developed and the assessment algorithms are in particular very appropriately structured to capture the complex needs of patients evaluated for palliative care, in COPD the approaches are less clear and focused and there is a need to further research in this field. Therefore I conceptualized several outcome measures which I argumented as being appropriate to measure quality of life impairment in COPD patients needing palliative care.

In the second section I elaborate on the future research directions envisaged. They are embedded in the previous topics discussed in the first section. If in the first section I discussed patient-reported outcomes in COPD patients and in the end I streamed the discussion towards the end-stage COPD and palliative care (using this latter topic as a transition towards the future research directions) in the second section I consider the early palliative care in end-stage COPD. Early palliative care is different from end-of life care in terms of goals and approaches and in COPD in particular it is not known how the moment of initiation of early palliative care can be documented with the help of patient-reported outcome measures. I plan to fill in this gap by doing research regarding this issue and I also plan to consider the symptom clusters which are able to predict the need for palliative care, frailty as a patient-reported outcome in this setting and to conceptualize pre-end stage COPD with the help of short-burst oxygen therapy as a clinical and therapeutic marker of the eligibility for early palliative care.

The third and the last section include the main scientific papers which were relevant for my current view of the presented research aspects.

REZUMATUL TEZEI

Pentru un cadru didactic cu integrare clinică dezvoltarea profesională continua reprezintă abordarea cheie pentru competitivitatea profesională. Această dezvoltare trebuie să fie multilaterală pentru că acest rol de cadru didactic implică educarea studenților, rezidenților, îngrijirea pacienților și cercetarea cinică. De aceea este necesar ca activitățile didactice, clinice și de cercetare să fie ameliorate constant și ca noi subiecte de interes să fie permanent adaugate pentru a îndeplini obiectivele personale, întruni criterii de promovare și pentru a contribui la creșterea vizibilității și a prestigiului Universității în care un asemenea cadru didactic lucrează.

Sunt medic primar Pneumologie ca și pregătire clinică dar cariera mea reală a început ca și Asistent Universitar Pneumologie, în cadrul Universității de Medicină și Farmacie Grigore T Popa din Iași, iar acest context academic a deschis pentru mine noi orizonturi profesionale și a stimulat dezvoltarea multora dintre deprinderile pe care le-am dobandit ulterior. De subliniat în primul rând faptul că pe parcursul acestei etape profesionale, am avut ocazia să mă instruiesc și să realizez cercetare clinică de calitate initial în afara țării iar ulterior să dezvolt acest domeniu professional după revenirea în țară. În calitate de bursier de Cercetare Clinică, m-am focalizat pe patient-reported outcomes și în special pe calitatea vieții/calitatea vieții legate de sănătate, status de sănătate. Pe baza acestei experiențe inițiale m-am implicat ulterior în mod constant în proiecte de cercetare împreună cu studenți sau cu colegi din Universitate din acestea rezultând un număr de publicații științifice foarte bine primite (si citate), de curând vizibilitatea cercetării fiind recunoscută prin includerea în ediția 2020 a clasamentului celor 2% cei mai citați autori la nivel mondial, clasament elaborate de către profesorii Universității din Stanford (Updated science-wide author databases of standardized citation indicators). Ulterior, cariera mea academică s-a modificat ca și subiect de predare , acesta devenind îngrijirile paliative, iar aceast pasaj nu numai ca nu m-a împedicat dar m-a motivat și mai mult să dezvolt și domeniile de cercetare de interes păstrând calitatea vieții care este un parametru cheie pentru ingrijirile paliative dar și adaugând alte outcome measures care ar putea fi relevante pentru acest paliația bolilor respiratorii terminale.

Astfel de-a lungul carierei mele am cladit pe experiențele anterioare pentru fiecare dintre domeniile didactic, clinic sau de cercetare. În ceea ce privește ultimul domeniu, de dezvoltare a carierei, teza de abilitare pe care o prezint în cele ce urmează descrie continuitatea cercetării pornind de la preocupările inițiale privind status-ul de sănătate în bolile pulmonare (în special în bronhopneumopatia obstructiva cronica, BPOC) la preocupările actuale și viitoare privind documentarea adecvării patient reported outcomes actuale sau identificarea unora noi pentru BPOC-ul terminal. Teza de abilitare prezentată mai jos este structurată pet rei secțiuni, pe baza criteriilor și recomandarilor Consiliului Național pentru Atestare a Titlurilor, Diplomelor și Certificatelor Universitare (CNATDCU).

Prima secțiune începe cu un preambul ce privește profilul și traiectoriile mele professionale. Această secțiune include apoi trei capitol care abordează următoarele subiecte:

1. Status-ul de sănătate/calitatea vieții legate de sănătate/calitatea vieții în BPOC
2. Relevanța emergentă a simptomelor extrarespiratorii în BPOC
3. Outcome measures in îngrijirile paliative pentru BPOC-ul terminal

Primul capitol reprezintă o perspectivă elaborată asupra principalelor aspect legate de status-ul de sănătate ca și patient-reported outcome measures în BPOC. În teza mea de abilitare utilizez acest termen, status de sănătate și argumentez această opțiune prin prisma nevoii de a reflecta într-o maniera mai clară faptul că mă refer la calitatea vieții (și în special deteriorarea ei) în relație cu boala respective. Așa cum am menționat anterior, status-ul de sănătate/calitatea vieții la pacienții cu insuficiență respiratorie cronică de varie cauze a fost subiectul meu de cercetare de început. Teza mea de doctorat a fost efectuată pe un subset de pacienți avand ca boala de baza BPOC.
Mi-am păstrat acest interes și ulterior de exemplu studiind evaluarea status-ului de sănătate la pacienții cu spitalizări pentru exacerbări BPOC si publicand diferite articole despre acest subiect de interes.
Capitolul al doilea discuta relevanța emergentă a simptomelor extrarespiratorii în BPOC. Dintre acestea fatigabilitatea este cea mai studiată. De asemene am studiat acest simptom în ceea ce privește asocierea lui cu alți marker de severitte a bolii, luand în considerare faptul că acest simptom este mai frecvent identifict la pacienții cu BPOC mai sever. Ulterior am discutat si despre alte simptome extrarespiratorii și în particular despre asocierea lor la pacienții cu spitalizări pentru BPOC excerbat demonstrând că creșterea numărului simptomelor concomitente detectate la același pacient s-a asociat cu o creștere proporțională a impactului asupra status-ului de sănătate și a celui functional.
În ultimul capitol am discutat despre outcome measures care sunt relevante pentru evaluarea necesității de instituire a îngrijirilor paliative în BPOC. Dacă în oncologie paliația este foarte dezvoltată și algoritmii de evaluare în particular sunt foarte bine structurați pentru a capta necesitățile de îngrijire complexe ale pacienților evaluați pentru îngrijiri paliative, în BPOC metodele de evaluare sunt mai puțin clare și specifice, și de aceea există nevoia de a aprofunda acest aspect prin intermediul unor noi studii. De aceea am conceptualizat mai multe outcome measures pentru care am adus argumente privind relevanța lor pentru a măsura deteriorarea calității vieții la pacienții cu BPOC care necesită îngrijiri paliative.
În a doua secțiune am elaborat asupra principalelor direcții de cercetare pe care le am în vedere. Acestea derivă din subiectele de cercetare anterioare care sunt enumerate și discutate în prima secțiune. Dacă în aceasta am discutat patient-reported outcomes pentru pacienții cu BPOC în general iar în final am direcționat discuțiile către BPOC-ul terminal și îngrijirile paliative (utilizând acest ultim subiect ca de tranziție către direcțiile de cercetare ulterioare), în secțiunea a doua am trecut în revistă stadiul actual al cunoasterii privind paliația precoce la pacienții cu BPOC terminal. Paliatia precoce este diferită ca și obiective si abordari comparative cu paliatia terminala iar în BPOC în particular nu se cunoaste modul în care patient reported outcomes pot fi utilizate pentru a documenta momentul de inițiere a paliatiei precoce. Doresc sa remediez aceste hiatus-uri prin intermediul cercetărilor clinice descrise mai jos și de asemenea doresc sa studiez simptomele grupate (clusters) care pot prezice necesitatea initierii îngrijirilor paliative precoce fragilitatea/vulnerabilitatea ca si patient-reported outcome cu ajutorul căruia se poate de asemenea stabili utilitatea paliatiei precoce, si de asemenea conceptualizarea BPOC preterminal cu ajutorul necesitații de oxigenoterapie în pulsuri scurte (short burst) considerat ca si marker clinic si

therapeutic pentru eligibilitatea pentru îngrijiri paliative precoce. Secțiunea a treia si ultima include principalele articole relevante pentru viziunea mea actuală privind subiectele discutate.

SECTION I: PROFESSIONAL, SCIENTIFIC AND ACADEMIC ACHIEVEMENTS

Introduction: overview of the achievements to date

I am a proud citizen of Iasi, born and educated in this "seven hills city", and the various stages of my professional development are all linked to prestigious institutions located in my native city. My medical professional development is "lived" since 1989 with the University of Medicine and Pharmacy Grigore T Popa in Iasi, an old institution with modern views and excellent reputation at both national and international levels. "My" university shaped throughout the years my medical thinking, my professional behavior, my professional skills and the last but not the least the capacity to duly serving those in need of my help: patients, students, in-training physicians, colleagues from the workplaces.

I had the chance to have excellent mentors throughout the medical school, to become an academic physician in my late resident years and to be appreciated and promoted for my professional merits by the transparent, visionary and constructive leaders of the university who noticed my contribution towards institutional visibility, contribution which has been consistent and constant throughout the years.

I had the tremendous luck to be discovered when I was a student and get involved in an extracurricular activity represented by selecting and translating papers for the Romanian Edition of the renowned journal British Medical Journal. This triggered my interest in research which then streamed towards clinical research with skills developed and refined abroad and fructified back home in my PhD thesis and in the research published afterwards. Nowadays clinical research should not only be done in order to make the clinician more visible and to facilitate the career advance. Its results should also be used to improve the clinical practice ie the routine care of the patients. In order to achieve this desiderate, it is of paramount importance to make the clinical research applicable at the medical ward, by identifying outcome measures which can be then used to improve the care of the patients. Among them, patient reported outcomes in particular are very useful for this purpose because they directly reflect the subject perception of the disease and of its impact. They are also largely used in clinical research irrespective of the disease, because the information they bring in, complements in an adequate and useful manners that provided by the objective measures such as laboratory tests, imaging tests etc.

During my both clinical and academic careers I understood that medicine is a dynamic field and that the continuous professional development is a key approach for a competitive professional performance. Therefore palliative care and chronic wound nursing became new additions to my previous topics of interest. A special mention is deserved for palliative care which is my current teaching subject. Over the last decades, palliative care has been long recognized for its utility in oncology but rather marginally acknowledged for non-oncological, end-stage chronic diseases such as chronic respiratory failure, congestive heart failure, end-stage Alzheimer disease etc. The under use of palliative care in chronic conditions is in part due to the lack of applicable clinical research in the field. In end-stage COPD in particular there is a need to define, standardize and test for applicability various patient-reported outcomes especially in relationship to the functional

status, to the understanding of the disease impact and progression, perception of the disease burden, social or spiritual outcomes.
As a clinician, academic physician and researcher, I am aware of these knowledge gaps and I would like to reduce them by using the following past and the current skills to improve the future professional performance at the bedside as well as in teaching and research.

- **Academic achievements:** I started my academic career in early 2000 as an Assistant Lecturer in Pulmonary Disease. In this role I instructed students from the Faculty of Medicine in various practical aspects of Pulmonary Disease in both Romanian and English language teaching programs, I coordinated graduation theses for various students who are now achieved clinicians and I began my first steps in clinical research. In 2013 I ended up this junior career and switched the teaching direction to Palliative Care as a Lecturer. I was handled a new teaching direction developed in order to better adapt the curriculum of the nursing students to the care requirements they are facing upon graduation. This teaching switch allowed me to further demonstrate my skills and contributed a lot to my professional development. After 5 years and by remaining in the same teaching field I was promoted to Associate Professor position. The teaching of this topic allowed me to better understand how important palliative care is also outside oncological conditions. Since starting the teaching in the field of Palliative Care I tried to highlight the practical importance of this specialty for nurses. Consequently, I introduced the use of Edmonton Symptom Assessment Scale (ESAS), clinical assessment algorithm and palliative care nursing plan components in the practical teaching for nurses in order to familiarize them with tools routinely used in the real life in the palliative care setting. I also elaborated the first didactic book on palliative care which can be used by students in nursing, medicine or by young graduates willing to stay informed regarding palliation. This book includes various aspects of palliative care and as a matter of originality it also includes a particular form of spiritual care approach which was recently developed at the time of drafting of this manual and which Is represented by dignity therapy. At the time of publication of this manual, it was the first describing this approach to students in Romania, and soon afterwards this approach was included in curricula of other training bodies in the country. After starting to teach Palliative Care and also based on the observations derived from the daily activities at the clinical ward, I realized there is a significant training gap in the approach of chronic wounds, which are common in some categories of patients including those needing palliative care. I therefore elaborated a lecture series on chronic wounds management in palliative care which can be taken optionally by the students and which soon became very popular and raised a lot of interest.
- **Research Expertise**: as previously mentioned, I became interested in research since my student years, initially analyzing what others did and then doing my first timid steps with clinical research during my in-training years and presenting the related results at the European Respiratory Society congress. Subsequently I had the opportunity to really train in clinical research because between 2001-2002 I used to be a Clinical Research Fellow at the Salvatore Maugeri IRCCS in Italy, an institution renowned for its prestige in clinical research in chronic pulmonary diseases and chronic respiratory failure. This fellowship allowed me to develop clinical research skills and equally to enjoy doing it. My research dealt with the study of some patient-reported outcomes

(health status/health-related quality of life) in patients with chronic respiratory failure due to various underlying diseases. Based on this research, I did my PhD thesis (finalized in 2008) and evaluating the use of various variables to predict a favourable prognosis (as a result of a successful therapy) in patients with chronic respiratory failure due to chronic obstructive disease (COPD). Over the past 15 years I expanded this research field to other aspects regarding COPD, asthma or rare pulmonary diseases. The academic 'transition' from a Pulmonary Disease teacher to a Palliative Care senior teacher also impacted on my research interests, which more recently included various aspects of palliative care in COPD, a field which is currently of high interest due to the increase of prevalence of subjects with end-stage COPD due to the need to better understand when such a patient requires this type of care and the last but not the least, due to the limited body of evidence coming from equally limited number of existing clinical studies in this particular setting. One important step in developing the skills as a researcher not only in defining the hypothesis and how to test it but also in managing the logistics of it ("scientific", "human" or "administrative") was to apply and win in 2013 a 2 year internal research grant with the University of Medicine where I work. This grant was an opportunity for me to establish a transition period from the research in COPD towards the research in end-stage COPD because it dealt with fatigue and its potential causes in this disease. This grant was also for me to establish and manage a multidisciplinary team which included physicans, statisticians, biochemists and for a short period of time even a student. The research idea was very valuable, the team worked very well and the results were accordingly very good: three papers published in journals with impact factor with a cumulative impact factor over 6 as follows:

***Antoniu SA**, Ungureanu D. Measuring fatigue as a symptom in COPD: From descriptors and questionnaires to the importance of the problem. Chron Respir Dis. 2015 Aug;12(3):179-88. **IF=1.64**, ISSN: 1479-9723*

***Antoniu SA**, Petrescu E, Stanescu R, Anisie E, Boiculese L. Impact of fatigue in patients with chronic obstructive pulmonary disease: results from an exploratory study. Ther Adv Respir Dis. 2016 Feb;10(1):26-33. **IF=2.74**, ISSN: 1753-4658*

***Antoniu SA**, Boiculese LV. Palliative care outcome measures in COPD patients: a conceptual review. Expert Rev Pharmacoecon Outcomes Res. 2016;16(2):267-74. **IF=1.78**, ISSN: ISSN: 1473-7167*

The first evidence that the research in palliative care was worth being done and even competitive came in 2015 when I won the European Association of Palliative Care Award , for the abstract

Antoniu SA, Munteanu E, Petrasescu V, Ailiesei L, Miron L. ,,Analysis of determinants of impaired role functioning across prevalent cancers"

I am also a member of the national team of the **COST Action CA 16125** ,,European network for translational research in children's and adult interstitial lung disease" **2017-2021** includes at European level both pulmonary disease adult specialists and pediatricians.

Over the last 10 years have been using my research experience for evaluative purposes. I have served as an Expert Evaluator for various National (UEFISCDI) and International funding bodies (European Commission, European Research Council etc).

I published more than 100 scientific papers in journals indexed in the Clarivate Analytics (formerly known as Web of Science) reaching a H-index of 14, and a cumulative impact factor of about 300. Most recently I was included in the top 2% most cited researchers worldwide, the updated list for 2020 prepared by experts from Stanford University being published in PLoS Biology Journal (Updated science-wide author databases of standardized citation indicators) ((Ioannidis et al., 2020).

INTERNATIONAL SCIENTIFIC VISIBILITY

- HIRSCH INDEX(CLARIVATE ANALYTICS): 14
- NUMBER OF PUBLICATIONS IN CLARIVATE ANALYTICS DATABASE: **124**
- CUMULATIVE IMPACT FACTOR (main author): over 300
- TOTAL NUMBER OF CITATIONS WITHOUT SELF-CITATIONS(CLARIVATE ANALYTICS): 695
- MEAN CITATION NUMBER/PAPER PUBLISHED: 5.99
- HIRSCH INDEX (GOOGLE SCHOLAR):20
- HIRSCH INDEX (SCOPUS):15, Scopus ID https://orcid.org/0000-0003-3727-231X
- ORCID: https://orcid.org/0000-0003-3727-231X

- **Professional (Clinical) Expertise**: in 1996 after graduating the Faculty of Medicine, I enrolled in a Pulmonary Disease Residency program in Pulmonary Disease and I had the opportunity to apply to the bedside the information studied in the previous years. I then became Consultant in Pulmonary Disease and successfully integrated the academic activity with clinical care and research. At this stage I realized that a considerable percentage of the "acute" patients (20-30%) seen by me routinely would benefit for palliative care, but there is no standardized program of the kind and, equally important, no measures to monitor adequately its effectiveness. This is not only due to the lack of a dedicated clinical infrastructure but also to the fact that there is a need for clinical outcome measures which should be used in routine palliative care for end stage respiratory diseases in order to document its effectiveness and most importantly the patient-related effectiveness. In the meantime I started to teach palliative care and this came as a supplementary piece of motivation towards a better clinical specialization in palliative care. Therefore I attended a supra-specialty training in palliative care. This helped me a lot to better understand the practice of palliative care but also to notice the limited development of palliative care for respiratory disease compared to the complexity of the approach available in oncology. When trying to explain this I realized that there are two main reasons: one is represented by the limited awareness of the need for palliative care for end-stage chronic pulmonary diseases and the other one is represented by the lack of outcome measures which should be used in practice to document the depth of the needs for palliative care and the improvements resulting from applying palliative care approach. I believe that in clinical practice in particular patient-reported outcomes are very important instruments to document the perceived impact of the disease, and that such measures are also relevant in palliative care. However such patient-reported outcomes should first

be developed, validated and tested for their properties in clinical research studies and then implemented in clinical practice. Such an approach is perfectly feasible as demonstrated by the COPD Assessment Test (CAT) which is a health status instrument initially used in clinical trials involving COPD patients and then became a tool to monitor the disease in routine clinical practice. With this clinical professional profile and with my constant interests in clinical research I am convinced that I can fulfill the above mentioned desiderate and therefore I chose to elaborate on developing this direction in the current habilitation thesis. In the remaining part of this section of the habilitation thesis firstly I am going to review the existing knowledge in the fields of patient-reported outcome measures as applied to chronic obstructive pulmonary disease (COPD). These are mainly represented by health status/health-related quality of life, a patient-reported outcome which has a multivalent applicability in this setting, ie in both stable and exacerbated phase, in evaluating the efficacy of various types of inhaled therapies, in evaluating the impact on non-pharmacologic approaches such as long-term oxygen therapy, the only method able to improve survival in end-stage COPD. Secondly, I am going to elaborate on the emerging importance of extra-respiratory symptoms with a special focus on fatigue, a symptom which is also relevant due to its impact on health status in palliative care too. Finally I am going to discuss the existing data on the outcome measures in palliative care as applied to end-stage COPD.

CHAPTER 1. HEALTH STATUS/HEALTH-RELATED QUALITY OF LIFE ("QUALITY OF LIFE") IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

1.1 State of the art

Patient-reported outcome (PRO) is a class of outcome measures which are nowadays widely used in clinical trials in order to integrate the direct input from the patient with other outcome measures (eg physiologic, clinician-related). PROs can include for example scales for measuring symptoms or functional status or tools able to measure quality of life. PROs have the big advantage to reflect the patient perception on the own health, the information they provide making the picture on the issue studied more comprehensive (Velentgas P, 2013).

Quality of life represents a broader concept encompassing physical, psychological, social and spiritual aspects of life. It can be measured in healthy as well as in diseased patients and gives a holistic view on the functioning of a subject in the four specific areas mentioned above (Carone et al., 1997, Curtis et al., 1997).

Quality of life is a very important PRO measure for research as well as for clinical practice. The improvement of the quality of life is currently considered as one of the main therapeutic goals across all major chronic conditions irrespective of the severity of the disease. Improvement of the quality of life is also the major desiderate in palliative care as stated by the World Health Organization(WHO, 2002, WHO, 2020).

The health related-quality of life (HRQoL) and the health status (HS) can be considered as "clinical refinements" of the broader generic concept of the quality of life and are patient reported outcome measures which have been extensively used over the last decades in order to quantify the subjective impact of the disease on the own health, as perceived by the patient. They can be considered as similar measures of the perceived health as described by the patient, and they are both components/domains of the quality of life. They have been therefore often used in an interchangeable manner although they do not describe exactly the same aspects of the quality of life. Health-related quality of life measures the impairments of various health determinants whereas the health status can be considered as being the disease-related quality of life (Jones, 2001, Tsiligianni I, 2011). However, because they are measures of the quality of life often they are mentioned as being "quality of life".

Quality of life can be measured in healthy individual or in those with various conditions, and in this latter category the major focus of clinical research was on chronic conditions.

Health status and health-related quality of life are quantified with scores derived from various questionnaires. Such questionnaires can be classified as generic or disease specific(Antoniu et al., 2003)

Generic questionnaires investigate in a more generic manner as their defining term says the factors which impair the health state. They can be used in healthy populations, in various diseases or irrespective of the disease when for example a determinant of health has to be evaluated across pathologies.

Disease-specific questionnaires can only be used in diseases or in disease groups. They are usually devoted to the assessment of the impact of symptoms on daily functioning(Jones, 2001).
Therefore it is easy to understand why in clinical research health status/health-related quality of life are nowadays common PROs reflecting the way the disease can influence at various moments (of measurement) the quality of life. The most common use in research and more and more often in clinical practice is to find out if various pharmacological (most commonly) or non-pharmacological therapies are able to exert improvements which can be perceived and reported by the patient(Antoniu et al., 2003, Jones, 2001).
Although health status/health-related quality of life can be used in acute diseases, their involvement is more purposeful in chronic diseases such as for example the chronic obstructive pulmonary disease (COPD).
COPD is a chronic inflammatory disease of the lungs characterized by progressing airways obstruction and linked with tobacco smoking and/or with exposure to other inhaled noxious particles(GOLD, 2018)
COPD is an increasing public health problem, being associated with significant disease-related, economic and social burdens: in 2015 the number of Year Lived with Disability (YLD) for COPD (all age groups) being 12047000 (Global, 2017, Vos et al., 2016). COPD is associated with COPD is the fourth mortality cause worldwide and is projected to become the third over the next decade (Murray et al., 2012, Lozano et al., 2012, Global, 2017). In 2015 a number of 3.2 millions of patients with COPD died at global level, this representing a 11.6% compared to the 1990 figure(Global, 2017).
COPD has two disease states, stable and exacerbated, and manifests clinically with chronic respiratory symptoms such as dyspnea, cough associated or not with sputum production which increase in severity in parallel with airways obstruction, and which during exacerbations (inflammation flares) further aggravate on transitory basis(GOLD, 2018). Among the respiratory symptoms above described, dyspnea is the most common clinical manifestation of COPD and is used in routine practice and in clinical research as a clinical marker of the disease. Currently it is recommended that in COPD disease assessment approach should not only be based on spirometric monitoring but should also take into consideration (Jones, 2013, Jones et al., 2009, GOLD, 2018):

- Symptoms severity (dyspnea, measured with modified Medical Research Council (mMRC) dyspnea scale
- Health status assessed with COPD Assessment Test (the CAT test)
- The number of disease exacerbations over the previous 12 months
- Presence of comorbidities

Health status is a key outcome measure in the management of COPD and this is demonstrated by the fact that the improvement in the health status is included among the main therapeutic aims along with the reduction in the number of moderate to severe exacerbations, in the severity of stable state symptoms, in the risk of COPD-related complications and with improvement in survival.In COPD the health status data is important for clinical research but it is also important

for the clinician who is able to make an idea on the perceived severity of the disease as reported by the patient. Because it was demonstrated that health status does not correlate with "physiologic" severity of the disease, ie with that of the airways obstruction, this means that it is possible that in some patients with mildly impaired lung function, health status can be significantly altered. In such patients disease control is going to be improved by intervening on the health status determinants which contributed to this worsening. Health status/health-related quality of life can be measured in COPD alike in other chronic conditions by the means of two types of questionnaire, namely the generic questionnaires respectively the disease-specific questionnaire.

Generic questionnaires have been widely used in COPD in order to evaluate the effects of various interventions on various health domains. Among them, Medical Outcome Study Questionnaire Short Form 36 (also called "SF-36"), Nottingham Health Profile, Sickness Impact Profile, EuroQol-5D.

SF-36 is the generic questionnaire with 36 items generating 8 health state scores(Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, Mental Health) and two summary scores(Mental respectively Physical) (Ware and Sherbourne, 1992). It is the generic questionnaire the most commonly used in COPD to evaluate the effects of various pharmacological and non-pharmacological interventions. For example in an 1 year study evaluating the efficacy and safety of inhaled tiotropium bromide SF-36 scores changes as compared to baseline demonstrated an improvement in health-related quality of life as a result of this therapy (Casaburi et al., 2002). Furthermore when applied in a real-life setting, this questionnaire was able to detect improvements in physical functioning which were both statistically and clinically meaningful (Rau-Berger et al., 2010). In pulmonary rehabilitation applied in patients with COPD, SF-36 also proved its usefulness (Boueri et al., 2001). Two shorter versions, SF-12 and SF-6 were subsequently developed, and they have also been used as utility measures, ie tools allowing outcome measures such as quality-adjusted life years (QALYs). SF-12 was also used in COPD patients and was found to differ statistically among different classes of disease severity (Martín et al., 2008).

Notthingham Health Profile is another generic questionnaire with 38 items, which was has been used in COPD. It generates scores for physical abilities, energy level, sleep, pain, social isolation, and emotional reactions(Hunt et al., 1981). NHP was used in studies which evaluated the effectiveness of lung volume reduction surgery in patients with advanced COPD (and emphysema) and in studies evaluating inhaled therapies such as bronchodilators of inhaled corticosteroids in the same disease(van Schayck, 1997, van Schayck et al., 1995, van Schayck et al., 1992, Cooper et al., 1995).

The Sickness Impact Profile is the most extensive generic questionnaire used in COPD. It has 136 items and generates a total score, two general scores for physical domain and for psychosocial domain and 12 domain scores covering a broad range of daily activities from sleep and rest to feeding, house care, to communication, reactive behavior or emotional behavior (Bergner et al., 1981). In COPD it was applied in patient undergoing long-term oxygen therapy in order to evaluate their health status and its predictors (Prigatano et al., 1984).

EuroQol-5D is a questionnaire including two components: an evaluative component (with a visual analogue scale) and a 5 item descriptive component for mobility, self-care, usual activities, pain/discomfort and anxiety/depression which can generate various health states(EuroQol, 1990). EuroQoL-rD can also be used to calculate QALY or to evaluate health status in COPD including hospitalisations for COPD severe exacerbations(Antoniu et al., 2014).

In COPD several disease-specific questionnaires able to evaluate the impact of the chronic respiratory symptoms on daily functioning have been more commonly used. They include: Saint-George Respiratory Disease Questionnaire, Chronic Disease Respiratory Questionnaire, COPD Assessment Test and Clinical COPD Questionnaire. These questionnaires were more commonly used in various studies performed in COPD setting and are going to be discussed in this paragraph. The Maugeri Foundation questionnaire which was developed for patients with chronic respiratory failure (including those with COPD and chronic respiratory failure), is going to be described in the chapter regarding the patient-reported outcomes in chronic respiratory failure.

Saint George Respiratory Questionnaire (SGRQ) is the disease specific questionnaire the most commonly used to measure health status in COPD(Jones, 1991). Despite being labelled as a disease-specific questionnaire, SGRQ was also used in asthma, cystic fibrosis proving its ability to evaluate the worsening of the health status as a result of chronic respiratory symptoms of these diseases. It has 50 items generating a total score and three domain scores for symptoms, activity and impact. It was extensively evaluated in pulmonary rehabilitation, in evaluating various pharmacological therapies. Among the initial studies using SGRQ to assess an inhaled therapy is the one performed in COPD patients taking inhaled salmeterol and in whom health status was evaluated in a combined manner ie by using a generic and a disease-specific questionnaire(Jones and Bosh, 1997).This study was the first which outlined the importance of the health status in detecting the perceived improvement of the disease, this outcome measure being more accurate when compared to lung function variables in demonstrating the efficacy of the inhaled compound(Jones and Bosh, 1997). This questionnaire also has the ability to detect and quantify a clinically important change in health status (ie which can be perceived by the patient) which in terms of improvement means a score (for domain or total) reduction of at least 4 units of score. Some more data on SGRQ as applied specifically to the inhaled therapies used in COPD are going to be discussed below. The original version of SGRQ was validated for various chronic respiratory diseases and a COPD version (SGRQ-COPD) was subsequently developed and used in COPD studies (Meguro et al., 2007).

Chronic Respiratory Disease Questionnaire is the oldest disease specific questionnaire which was purposefully developed to assess health status in COPD patients enrolled in rehabilitation programs. This explains why the questionnaire has domains for dyspnea, fatigue, emotional functioning and coping; a total score can also be calculated (Guyatt et al., 1987a, Griffiths et al., 2000).

Clinical COPD Questionnaire is a disease specific questionnaire with 10 items generating three domain scores, symptoms, functional and mental respectively with a total score. CCQ(van der Molen et al., 2003b). It can be used in various settings including in real life, in order to monitor

day to day or longer period variations of health status. It was more commonly used in the setting of rehabilitation but it was also shown to be a valid health status measure in hospitalizations for COPD exacerbations (Kon et al., 2014, Antoniu et al., 2014).

COPD Assessment Test (CAT test): CAT test is the health status measure the most recently developed(Jones et al., 2009). It has eight items regarding respiratory symptoms including exertional dyspnea, sleep, energy, confidence in leaving home and activity limitation. It is a valid, very easy to use health status measure and is currently used for risk stratification described above. Since its development CAT test has been extensively used to assess health status with inhaled therapies, pulmonary rehabilitation in stable COPD patients and was also found to be a good instrument to assess the health status during COPD exacerbations. It is also use in daily practice to assess the health status in stable COPD patients in order to document their risk for subsequent exacerbations and to set up a therapy able to reduce it. This approach is recommended by the Global Initiative for Obstructive Lung Diseases and by the related management guidelines (GOLD, 2018).

Maugeri Respiratory Failure questionnaire was originally a 28-item questionnaire developed to evaluate the health status in chronic respiratory failure which is a common denominator and the final stage of various chronic respiratory diseases including COPD. A shorter, 26 item version was subsequently developed and extensively tested in clinical trials (Vidotto et al., 2007). Therefore the importance of health status as an outcome measure in COPD is rooted not only on its extensive use as a clinical research tool, but also on its clinical practical value which was more recently outlined, leading to its incorporation in the routine battery of clinical evaluation of COPD patients as recommended by the GOLD (Global Initiative on Obstructive Lung Disease) Program.

This research direction is documented with the following papers:

Antoniu SA. UPLIFT Study: the effects of long-term therapy with inhaled tiotropium in chronic obstructive pulmonary disease. Expert Opin Pharmatoher 2009 10(4):719-22 **Impact factor 2.07,** ISSN: 1465-6566 **(reproduced with permission)**.

Antoniu SA, Carone M, Sampablo I. Triple inhaled therapy in stable chronic obstructive pulmonary disease: the earlier the better ? Expert Opin Pharmacother 2010 11(6):1039-1042 **IF= 2.40 (reproduced with permission)**

Antohe I, **Antoniu SA**, Gavrilovici C. Triple fixed inhaled therapy in frequent chronic obstructive pulmonary. disease exacerbators: potential advantages for various degrees of airways obstruction. Expert Opin Pharmacother 2018 19 (3): 287-9, **IF=3.03 (reproduced with permission)**

Antoniu SA, Rajnoveanu R, Ulmeanu R, Mihaltan F, Grigore M. Evaluating revefenacin as a therapeutic option for chronic obstructive pulmonary disease. Expert Opin Pharmacother 2020 21(9): 997-1004. **IF pentru 2019=2,87 (reproduced with permission)**

Carone M, **Antoniu S**, Baiardi P, Digilio VS, Jones PW, Bertolotti G; QuESS Group. Predictors of Mortality in Patients with COPD and Chronic Respiratory Failure: The Quality-

of-Life Evaluation and Survival Study (QuESS): A Three-Year Study. COPD. 2016;13(2):130-8**, IF=2.47,** ISSN: 1541-2555 **(reproduced with permission)**.

Antoniu SA, Puiu A, Zaharia B, Azoicai D. Health status during hospitalisations for chronic obstructive pulmonary disease exacerbations: the validity of the Clinical COPD Questionnaire. Expert Rev Pharmacoecon Outcomes Res. 2014 Apr;14(2):283-7. **IF=1.66**, ISSN: 1473-7167 **(reproduced with permission)**

1.2 Health status /health-related quality of life and inhaled therapies in stable COPD

1.2.1 Introduction

As mentioned before, such questionnaires were initially used for clinical research purposes only. In COPD most of this research was focused in documenting the efficacy and the effectiveness of various inhaled therapies which are used on regular basis for the treatment of the stable state. In this respect there exists a lot of studies on various types of inhaled therapies in COPD, because virtually for any new such therapy health-related quality of life/health status should be used as an outcome measure in clinical trials done before it goes on the market. Health status can also be used to document the effects of non-pharmacological interventions which can be done in stable COPD. Such interventions are mainly represented by pulmonary rehabilitation and by long-term oxygen therapy. More recently questionnaires able to document the transitory worsening of the health status as a result of an exacerbation were developed and demonstrated to reliably evaluate the health status dynamics during exacerbation episode and during the subsequent recovery.

1.2.2 Health status/health related quality of life and inhaled therapies in stable COPD

An initial study which was done with the Chronic Respiratory Disease Questionnaire (CRQ) in COPD evaluated salbutamol, a short-acting beta2 agonist given regularly in COPD patients. Improvements in the domains for dyspnea, physical functioning and mental functioning of the CRQ (Guyatt et al., 1991, Guyatt et al., 1987b). Salbutamol is no longer used on regular basis in COPD, being currently replaced by compounds of the same class or of antimuscarinic type each having a longer duration of action.

The long-acting bronchodilator which was initially tested for its effects on health status was salmeterol which is an inhaled long-acting beta2 agonist (LABA). Salmeterol is no longer used as a monotherapy in COPD but at that time a 16 week course of inhaled salmeterol 50 mcg given twice daily was found to improve health status as assessed with SGRQ and with SF-36(Jones and Bosh, 1997).

Inhaled formoterol, another LABA was evaluated in various studies having various comparators such as for example its combination with budesonide, budesonide alone, inhaled ipratropium bromide (a short acting antimuscarinic inhaled compound) or placebo. For example in one study formoterol significantly improved the health status (measured with SGRQ) only in combination with budesonide and not alone, when both were compared to placebo(Szafranski et al., 2003). In

the other study evaluating the changes in health status (measured again with SGRQ) produced by the inhaled combination budesonide+formoterol versus formoterol, versus budesonide versus placebo both the combinations and formoterol alone were superior to placebo in improving health status whereas budesonide did not produce any significant effect compared to placebo (Calverley et al., 2003). When compared to inhaled ipratropium bromide, over a period of 3 months formoterol was able to improve significantly health status (SGRQ) when compared to placebo (Dahl et al., 2001).

Long-acting antimuscarinic agents (LAMAs) such as tiotropium bromidum and subsequently other compounds such as aclidinium bromide or glycopyronium or umeclidinium were also evaluated for their effects on health status. In clinical practice relevant are the sustained beneficial effects of a therapy on health status and therefore I am going to focus this short discussion on several studies which had a duration of 52 weeks (or more).

Tiotropium bromide was initially evaluated in two 52 weeks studies: one of them evaluated this in patients with COPD compared to placebo and using a battery of questionnaires , SF-36 and SGRQ(Casaburi et al., 2002). This study demonstrated that tiotropium improved health status as measured with each of the two questionnaires: baseline SGRQ domain scores as well as the total score were significantly improved compared to placebo, whereas SF-36 exhibited significant improvements in physical domains such as physical functioning, role functioning or general health) and in the physical summary score, no improvements in the mental components being detected(Casaburi et al., 2002).

In another report of two paired study tiotropium and ipratropium 1 year therapy were compared in COPD patients. Health status was also evaluated with SF-36 and SGRQ. Similarly with the previous study tiotropium improved physical domains scores of the SF-36 a finding which could not be demonstrated with inhaled ipratropium. Impact domain score of SGRQ was significantly improved by tiotropium and not by ipratropium whereas symptom and activity scores were comparably improved by both inhaled agents. Total SGRQ was improved in a sustained manner by tiotropium whereas ipratropium was associated with an initial improvement and a subsequent deterioration to the baseline levels of this measure (Vincken et al., 2002). The long-term effects of tiotropium were subsequently evaluated in various large cohort studies and the UPLIFT study was reviewed by me, the findings of this paper being presented below.

Aclidinium bromide is another long-acting antimuscarinic compound which can be given as a twice daily regimen, and this particular pharmacological property allows a better control of nighttime or early morning symptoms in COPD patients. Aclidinium was evaluated in a 1 year study in patients with moderate to severe COPD in whom health status was evaluated with EuroQOl-5D and SGRQ: both score sets were constantly found to be improved as compared to baseline (Tashkin et al., 2012).

Inhaled corticosteroids: inhaled corticosteroids can be used as a monotherapy in asthma and are no longer used in this form in COPD. Previous studies evaluating the efficacy and the safety of inhaled corticosteroids in COPD found they were notably effective only in reducing the exacerbations rate. In a longer duration study fluticasone propionate was not able to improve health

status (SGRQ) but was able to slow its deterioration over the study period(Spencer et al., 2001). Such findings did not completely discourage the use of such compounds in COPD but instead prompted the evaluation of their combination with LABAs.

Inhaled bronchodilator combinations were developed as a result of the unmet therapeutic need in more severe airways obstruction. In such patients there is a poorer control of dyspnea with one bronchodilator and a poorer health status. It was expected that a combination of two inhaled bronchodilators with different mechanisms of action would produce a more sustained bronchodilation. In a 52 weeks study evaluating efficacy and safety of tiotropium+olodaterol, comparing them to those of the monocomponents, health status was evaluated with SGRQ and it was found that the most significant improvements in the health status were obtained with the combination(Buhl et al., 2015).

Inhaled corticosteroids+LABA combinations: such combinations are nowadays used in patients with more impaired lung function and with frequent disease exacerbations. The best known such combinations are budesonide+formoterol and salmeterol+fluticasone. Budesonide+formoterol combination was evaluated in two clinical trials with similar design which were discussed under formoterol paragraph. As mentioned there the combination was found superior to each of the components and to placebo in improving the health status. This effect was mostly due to formoterol and to a lesser extent to the inhaled corticosteroid budesonide(Calverley et al., 2003, Szafranski et al., 2003). Inhaled salmeterol/fluticasone was evaluated for its effects on lung function, health status (SGRQ), exacerbations rate and mortality in a 3 year study, the TORCH study. In this study combination therapy produced after 3 years of use a significant improvement in the baseline health status as compared to salmeterol or fluticasone or placebo(Calverley et al., 2007).

Triple inhaled therapies (three compounds in a single inhaler, ie LABA+LAMA+inhaled corticosteroids) are the most recent addition to the therapeutic armamentarium available to COPD. I recently reviewed one such study and the findings of this paper are presented below.

The data on health status and inhaled therapies discussed above are not exhaustive, many other studies involving inhaled therapies being available to be analyzed for the health status. The aim of this discussion was to demonstrate that clinical efficacy of such therapies can be measured with non-physiological variables such as health status in a standardized, quantifiable and reliable manners on the one hand, and on the other hand to demonstrate the purposefulness of the health status in evaluating the "perceived" efficacy of such therapies in COPD.

Personal contribution

Antoniu SA. UPLIFT Study: the effects of long-term therapy with inhaled tiotropium in chronic obstructive pulmonary disease. Expert Opin Pharmatoher (2008) 359(15):1543-1554 **IF=2.07,** ISSN: 1465-6566 **(reproduced with permission)**

Antoniu SA, Carone M, Sampablo I. Triple inhaled therapy in stable chronic obstructive pulmonary disease: the earlier the better ? Expert Opin Pharmacother 2010 11(6):1039-1042 **IF= 2.40 (reproduced with permission)**

Antohe I, **Antoniu SA**, Gavrilovici C. Triple fixed inhaled therapy in frequent chronic obstructive pulmonary. disease exacerbators: potential advantages for various degrees of airways obstruction. Expert Opin Pharmacother 2018 19 (3): 287-9, **IF=3.03 (reproduced with permission)**

Antoniu SA, Rajnoveanu R, Ulmeanu R, Mihaltan F, Grigore M. Evaluating revefenacin as a therapeutic option for chronic obstructive pulmonary disease. Expert Opin Pharmacother 2020 21(9): 997-1004. **IF pentru 2019=2,87 (reproduced with permission)**

The evaluation of long-term effects of inhaled therapies were performed in several large-cohort studies such as the UPLIFT study. This included health status as an outcome measure and therefore below I chose to review the relevant clinical data.

Personal contribution

Antoniu SA. UPLIFT Study: the effects of long-term therapy with inhaled tiotropium in chronic obstructive pulmonary disease. Expert Opin Pharmatoher (2008) 359(15):1543-1554 **IF= 2.07,** ISSN: 1465-6566 **(reproduced with permission)**

The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) Trial was a 4-year, randomized, double-blind, placebo-controlled parallel-group trial aimed at evaluating the effects of long-term therapeutic intervention with tiotropium bromide on lung-function decline, morbidity and mortality in patients with moderate-to-very severe stable COPD(Tashkin et al., 2008).

Methods and results

The primary endpoint was the effect of inhaled tiotropium on forced expiratory volume in 1 sec (FEV1) decline rate.

Secondary endpoints included, among others, the decline rate of forced vital capacity (FVC), health-related quality of life (HRQoL) measured with the Saint George Respiratory Questionnaire (SGRQ), COPD exacerbations and related hospitalizations.

Adverse events, all-cause mortality and respiratory mortality were also recorded throughout the study. Patients were randomized to receive 18 μg of inhaled tiotropium or matching placebo once daily and were allowed to use other COPD medications except for short-acting anticholinergics (ipratropium bromide).

A total of 5993 patients was randomized: 3006 to placebo (P) and 2987 to tiotropium (T). T improved HRQoL significantly throughout the study, the overall mean difference between the groups being 2.7 ($p < 0.001$), and produced clinically significant HRQoL improvements in significantly higher proportions of patients than P.

T was associated with a significantly lower risk of COPD exacerbation or hospitalization [hazard ratio (HR) for both events being 0.86; $p < 0.001$ for exacerbations] and significantly reduced the duration of exacerbation (12.11 days versus 13.64 days, $p=0.001$).

A total of 941 deaths of any cause was reported over the period included in intention-to-treat analysis, 14.9% in T and 16.5% in P (HR 0.89, $p=0.09$).

Discussions

The UPLIFT Study demonstrated that, in stable patients with moderate-to-very-severe COPD, long-term therapy with T alone or in combination with other medications was significantly beneficial in terms of COPD-related morbidity reduction and HRQoL improvement, and that T had a good cardiovascular safety profile. Furthermore, in COPD patients with less severe COPD not requiring concomitant therapy with inhaled corticosteroids or with other long-acting beta2 agonists, the therapeutic effect of T on lung-function decline was significant. The effect of T on all-cause mortality was neither significantly beneficial nor, more importantly if safety is considered, significantly deleterious, but further analysis on respiratory cause mortality, and on mortality rates according to COPD disease severity, are certainly required.

Conclusions

The UPLIFT Study which was done on smoking-related COPD showed that, in terms of lung-function decline, the maximum therapeutic benefit was in patients with moderate COPD. This means that, as a therapeutic intervention, the effects of inhaled tiotropium therapy on lung function preservation were comparable to sustained smoking cessation. In terms of impact on health status/health-related quality of life, tiotropium exerted a sustained beneficial effect over the four year study period, and produced clinically meaningful improvements in a higher proportion compared to conventional therapy only (Antoniu, 2009). After the seminal Lung Health Study which evaluate the impact of various therapies on lung function decline, the UPLIFT study has the merit of providing valuable results on the same issue and of integrating health status in monitoring the disease course in patients undergoing regular therapy with an inhaled antimuscarinic agent. However the UPLIFT study although considering all-cause mortality as an endpoint did not go further to study the predictors of mortality and more specifically if heath status could be used as an outcome measure for mortality risk.

The rationale for use of triple inhaled therapy in COPD was postulated long before. This was represented by the need to use a maximal inhaled bronchodilation and inhaled corticosteroids in an inhaled regimen which should act in a synergistic manner in patients with more advanced COPD. An early short-term 12 week study evaluated the effects of addition of tiotropium to BUD/FOR inhaled combination on various outcome measures which included health status measured with the SGRQ (Welte et al., 2009). The results of this study were reviewed below(Antoniu et al., 2010).

Personal contribution

Antoniu SA, Carone M, Sampablo I. Triple inhaled therapy in stable chronic obstructive pulmonary disease: the earlier the better ? Expert Opin Pharmacother 2010 11(6):1039-1042 **IF= 2.40 (reproduced with permission)**

Methods and results

This was a randomized double-blind parallel group study enrolling ex-smokers with stable (GOLD stage II-IV) COPD. The primary efficacy endpoint was represented by the change from baseline

in trough FEV1 and change from baseline in health status was included as a secondary efficacy endpoint along with change from baseline in inspiratory capacity posttreatment FEV1 respectively FVC changes or in COPD-related symptoms. Included were also time to the next severe exacerbation and the number of severe exacerbations per patient.
The cohort analysed included 660 patients (331 receiving TIO 18 µg daily as a monotherapy and 329 patients receiving TIO added to BUD/FOR 320/9 µg twice daily. Both groups were homogeneous at baseline in terms of the outcome measures analysed. Triple therapy TIO/BUD/FOR was found to result in a significant improvement of the lung function variables mentioned above compared to TIO monotherapy. Baseline health status was also significantly improved compared to baseline (3.8 with the triple compared to 1.5 with the monotherapy, p=0.023). A significantly higher number of patients receiving triple therapy exhibited clinically meaningful improvements in health status compared to baseline (49.5% versus 40%, p=0.016). Deterioration in health status compared to baseline was found in comparable proportions of patients in both groups (27.6 versus 29.7%). A significant therapeutic benefit in favour of triple therapy was also reported with the exacerbation-related endpoints.

Discussions
The study included COPD patients with various stages of severity according to the classification in force at the date of paper publication. Overall, the triple therapy regimen was found to be superior to TIO monotherapy on each of the outcome measures considered and this might be have been done to the fact in the stage II subset double bronchodilation was more efficient than in the other stage III or IV of the GOLD. However, an analysis of efficacy according to disease severity subsets was not performed and therefore this hypothesis cannot be checked against the results.

Conclusions
The triple inhaled therapy was demonstrated to be efficacious irrespective of the disease severity stage, but additional long-term data on its effects, especially in subjects with less advanced COPD, are needed in order to document better its uniform efficacy in all COPD stages or its 'selective' efficacy in certain stages.

Personal contribution

Antohe I, **Antoniu SA**, Gavrilovici C. Triple fixed inhaled therapy in frequent chronic obstructive pulmonary. disease exacerbators: potential advantages for various degrees of airways obstruction. Expert Opin Pharmacother 2018;19(3): 287-9,**IF= 3.03 (reproduced with permission)**

If previous studies focused on single component respectively on combined double inhaled therapies, more recently triple combinations for inhalation were evaluated in phase III clinical trials.

One such study was the FULFIL trial which was a phase III randomized double-blind, multicentric study comparing the effects of once-daily triple therapy represented by fluticasone furoate/umeclidinium/vilanterol 100 μg/62.5 μg/25 μg (FF/ UME/VI in Elipta Inhaler©) with twice daily budesonide/formoterol 400 μg/12 μg (BUD/FOR in Turbuhaler©) over 24 weeks(Lipson et al., 2017).

Methods and results

The intention to treat sample analyzed amounted 1810 patients with stable COPD, 911 in the FF/UME/VI arm, and 899 in BUD/FOR arm. There was an extension phase of the core trial up to 52 weeks which included a subset of 430 patients, 210 on FF/ UME/VI, respectively 220 on BUD+FOR.

Inclusion criteria were represented by forced expiratory volume in the first second (FEV1%predicted) less than 50% and CAT score of at least 10 or FEV1%predicted between 50-80% and CAT score of at least 10 and either at least 2 moderate exacerbations over the last 12 months or at least 1 severe exacerbation during the same interval.

There were two primary endpoints one related to the lung function and represented by the changes from baseline in trough FEV1 and the other one represented by changes from baseline in health status measured with SGRQ. Among the secondary endpoints included were the proportion of patients who compared to baseline experienced clinically meaningful improvements in trough FEV1 (of at least 100 ml) and the proportion of patients with clinically meaningful improvements in health status (ie a decrease in baseline score of at least 4 units).

Discussion

Other studies evaluating the triple combination also considered health status as an efficacy outcome measure: one such study lasting 12-week and in which 660 patients were enrolled, demonstrated that budesonide + formoterol added to tiotropium were superior to tiotropium alone in improving lung function, health status, and in reducing exacerbations rate (Welte et al., 2009).

The design of this study denotes the relevance gained by health status as a meaningful outcome measure in both clinical trials setting and in real life (for the latter context CAT is used to document the burden of the disease and to stratify COPD patients according to the risk of subsequent exacerbations).

In terms of therapeutic effects, FF/ UME/VI was superior to BUD/FOR in improving health status, although both inhaled combinations produced clinically meaningful improvements compared to baseline in intention to treat population (-6.6 versus 4.3, $p<0.001$).

Conclusions

The results of this analysis demonstrate that health status remain the most important patient-reported outcome measure which can be used in order to document the impact of therapy on perceived disease-related burden (Antohe et al., 2018).

Personal contribution

Antoniu SA, Rajnoveanu R, Ulmeanu R, Mihaltan F, Grigore M. Evaluating revefenacin as a therapeutic option for chronic obstructive pulmonary disease. Expert Opin Pharmacother 2020 21(9): 997-1004. **IF pentru 2019=2,87 (reproduced with permission)**

The development of revefenacin, a long-acting anticholinergic optimized for nebulization use was evaluated in a review. The analysis of the basic pharmacology profile demonstrated the suitability of the compound for once daily dosing, its sustained bronchodilating effect and the very good safety and tolerability.

Reviewed were

- Preclinical development of the compound which included inhalation studies in dogs
- Basic clinical pharmacology in humans: pharmacodynamics, pharmacokinetics and metabolism
- Clinical efficacy data: phase I studies demonstrating safety and tolerability of inhaled formulation in healthy individuals, phase II exploring clinical pharmacology of revefenacin in COPD patients early efficacy and safety, phase III in which efficacy was studied with relevant endpoints such as lung function change or health status change compared to baseline and to comparator used.

In one of the phase III studies included in this review health status was involved as an outcome measure and in one such study it was measured with a battery of disease-specific questionnaires, namely SGRQ, CCQ and CAT. Efficacy results were reported with SGRQ scores which were found to be improved at the end of 52 weeks of dosing. One of the efficacy endpoints was represented by the proportions of patients exhibiting clinically significant improvements (53% with revefenacin 175µg, 42%with revefenacin 88µg, and 45% with tiotropium 18 µg)(Ferguson et al., 2019, Antoniu et al., 2020).

Conclusions

The analysis of the efficacy and safety data related to nebulized revefenacin demonstrated that on long term basis this medication was able to produce a perceived (clinically meaningful) therapeutic effect in a significant proportion of patients.

1.2.3 Conclusions

Health status/health-related quality of life can be assessed in COPD with generic questionnaires (health-related quality of life), disease-specific questionnaires(health status) or both in order to gain a more comprehensive picture on the impact of the disease and of its symptoms on the ability of the patient to function daily from both mental and physical points of view.

Inhaled therapies are the most relevant example of an application of health status/health-related quality of life use in both clinical trial (drug development) or in real life settings. Practically all inhaled therapies developed for inhalation use and for regular administration were evaluated in late phase of clinical development (phase III studies) for their effect on health status/health-related quality of life and the clinical data presented in this subchapter demonstrate this therapeutic benefit is due to bronchodilators single inhalers, to bronchodilator combination, to bronchodilator and corticosteroid combination or to triple combination. Most recent data are available for long-acting bronchodilators often for dosing periods ranging from 12 to 52 weeks and there are studies such as UPLIFT study which examined the effect of long acting bronchodilators over even longer periods of time. Most recently, a revival of previously used inhalation routes and it is the case of nebulization was reported with long-acting anticholinergic revefenacin, optimized for once daily use and able to improve health status also in a clinically meaningful manner. Therefore the efficacy of inhaled therapies in stable COPD can be monitored with health status as an outcome measure, and the routine use of CAT test is the clearest demonstration of this.

1.3 Health status/health-related quality of life in end-stage COPD and long-term oxygen therapy

1.3.1 Introduction

In COPD, progressive airways inflammation leads to impairment in gas exchanges at pulmonary level and with development of hypoxemia associated or not with hypercapnia. Chronic hypoxemia can be apart from severe airways obstruction (FEV1%pred under 30%) one of the hallmarks of end-stage COPD has major systemic consequences due to its deleterious effects on heart, skeletal muscle or nervous systems normal functioning and is associated with a significant reduction in survival. In patients with end-stage COPD long-term oxygen therapy (LTOT) is the only therapeutic method which is able to improve survival. This was demonstrated by two major studies, the Medical Research Council (MRC) study and the Nocturnal Oxygen Therapy Trial (NOTT) study. Such studies which are discussed in this section showed the effectiveness of this method mainly using physiological outcome measures but have the great merit of identifying the main therapeutic option able to improve survival in patients with advanced COPD who are eligible for. Indeed the NOTT study mentioned the Sickness Impact Profile, a very elaborated generic questionnaire described earlier in this chapter, as being used as an outcome measure but few details were subsequently given on its ability to predict mortality.

However, another significant merit of these two studies is the demonstration that some of the outcome measures used to monitor the patients were able to predict an increased risk of mortality. More recently, studies performed in patients with end-stage COPD requiring LTOT considered health status as an outcome measures for evaluating the more “subjective”, as perceived by the patient effect of this therapeutic method and one such study such as that co-authored by me with Dr Carone and Professor Paul Jones even examined the ability of health status to predict mortality in such patients. These studies are also discussed in this section, the latter being detailed due to its

originality and to the fact that I was part of the team doing the analyses while functioning as an European Respiratory Society Fellow at the IRCCS in Veruno, Italy.

1.3.2 Scientific rationale for long-term oxygen therapy in COPD

LTOT is aimed at correcting the chronic hypoxemia by increasing the concentration of oxygen which reaches the alveolar-capillary membrane in the lungs. This in turn can improve the aerobic metabolism in brain, heart and skeletal muscles and can also reverse hypoxemia-induced vasoconstriction in pulmonary artery branches and the hypoxemia-induced erythropoietin release in the kidney. Consequently LTOT can delay the development of cor pulmonale and of the secondary polycythemia or if they are already produced to reduce their severity.
Two main large cohort studies evaluated the effects of LTOT and provided evidence for the scientific rationale of this method in chronic hypoxemia caused by COPD.
The MRC study was a randomized controlled trial enrolling patients with chronic bronchitis or emphysema (which are now both included in the pathologic definition of COPD) and severe arterial hypoxemia. The analysed sample included 87 (n=42 receiving LTOT and n=45 in the no-oxygen control) patients who were randomized to LTOT at least 15 hours/day and a flow rate of 2l/min and were followed up for five years. Mortality rates were 19/42 in the LTOT arm and 30/45 in the control arm. Males had a better therapeutic benefit from this method which however was not apparent until about 500 days of LTOT. Females in the control group had a very poor outcome with a mortality rate of 8/12 over 3 years. Mortality was best predicted by the partial pressure of carbon dioxide in arterial blood+hematocrit. On short-term basis the COPD related morbidity or mortality were not significantly influenced by the LTOT, but on long-term basis patients who were less severe at baseline the survival benefit was also attributed to LTOT (MRC, 1981).
The data from this study was the basis for the early recommendation of LTOT in COPD by the management guidelines.
The NOTT study was another randomized study in which 203 patients with COPD were allocated to either nocturnal (12 hour) or continuous (equivalent of LTOT) oxygen therapy, these patients being followed up for at least 12 months (mean follow up duration was 19.3 months). One year mortality rate was 20.6% in patients in the nocturnal oxygen therapy arm and 11.9% in patients with continuous oxygen therapy, a patient undergoing nocturnal oxygen therapy having a 1.94 higher mortality risk as compared to a patient in continuous oxygen therapy arm. LTOT appeared to be beneficial in patients with more preserved exercise capacity, lower hematocrit and lower pulmonary artery pressure (NOTT, 1980). Unlike MRC study, the NOTT study considered patient reported outcomes such as quality of life(measured with Sickness Impact Profile), personality(Minnesota Multiphasic Personality Inventory) or mood (Profile of Mood States) and reported that both oxygen regimens improved quality of life as compared to baseline, without providing specific data on this issue.
POMS scores however were analyzed in relationship to their ability to predict mortality and it was found that a survival benefit was associated with scores higher than a certain cut off value(NOTT, 1980).

These data highlighted that LTOT should not only be prescribed during night but also during daytime and that a daily effective minimal duration should be around 15-16 hours/24.

1.3.3 Indications and contraindications for LTOT in end-stage COPD

Indications and contraindications of LTOT in end-stage COPD are based on the results of some of the studies discussed in the beginning of this section.

The indications of LTOT in end-stage COPD are the following(GOLD, 2018):

- Chronic severe hypoxemia with paO2 ≤55 mmHg or SaO2≤88% while breathing air and in the stable state
- Chronic mild to moderate hypoxemia with paO2=56-59 mmHg or SaO2 89% when one or more of the following are associated congestive heart failure, cor pulmonale or secondary polycythemia defined with a hematocrit>55%

Contraindications of LTOT can include:

- Continuation of smoking
- The patient does not meet one of the eligibility criteria above listed
- Patient is not motivated, refuses or does not have the means for LTOT
- The disease (end-stage COPD) is not in a stable state

1.3.4 LTOT oxygen systems

Currently three main types of LTOT administration systems are used in clinical practice and they are represented by:

a. Compressed medical oxygen cylinders
b. Oxygen concentrators
c. Liquid oxygen delivery system

a. Compressed medical oxygen cylinders

This is the oldest system for LTOT and its use is currently limited to some countries and mostly to under privileged, under-insured patients. It is the most difficult to use LTOT system, because of the limited autonomy of functioning of the cylinders and of the need for a technician to ensure a continuous cylinder supply. In order to help the patient to better anticipate the need to replace the cylinder, these were marked with a specific letters for each of the volumes of compressed oxygen stored within, for example B, E,D,H,G, M, each corresponding to a certain capacity and to a certain duration of appropriate provision (measured in hours) of oxygen at a certain constant flow rate of for example 2l/min (Hardavella et al., 2019, Petty, 2000). More recently, oxygen conserving devices were developed in order to increase the duration of use of oxygen delivery by

the same cylinder (Hardavella et al., 2019). Portable cylinders also allow a limited mobility of the patient.

b. Oxygen concentrators

Delivery of oxygen by oxygen concentrator is by far the most common method of LTOT worldwide. The principle of oxygen supply is simple, the device connected to a power source extracts the oxygen from the breathing air, eliminates the nitrogen and delivers oxygen at higher levels compared to those in the air (93-98%, "concentrated"), hence the name of the system. The device is very easy to be used but requires indications to maintain it appropriately (including filters cleaning) and delivers higher concentrations of oxygen at lower flow rates. The classical oxygen concentrator does only allow a limited ambulation of the patient around the device, but this limitation is minimized by the portable concentrator which works with a rechargeable battery and which can also benefit from an oxygen conserving device (Hardavella et al., 2019).

c. Liquid oxygen delivery system

This is considered as being the most effective, yet the most expensive system for oxygen delivery in LTOT. It consists of two tanks, a bigger one which acts like a storage device and stores oxygen at very low temperatures in liquid phase. This method of "freezing" the oxygen allows that a very high volume of gaseous oxygen is compressed in a relatively small container. The smaller tank is the delivery tank, is a portable reservoir which is filled from the storage tank and has a heating system incorporated in its structure. Liquid oxygen in this portable reservoir is heated on its way to the delivery cannula system so that it becomes gaseous again and has a temperature appropriate for safe inhalation in the airways. The concentration of oxygen delivered by this system is 100%. This system also functions with a rechargeable battery and allows ambulation. Alike those using the portable concentrator, patients using it can go shopping, walking etc provided the duration of activity is appropriate for the autonomy of the delivery device.

1.3.5 Health status in end stage COPD receiving LTOT

Health status has become over the last decades a very popular PRO measure to monitor COPD course. As described throughout this chapter, there are various disease-specific questionnaires which can be validly used in various COPD-related settings irrespective of disease severity or of its stable or exacerbated state. In end-stage COPD the use of health-status is even more useful in an attempt to better capture the disease severity (increased clinical burden) as perceived by the patient because in this particular situation the conventional physiological outcome measure are no longer as useful as in milder COPD stages. Furthermore, a therapeutic method which is able to improve health status despite not being able to improve for example lung function or to significantly reduce the airways inflammation is seen as a valid approach because it focuses on patient perceived impairment and on its perceived clinical improvement. Such considerations are concordant and can even be considered as being one of the main binding loops with approaches

the palliative care and especially of those of early (pro-active) palliative care which target the broader concept of quality of life.
The data and the other information presented and discussed below support the use of health status as one of the main outcome measures which should be used in patients with end-stage COPD undergoing LTOT.

Personal contribution

Carone M, Antoniu S, Baiardi P, Digilio VS, Jones PW, Bertolotti G; QuESS Group Predictors of Mortality in Patients with COPD and Chronic Respiratory Failure: The Quality-of-Life Evaluation and Survival Study (QuESS): A Three-Year Study. COPD. 2016;13(2):130-8**. IF=2.47,** ISSN: 1541-2555 **(reproduced with permission)**.

The objective of the QuESS study was to demonstrate that in patients with COPD and chronic respiratory failure (CRF) undergoing LTOT, poor health status can predict mortality.
As demonstrated previously in this section, LTOT is apart from smoking cessation the only therapeutic method able to improve survival in COPD. However there are few data on the outcome measures which can be used to predict mortality in patients with COPD and LTOT. Some studies for example focused on physiological measures such as FEV1 or such as severity of hypoxemia (paO2). For example, it was estimated that when FEV1 is about 1 liter, the life expectancy is approximately 4 years and decrease to half when FEV1 is reduced to 0.5 liter(Burrows, 1985). Some studies identified FEV1, paO2 and paCO2 as predictors of mortality irrespective of the gender or FEV1 as a predictor of mortality in males (Chailleux et al., 1996, Ström, 1993).
More recently it was demonstrated that in patients with COPD health status is impaired and therefore the evaluation of this outcome measure as a potential predictor of mortality in such patients become justified (Carone et al., 1999, Okubadejo et al., 1996, Prigatano et al., 1984).
For example one such study performed in males with COPD demonstrated that apart from FEV1 and peak oxygen uptake (VO2max) health status was also able to predict mortality whereas the other one similarly performed in a male population of COPD patients found that health status was an independent predictor of mortality (Oga et al., 2003, Domingo-Salvany et al., 2002).
Another study was performed in a population of COPD patients which included both females and males and also identified health status as a predictor of mortality and of morbidity (subsequent hospitalisations) (Fan et al., 2002)
Our study focused on end stage COPD patients having CRF receiving LTOT and used both SGRQ and MRF26 questionnaires to document health status. Also the study evaluated mortality and its predictors over a 3 year period (Carone et al., 2016).

Methods

This was a prospective multicenter multinational study performed in 21 centers located in 7 countries (Italy, Spain, UK, USA, Canada, Japan and Czech Republic). Patients with various

underlying pathologies and receiving LTOT at the time of enrollment and who consented to participate to the study were included from January 1999 to December 2000 and then followed up for up to 3 years. In this study only the cohort of patients having COPD and CRF were included. Patients' visits' were performed at baseline, 6, 12, 24 and 36 months from baseline. Included (in this anlysis) were outpatients with stable COPD and CRF, ex-smokers, requiring LTOT with or without nocturnal mechanical ventilation. Excluded were COPD inpatients with unstable disease, those with a history of allergic rhinitis, asthma, drug use, poor motivation, major psychiatric disorders, neuromuscular disorders, lung cancer or those unwilling to participate. The study was coordinated from Salvatore Maugeri IRCCS in Veruno, Italy and received the ethical approval for its conduct.

Measurements

The following parameters and variables were recorded at baseline: age, gender, comorbidities, nutritional status, medications, LTOT(years of use, source, flow rates, hours/day), mechanical ventilation, pulmonary function tests (FEV1, forced vital capacity FVC, FEV1/FVC), arterial blood gas(ABGA) analysis in room air, exercise capacity as assessed with the shuttle test, dyspnea measured with MRC dyspnea scale, health status measured with SGRQ and MRF26, quality of life measured with SF-36, emotional distress measured with the Hospital Anxiety and Depression Scale (Singh et al., 1992, 1960, Stewart et al., 1988, Jones et al., 1992, Vidotto et al., 2007, Zigmond and Snaith, 1983).
The following parameters and variables were collected at follow ups: all the above plus data concerning exacerbations, hospitalizations, antibiotics and corticosteroids use during the interval from the last follow up or from baseline. For patients who died during the follow up period date and cause of death were recorded.
Lung function was measured with spirometry which was performed in accordance to the American Thoracic Society criteria (1995).

Statistical analysis

Univariate analyses were performed using unpaired t-tests in patients who survived respectively in those who died.
Survival analysis was performed with Kaplan-Meiers and with Cox semiparametric hazards method using some of the outcome measures mentioned above which included age and which were found to differ statistically for their baseline values between those who survived and those who died. In order to increase the reliability of these survival analyses, cut-off values were calculated with the receiver-operating curve (ROC) method for these outcome measures. Gender was also considered as an "outcome" measure and included in the survival analysis.
A further statistical refinement was represented by the backward elimination approach.

Results

1. Baseline characteristics

Baseline cohort included 319 COPD patients receiving LTOT. A number of 10 were lost to follow up due to the withdrawal of 2 investigating centers. Comorbid conditions were found at baseline as follows: one in 18%, 2 in 13% and at least three in 23% of the enrolled patients. Home mechanical ventilation was also associated to LTOT in 23 patients. At 12 months follow-up complete datasets were available for 221 patients whose main baseline characteristics are presented in the **Table 1.1.**

Table 1.1 Relevant baseline characteristics for the analyzed sample

	All patients(n=221)	LTOT n=198	HMV n=23	p-value
Age (years, SD)	67.8 ± 8.2	68.4 ± 7.8	63.0 ± 9.6	**0.003**
Male sex (%)	72,4	72,2	73,9	0.893
BMI (kg/m2, SD)	26.2 ±5.5	26.1 ±5.3	27.3 ±6.5	0.512
FVC (% predicted, SD)	59.6±19.9	60.1±20.0	55.3±19.5	0.302
FEV 1 (% predicted, SD)	34.4±15.2	34.4±15.0	34.2±18.0	0.765
6MWT (meters, SD)	179±120	180±123	174±99	0.234
O 2 -rest (L/min, SD)	1.7±0.7	1.7±0.7	1.6±0.9	0.887
MRC-Dyspnea (Units of score, SD)	3.2±1.3	3.2±1.3	3.2±1.4	0.899
SF36-MCS(units of score, SD)	47.4±11.5	47.4±11.4	47.8±12.6	0.787
SF36-PCS(units of score, SD)	34.3±9.5	34.2±9.7	35.4±7.0	0.668
SGRQ-Total (units of score, SD)	53.1±17.3	53.5±17.2	49.6±17.7	0.305
SGRQ Impact (units of score, SD)	44.4±19.3	44.6±19.5	43.0±18.2	0.717
MRF26-Total (units of score, SD)	43.8±25.4	44.0±25.5	42.8±25.1	0.838
MRF26 Activity (units of score, SD)	42.7±28.9	43.2±28.9	37.8±28.6	0.393

The mean number (SD) of years of LTOT 2.8± 2.5 and that for HMV was 2.5± 2.5. At the last follow up, 178 patients were alive and 43 of them had died over this period, yielding a 3 year mortality rate of 19%.

As expected, mortality rate was almost 2 fold higher in males compared to females (22.5% versus 11.7%, p=0.064). Among the identified causes of mortality, the commonest was found to be respiratory related (identified in 33 patients and due in 85% of them to acute on chronic respiratory failure). Non-respiratory causes of death were reported in 10 patients and most of them (60%) were due to cardiac diseases.

Univariate analysis for 3 years all-cause mortality

Among the variables and parameters compared via univariate analysis between the group of patients who survived at 3 year follow up and the one who died in this period of time, statistically significant differences were detected in baseline values for age (70.30 ± 5.40 in dead versus 67.21 ± 8.62 in survived, p=**0.030**) FVC(%pred, 53.76 ± 17.49 in dead versus 61.07 ± 20.27 in survived, p= **0.030)**, oxygen flow rate at rest(l/min 1.95 ± 0.56 in dead versus 1.59 ± 0.73 in survived, p= **0.003)**, SGRQ scores for Impact and the Total scores (Impact: 50.58 ± 18.49 in dead versus 42.91 ± 19.31in survived, p=**0.020** ; Total: 58.79 ± 16.46in dead versus 51.70 ± 17.20 in survived, p= **0.020)**, MRF-26 Activity and Total scores (Activity: 53.85 ± 30.35 in dead versus 39.97 ± 27.93 in survived, p= **0.004**;Total: 52.24 ± 24.49 in dead versus 41.81 ± 25.26 in survived, p= **0.020**).

Kaplan Meier survival- all cause mortality

As mentioned in the methodology section we identified cut-off values using ROC method for age (67 years), FVC (%pred) 49.5%, oxygen flow rate at rest (1.75 l/min), SGRQ Total score 61.5 and MRF-26 Total score (40.4) and after entering these values in the Kaplan-Meier modelling, only the values for oxygen flow rate at rest, SGRQ Total and MRF26 Total were found to be associated with a statistically significant difference in survival.

For the age, patients older than 67 years who were prevalent (n=132) in the analyzed sample had a trend towards reduced survival likelihood but this did not differ significantly from that of the "younger" patients (age ≤67, n=89) (p value calculated with log rank test =0.178, **Fig 1.1**).

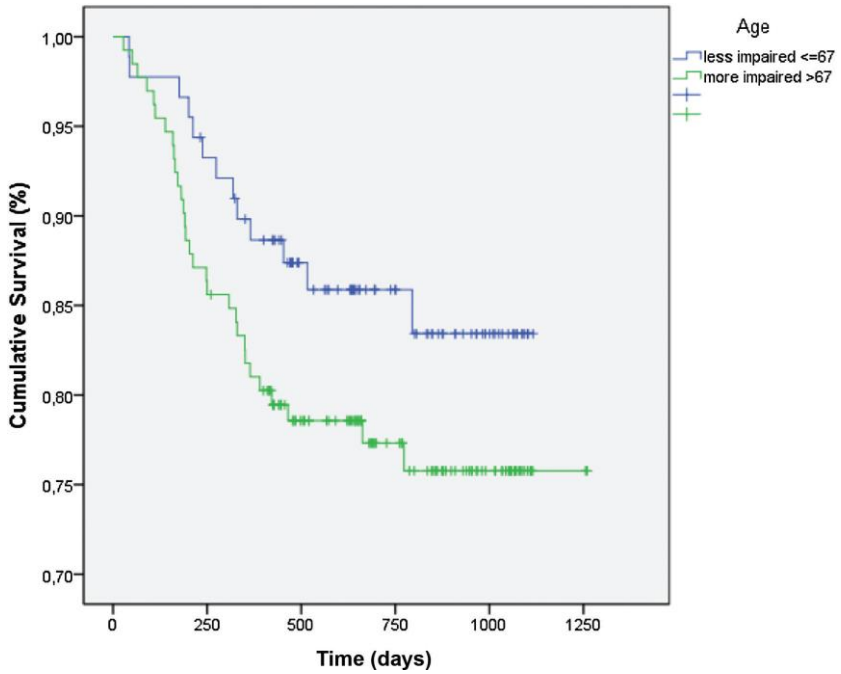


Fig.1.1 Kaplan-Meier survival curve for age

When we performed the same analysis taking into consideration FVC%pred as an outcome measure, the same type of non-significant difference was also found for this variable, COPD patients having better lung function as assessed with FVC (ie having values above the cut off value identified with ROC, exhibited a trend for better survival than those with lower values (data not shown for the p value calculated with log rank test). FEV1%pred was not entered in any of the survival modelling because the univariate analysis did not identify any statistically significant differences between those who survived versus those patients dead at 3 years from enrollment in the study (baseline).

a). Oxygen flow rate at rest

Oxygen flow rate at rest is an indirect indicator of the severity of hypoxemia. In our analysis it was found that patients who at baseline were less hypoxemic (n=97) (ie required less than 1.75l/min oxygen flow rate at rest had a 3 year survival rate of 78% compared to 59% in more hypoxemic patients (n=112), p=0.001 with log rank test (***Fig. 1.2*****).**

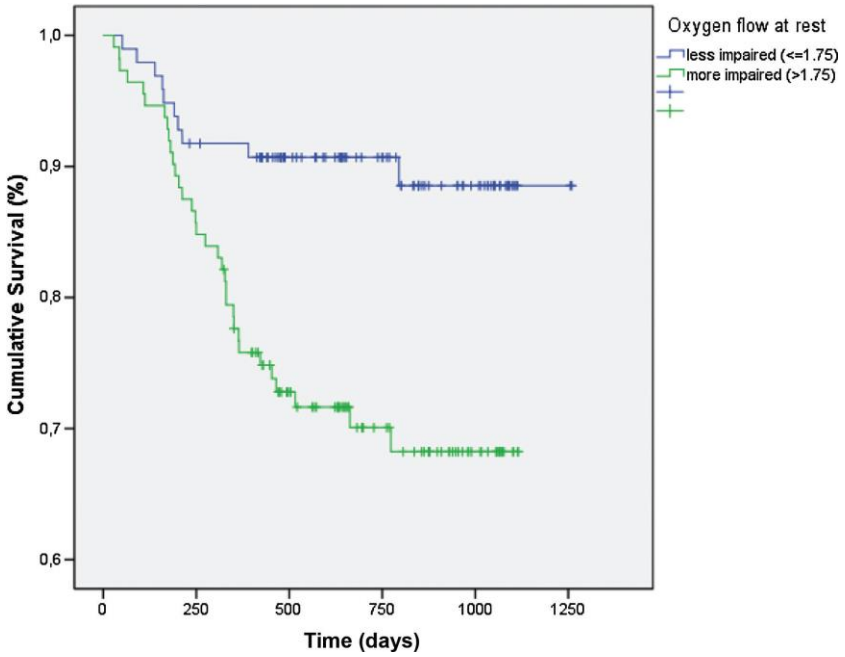


Fig.1.2 Kaplan-Meier survival curve for oxygen flow at rest

b). Health status

As described above, health status was measured with SGRQ a disease specific questionnaire (ie applicable in various chronic respiratory diseases including COPD) and with MRF26 which is a questionnaire designed for those having end stage chronic respiratory diseases and chronic respiratory failure.

Kaplan Meier analysis performed with the cut off value of the Total score of SGRQ identified a 76% 3 year survival rate in patients with better health status (n=141) who had scores $\leq$ 61.5 compared to 51% in patients with worse health status (SGRQ Total score more than 61.5, n=76, log rank test yielding p=0.001 **(*Fig 1.3*).** Similar results were demonstrated with the cut off value of 40.4 for total score of the MRF26 questionnaire: the 3 year survival rate was 54% in patients

with worse health status (scores higher than the cut off value, n=118) compared to 83% in n=103 patients having a better health status (MRF26 Total score ≤40.40), p=0.019 **(*Fig.1.4*).**

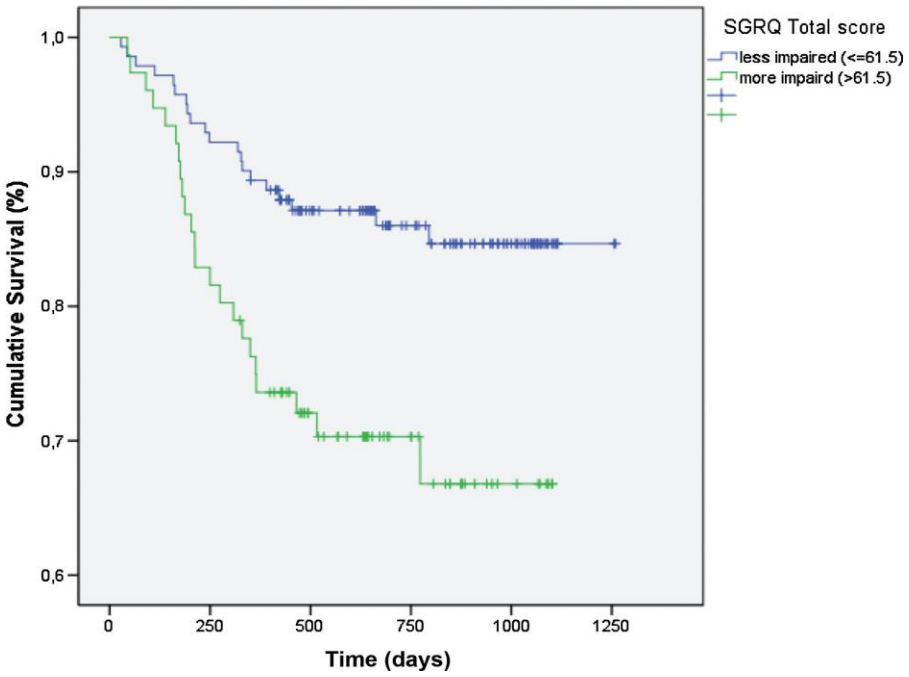


Fig1.3 Kaplan-Meier survival curve for health-status(SGRQ)

One of the main points of originality of this analysis was the fact that health status was studied with two disease-specific questionnaires namely SGRQ and MRF26.

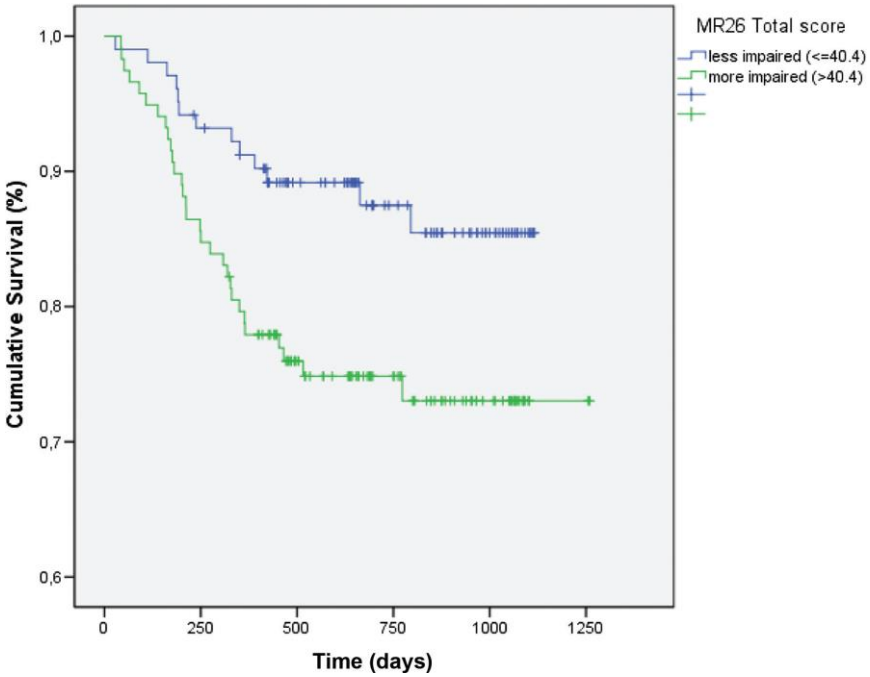


Fig.1.4 Kaplan-Meier survival curve for health status (MRF-26)

This approach was chosen because SGRQ is suitable for all stages of severity of COPD whereas MRF26 is more appropriate for advanced COPD. Their parallel use and analysis which is presented here allowed the researchers to draw a conclusion on their ability (namely on their scores ability) to predict mortality.

Cox survival analysis-all cause mortality

Two survival models were created with the Cox method and they included in Model 1 age, oxygen flow rate at rest and Total scores of SGRQ whereas in Model 2 Total score of SGRQ was replaced with the Total score of MRF26. According to Model 1 for example an increase in age of 1 year was associated with an increased in mortality risk of 6%, an increase in oxygen flow rate at rest was associated with an increased risk of mortality of 68%, an increase in health status (SGRQ) with 1 score point was associated with an increased risk of 2.4%. In the second model and for the Total score of MRF26 the increase in mortality risk was of 1.3% **(see Table 1.2)**.

Table 1.2 Cox models for predicting mortality (Mortality risk calculated as hazard ratio (HR) with 95% confidence interval)

	HR 95% confidence interval	p value
Model 1 (205 individuals and 43 deaths)		
Age(years)	1.06(1.01-1.10)	0.015
O2 flow rate at rest (l/min)	1.68(1.18-2.41)	0.004
SGRQ Total score	1.024(1.01-1.04)	0.011
Model 2 (207 individuals and 43 deaths)		
Age	1.06(1.01-1.10)	0.015
O2 flow rate at rest (l/min)	1.68(1.18-2.41)	0.004
MRF 26 Total score	1.013(1.00-1.02)	0.018

Furthermore an increase in the Total score of SGRQ of 4 units of score which corresponds to the minimally clinical important difference validated for this questionnaire was found to be associated with a 10% higher mortality risk over 1 year period.

Discussion

This analysis is among the few focusing on mortality risk analysis over a 3 year period and in patients with end-stage COPD. The other studies which are mentioned below (some of them being also described in a more detailed fashion in the section on health status and long-term oxygen therapy) reported on 1 or 2 year mortality risk predictors some of them in COPD of various severity levels, some of them in patients with end-stage COPD. The ANTADIR observatory study which enrolled more than 26000 patients receiving LTOT for various conditions, examined 3 year survival, 5 year and 10 year survival but mainly focused on various physiologic outcome measures and did not consider health status as an outcome measure across the subset populations considered (Chailleux et al., 1996).

In our analysis we found that health status along with oxygen flow at rest (indirect measure of hypoxemia severity) were strongest predictors of 3 year mortality in a population of patients with end-stage COPD receiving LTOT.
In our Cox survival modelling age was also found to be a predictor of mortality and when comparing with other studies, we found that this was also recognized as a predictor of mortality in the COPD subset of the ANTADIR observatory study which enrolled a stage of COPD similar to that considered in our study, but also in other studies which also enrolled patients with milder COPD (Chailleux et al., 1996, Domingo-Salvany et al., 2002, Oga et al., 2003).
Despite our study did not identify hypoxemia at rest as a predictor of mortality as did another study, we considered as mentioned above the oxygen flow rate at rest as a supplementary indicator for the severity of CRF and found that this outcome measure is a powerful predictor of mortality in our cohort of patients (Chailleux et al., 1996).
Hypercapnia was not demonstrated to be a mortality predictor in our cohort and this might be due to the fact that the number of patients with type II CRF and end-stage COPD was reduced. ANTADIR observatory study as well as the NOTT study identified it as a predictor of mortality (NOTT, 1980, Chailleux et al., 1996).
The severity of airways obstruction measured with the impairment of FEV1 was not found to be a predictor of mortality in our study or in others, but its decline was documented as a predictor of mortality in the Obstructive Lung Disease in Northern Sweden (OLIN) Study, which had the longest follow up published to date (20-year) and which also demonstrated that the age was also a predictor of mortality (Lundbäck et al., 2009).
The fact that FEV1 is not a predictor of mortality in patients with more advanced COPD can be explained by the fact that in such patients chronic hypoxemia results in pulmonary hypertension, cor pulmonale or poliglobulia, conditions which in themselves increase the risk of mortality. Interestingly however is the identification of FVC as a predictor of mortality in the univariate analysis: this finding deserves further study and can be explained by the fact that reduced FVC in end-stage COPD can be due to static hyperinflation or to extensive emphysema lesions which were both identified as predictors of mortality in patients with both less advanced and end stage COPD (Casanova et al., 2005, Haruna et al., 2010).
Our study measured the exercise capacity with an incremental test (the shuttle) test but did not identified an impaired exercise capacity as a predictor of mortality. As previously shown in this section one study which also used an incremental test, the classical cycling test found that VO2 max was the strongest predictor of mortality whereas the NOTT study which used a similar test also showed a higher mortality risk associated with a more impaired exercise capacity (statistical significance for the difference not known) (Oga et al., 2003, NOTT, 1980).Other studies using the 6 minute walking test found that exercise capacity measured with the distance walked in 6 minutes was a strong predictor of mortality in patients with advanced or in patients with moderate COPD (Pinto-Plata et al., 2004, Waschki et al., 2011).
These data led to the incorporation of the exercise capacity as assessed with 6 minutes walking test within the composite predictor index BODE, along nutritional status, severity of the airways

obstruction and severity of dyspnea. The BODE index is currently recognized as one of the main tools to predict morbidity and mortality in COPD (Marin et al., 2013a, Celli et al., 2004).
As previously mentioned, the main element of originality of this analysis is represented by the fact that health status was considered as an outcome measure and was documented as a predictor of mortality. Health status was measured in this study with two disease specific questionnaires, developed with different methodologies, one able to measure health status across a wider range of chronic respiratory conditions irrespective of their level of severity, the SGRQ, and the other focusing on measuring health status on the end-stage of this conditions, ie when they associate CRF. The fact that in our analysis the results which were presented prior to this discussion were concordant demonstrate that the questionnaires used are reliable tools for this specified setting (end stage COPD with chronic respiratory failure). SGRQ scores were also found to predict mortality in samples of COPD of all severities (Domingo-Salvany et al., 2002, Oga et al., 2003).

1.3.6 Conclusions

Therefore our data suggest that health status is a relevant predictor of mortality in patients with end-stage COPD and with CRF and support the further study of this relationship in larger cohorts with longer follow up periods. The studies presented in this section and in particular the QuESS study to which I participated and which followed up patients with CRF for a time interval long enough to allow an appropriate identification of predictors of mortality, highlight the importance of the health status measurement in patients with advanced COPD and with LTOT and the valuable information it can provide on the mortality risk, impact of the clinical burden of disease in patients with this disease, or on disease subsequent morbidity. As it is going to be discussed in the following section impaired health status in a patient with an advanced chronic disease is an important indicator of the need for palliative care eligibility and therefore the consideration of this patient reported outcome in such a setting is essential for an appropriate assessment of care needs.

1.4 Health status/health-related quality of life and COPD exacerbations

1.4.1 Introduction

Initially when the first health status questionnaires were developed, it was considered that they couldn’t measure this PRO in an appropriate manner during exacerbations because, due to the specific construction of questionnaires’ items these would not be able to capture appropriately the rapid dynamics of health status over shorter periods of time. This limitation was subsequently addressed with two newer questionnaires the CAT and CCQ which were tested in COPD exacerbations and in particular in severe exacerbations leading to hospitalisations. CAT test was evaluated in COPD patients with exacerbations: CAT scores were found to be measures of exacerbations severity along with steep lung function impairment and with the duration of symptoms recovery (Mackay et al., 2012). However this study analysed a pooled population with various degrees of exacerbations from mild to severe and did not consider a particular analysis of the kind in hospitalisations. Given both the limited body of existing data and the need to find out

if health status can also be measured in COPD hospitalisations, I performed a clinical study in which I used the Clinical COPD (CCQ) questionnaire to evaluate health status in COPD patients with severe exacerbations (hospitalisations).

1.4.2 Health status during hospitalisations for chronic obstructive pulmonary disease exacerbations

Personal contribution

Antoniu SA, Puiu A, Zaharia B, Azoicai D. Health status during hospitalisations for chronic obstructive pulmonary disease exacerbations: the validity of the Clinical COPD Questionnaire. Expert Rev Pharmacoecon Outcomes Res. 2014 Apr;14(2):283-7. **IF=1.66**, ISSN: 1473-7167 **(reproduced with permission)**

The objective of this study was to demonstrate that the CCQ disease-specific questionnaire can be reliably used to measure the health status in patients hospitalized for severe COPD exacerbations, the below described analysis being performed in order to validate the use of the Romanian version of this questionnaire in this particular setting. In this study I also used a generic questionnaire, the VAS component of the EuroQol-5D in an attempt to obtain a more complete picture of the health status worsening at the time of hospital admission. This study demonstrated that health status as measured with CCQ-Total score correlated with the VAS score of the EurQol($r=-0.51$, $p<0001$). Length of stay in hospital was used as a measure of exacerbation severity and the baseline CCQ total score was found to be a significant predictor for the length of stay being significantly worse in patients with longer (more than 7 days) hospitalisations (3.77 versus 2.55, $p<0.0001$) (Antoniu et al., 2014). With this data, me and my team of researchers were the first to demonstrate that CCQ can reliably be used to monitor COPD exacerbations including the most severe ones(Antoniu et al., 2014).

Materials and methods

This was a prospective study in which patients admitted in the University Clinic of Pulmonary Disease with a COPD exacerbation over a period of nine months and who consented to participate to this study were included in the sample. Patients who refused to participate, those who were too ill to be able to complete the questionnaires, those who were illiterate, those who had impaired mental status or those who had other respiratory acute or chronic diseases were excluded from the study. Among the variables analysed included were age, nutritional status measured with the body mass index (BMI), years with COPD diagnosis, gender and smoking status distribution within the sample. A battery of questionnaires and scales was also used. This included the generic questionnaire Euroqol-5D which was administered at baseline (within the first 24 hours from admission) and at the 7^{th} day of hospitalization (if applicable), the disease-specific Clinical COPD Questionnaire (CCQ) which was similarly given, the WHO Five Well Being Index(WHO-5) and

the Baseline Dyspnea Index(BDI) which were both given only at baseline. The tool for measuring dyspnea was used in order to have a measure for the severity of the respiratory symptoms in the exacerbated state and the well-being scale was used in order to have a measure of emotional distress (in this case depression), which is prevalent in patients with COPD and with a significant respiratory burden(Lucas-Carrasco et al., 2012, Mahler et al., 1984, van der Molen et al., 2003a, Rutten-van Mölken et al., 2006). CCQ was further administered 24 hours after the baseline administration for calculating a psychometric feature called test-retest reliability.

Statistical analysis

Statistical analysis mainly focused in documenting the relevant psychometric characteristics of the Romanian version of the CCQ, characteristics which are used in the conventional procedure of questionnaire validation in a certain language, a certain (clinical) setting or in both. In our case it was the second consideration.
Statistical analysis was performed with the MedCalc version 12 and we performed the following calculations: concurrent validity was estimated with correlations (Pearson's coefficient) among the baseline CCQ scores and the scores of the other questionnaires or scales. Intra-class correlation coefficient of the CCQ was calculated for the test-retest reliability, whereas CCQ responsiveness was calculated with the dynamics (improvements) of the scores at 7^{th} day of hospitalizations compared to baseline. Internal consistency was assessed with Cronbach alpha coefficient, divergent validity was calculated against a physiological variable which was chosen to be SpO2 at the time of admission, whereas the discriminant validity was calculated using the duration of hospitalization (also known as the length of stay) as an indirect measure of disease severity: total CCQ scores were compared in patients with early hospital discharge ≤7 days (EHD) versus those with late hospital discharge>7 days (LHD).

Results

The analysed sample included 80 patients with a mean age of 67.03 years and most of them were males (62/80, 77.5%) and ex-smokers (45/80. 56.2%).

Table 1.3 Baseline characteristics of the analysed sample	
Body mass index (BMI, kg/m2, SD, n*=64)	24.85 (4.63)
Known COPD diagnosis (mean, years, SD, n=23)	11.23 (9.52)
WHO-5 score (mean, SD, n=80)	19.55(20.24)
EQ-VAS baseline score (mean, SD, n=80)	27.91(25.18)
BDI score (mean, SD, n=79)	3.26(2.67)
CCQ-S baseline score (mean, SD, n=80)	3.6(1.27)
CCQ-F baseline score (mean, SD, n=80)	3.5(1.34)
CCQ-M baseline score (mean, SD, n=80)	3.6(1.63)
CCQ-T baseline score (mean, SD, n=80)	3.57(1.08)

*n refers to the number of patients in which this variable was measured

The baseline values of the outcome measures used to assess dyspnea severity, emotional status, generic and specific (health status) quality of life are presented in **Table 1.3**

Concurrent validity

All domain and total scores of the baseline CCQ were found to correlate significantly with the comparators which were WHO-5, EQVAS and BDI baseline scores.

The strongest correlations were found in CCQ-T scores with WHO-5 and with BDI and in CCQ-F with BDI (**Table 1.4**)

Table 1.4. Concurrent validity of the baseline domain and total CCQ scores

Scores of the comparator scales	CCQ-S scores (significance level)	CCQ-F scores (significance level)	CCQ-M scores (significance level)	CCQ-T scores (significance level)
WHO-5	-0.52(p<0.0001)	-0.56(p<0.0001)	-0.41(P=0.002)	(p<0.0001)
EQ-VAS	-0.32(p=0.005)	-0.54(p<0.0001)	-0.29(P=0.01)	(p<0.0001)
BDI	-0.37(p=0.0008)	-0.78(p<0.0001)	-0.30 (P=0.006)	(p<0.0001)

Divergent validity

Previous studies demonstrated that health status scores did not correlate with physiological measures of disease severity. In stable COPD this was represented by lung function as assessed with forced expiratory volume in one second (FEV1)(Jones et al., 1992).

In the setting of an exacerbated COPD and especially at the beginning of a severe exacerbation this variable is not reliable and therefore blood saturation as measured by pulse oximetry (SpO2) was chosen as a physiological measurement of the severity of the exacerbation episode.

The divergent validity of the baseline CCQ-T was measured in 54 patients and as expected, there was no correlation between CCQ-T and SpO2 (r=-0.09, p=0.48).

Repeatability

Repeatability was measured with intraclass correlation coefficients for both single and average masures and for the latter category this was found to be 0.97 for CCQ-S, respectively F and respectively T and 0.93 for CCQ-M.

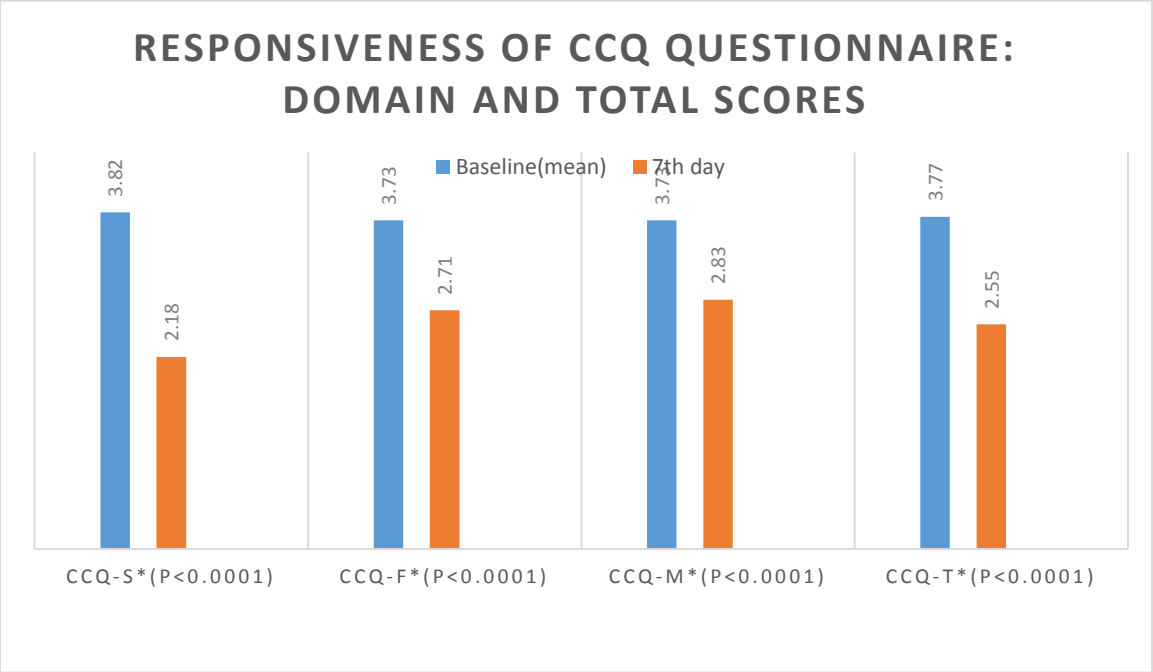
In the original validation study this coefficient was 0.94 for CCQ-T (van der Molen et al., 2003b).

Reliability

Reliability was measured as mentioned above with Cronbach's alpha coefficient which was found to have the highest value for CCQ-F (0.9) followed by 0.86 for CCQ-T, 0.7 for CCQ-S and 0.62 for CCQ-M.

Responsiveness

In patients who stayed in hospital at least 7 days all CCQ scores had lower values compared to baseline, and this dynamics corresponded to an improvement of health status which was both statistically and clinically significant (***Fig. 1.5*** values are means)



*p for the score difference

Fig.1.5 CCQ responsiveness

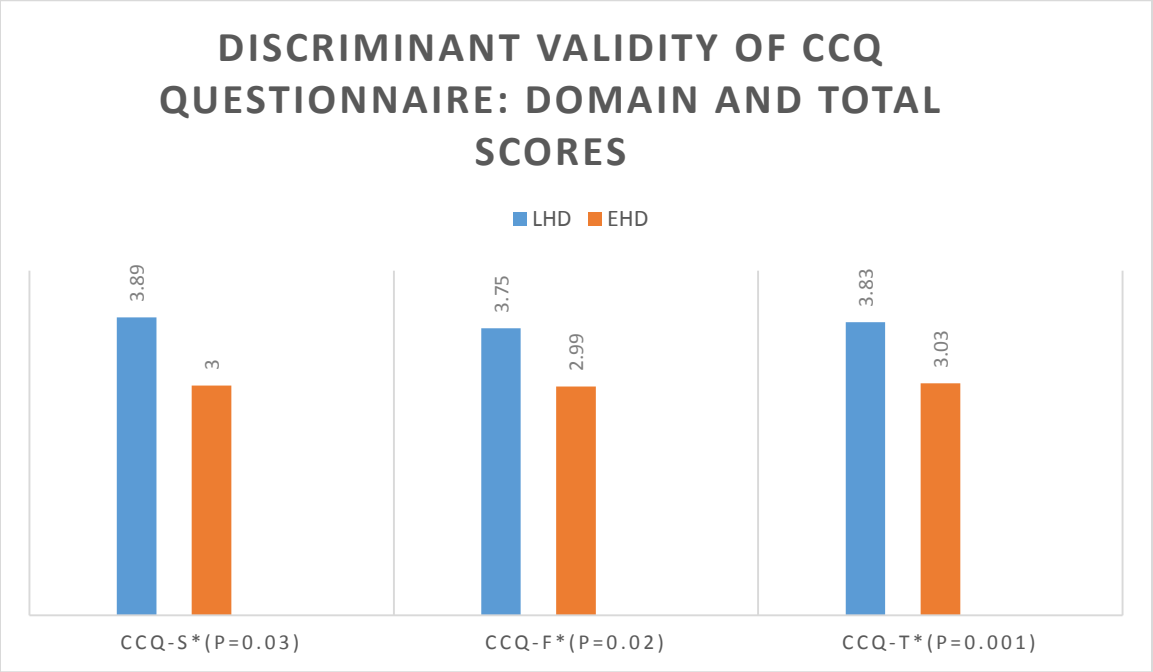
Discriminant validity

With this psychometric property the ability of the CCQ questionnaire to distinguish between patients who required longer hospital stays versus those with shorter hospital stays was measured all domain and the total score were found to be significantly lower in patients with shorter hospital stays (**Fig 1.6**, values are means)

Discussion

This study was among the few which demonstrated that health status is a reliable outcome measure in COPD exacerbations and that furthermore it can be validly used even in the setting of the most severe exacerbations (hospitalisations). CCQ was the health status questionnaire which was validated in this setting using the available Romanian version. The fact that health status was not found to correlate with the level of hypoxemia as measured by pulse oximetry is somehow concordant (from the point of view of health status physiological outcome measure correlation) with other studies such as the one validating the SGRQ (and using lung function instead) (Jones et al., 1992). Other studies did find such correlation between health status and severity of hypoxemia

(assessed with paO2) either in a population of mixed end stage respiratory disease and chronic respiratory failure or in patients with severe COPD undergoing long-term oxygen therapy for chronic respiratory failure (Carone et al., 1999, Okubadejo et al., 1996).



*p for the score difference

Fig.1.6 Discriminant validity of CCQ

Conclusions

The analysis presented above demonstrated that this health status questionnaire can be used in the setting of the COPD severe exacerbations and it also shown that the validation procedure was not only appropriate but also developed in an original manner.

1.4.3 Conclusions

Health status was not an outcome measure commonly used to evaluate the severity of an exacerbation in COPD until recently. Development of disease-specific questionnaires such as CAT or CCQ allowed however the generation of a good body of evidence regarding the validity and the usefulness of evaluating health-status in COPD exacerbation. One such piece of evidence comes from the validation study of the Romanian version of CCQ which was applied in the setting of hospitalization for COPD exacerbation (ie severe COPD exacerbation) and which was found to be valid as a tool for measuring health status and as an approach (health status measurement during exacerbations).

The data discussed so far in the section on health status during COPD assessment support the use of this PRO to assess the efficacy of various therapies, the severity of disease as perceived by the patient and also to monitor its dynamics during the exacerbating episode.
Among the pharmacological therapies which were evaluated for their efficacy, inhaled therapies considered most frequently health status to demonstrate their perceived beneficial effects.
As far as non-pharmacological therapies are concerned, the studies presented in this section highlight the importance of the health status measurement in patients with end-stage COPD undergoing LTOT and the valuable information it can provide on the mortality risk, impact of the clinical burden of disease in patients with this disease, or on disease subsequent morbidity.
Many such patients with end-stage COPD and who undergo LTOT are candidates for palliative care which, this approach being expected to reduce the sufferance and to improve the quality of life when the curative (conventional) therapy is no longer fully successful. Health status is a component of quality of life as discussed in the introductory part of this chapter and therefore it is expected that the palliative care is able to improve quality of life as a result of improvement of health status also. Therefore in this setting questionnaires such as CAT test, CCQ, SGRQ or MRF26 can be appropriately used to monitor the effectiveness of the palliative care measures and also to predict mortality.
Among the existing health status questionnaires CCQ and CAT can reliably be used in patients with COPD exacerbations due to their ease of use and also due to their structure which enable the physician to ascertain the impact of disease on daily functioning, mental status, functioning of the organ interested by the disease.
If other studies evaluated health status in patients with all types of COPD exacerbations in terms of severity in an attempt to answer various research questions, the analysis above presented used the validation procedure to prove that CCQ questionnaire can be used to assess COPD hospitalisations and that the information it provides during such a severe exacerbation can be useful to predict the length of stay, the speed of recovery, the burden of symptoms, the impairment of functional status and the emotional distress.
Consequently health status can be used as an add on to the other PROs such as dyspnea, other respiratory symptoms, or to physiologic outcome measures such as impairment of gas exchange (in severe exacerbations) in order to monitor the dynamics of recovery during these events.

CHAPTER 2: EMERGING RELEVANCE OF EXTRARESPIRATORY SYMPTOMS IN COPD

2.1 State of art

Classically, COPD was seen as a chronic disease characterized by the presence of progressive respiratory symptoms such as dyspnea and cough with sputum production. During many years such symptoms were considered as being responsible for the clinical burden of disease. However, more recently it was demonstrated that during the course of the disease the inflammation of the airways spreads systemically and also in end-stage COPD it is the chronic hypoxemia the one which as discussed in the previous chapter is responsible for the cardiac involvement (pulmonary hypertension, cor pulmonale, congestive heart failure), sarcopenia (due to chronic impairment of the skeletal muscles), mood disorders (due to cerebral hypoxemia) or hematological abnormalities (secondary policitemia). Therefore end-stage COPD can no longer be considered as a chronic disease confined to the lungs but rather as a systemic one. From a clinical point of view this means that in such stages we can expect that other so called extra-respiratory symptoms add to the existing chronic respiratory symptoms and this increase in number of the symptoms is associated with increased clinical burden and with a more impaired health status or *per ensemble* with more impaired quality of life. Some of these extra-respiratory symptoms such as fatigue, pain or symptoms of emotional distress such as depression and/or anxiety, have been inconstantly recognized as being relevant in COPD patients some other such as lack of appetite, drowsiness or nausea can be transient and increase the burden of disease during exacerbations (as demonstrated in an original paper published by me and presented below) or can be progressive and occur in patients with stable advanced COPD signaling the need for a more comprehensive therapeutic approach such as that encountered in palliative care. The extra respiratory symptom the most well studied in the setting of COPD is represented by fatigue. In COPD fatigue is currently recognized as being the main extra-respiratory symptom, is often under or mis-reported by the patients, and not enough tackled by the management plan of the disease. Sometimes patients do not mention fatigue among the main complains, or they describe dyspnea and fatigue in an intermingled, confuse manner. Undertreated fatigue can therefore represent a source of otherwise unexplained health status impairment in patients with optimal control of their respiratory symptoms and with low disease morbidity as a result of the therapies undergone.

Fatigue is a relevant issue for COPD management because of several reasons:

- As aforementioned it can impair health status
- It can influence in a negative manner the disease prognosis (morbidity, mortality)
- The perceived therapeutic improvement of fatigue can usually be noticed by the patient gradually over weeks and not over few days
- It can be a clinical marker of increased disease burden and in advanced COPD it can signal the need for early palliative care

The clinical importance of fatigue in COPD is not only given by its severity but also by its causes. Evaluation of fatigue severity and of its impact on functional status and on health status helps to identify its priority in the management plan whereas documenting its causes allows to develop specific therapeutic interventions.

Fatigue is actually the main extra-respiratory symptom in COPD and its inconstant consideration is due to the fact that it is still mainly taken into account in pulmonary rehabilitation programs (Antoniu et al., 2019, Antoniu et al., 2016). In this setting fatigue is investigated mainly for its physical component but more complex pulmonary rehabilitation programs also consider other dimensions of this symptom. In a study investigating fatigue from this complex perspective in COPD patients with the Multidimensional Fatigue Inventory, it was found that over 95% of the analysed patients presented with severe physical fatigue which was associated with reduced activity, reduced motivation, and mental fatigue (Wong et al., 2010)

Fatigue impacts significantly the daily lives of patients with COPD and can also negatively influence their health status/quality of life. This was demonstrated in various studies and one of them, in which patients hospitalized for a COPD exacerbation (inpatients) and outpatients with COPD were interviewed on their own experience with fatigue found that this symptom was a limiting factor for their physical, psychological (emotional and cognitive) and social activities. Furthermore and very interestingly, fatigue was found to impair the overall capacity to cope with disease and with this symptom in particular (Kouijzer et al., 2018).

Another study compared the fatigue in terms of severity and impact on various outcome measures in patients with COPD versus those without. Fatigue severity was evaluated with Checklist Individual Strength Fatigue and it was found that in COPD patients this symptom is overall more severe than in patients without this disease (fatigue severity score 35 versus 21, $p<0.001$) and that in the former group of patients the proportion of patients with severe fatigue was significantly higher(49% versus 10%, $p<0.001$) (Goërtz et al., 2019).

In COPD patients fatigue is currently considered as a symptom with multiple causes and this picture is even more complex if such patients have comorbid diseases. Chronic heart diseases are the most common comorbid conditions in COPD patients and a population-based study performed in such patients and comparing fatigue and the level of physical activity with those of patients without COPD found that the prevalence of low physical activity was higher in patients with COPD compared to that of the non-COPD patients. Clinically significant fatigue was identified as a predictor of low physical activity along with older age and a history of heart disease whereas obesity was the only significant predictor of low physical activity in non-COPD patients (Andersson et al., 2015).

Pain and especially chronic pain is also a common extra-respiratory symptom in patients with COPD. Chronic pain in COPD patients can be due to existing diseases such as most commonly ostheo-articular or can be present without an evident cause (HajGhanbari et al., 2012a, Andenæs et al., 2018, Fuentes-Alonso et al., 2020). Chronic pain found in COPD patients is labelled as “chronic non-cancer pain” and large cohorts surveys such as the Canadian National Population

Health Survey (n=69365) identified COPD as a risk factor for this form of pain along with epilepsy or thyroid diseases (Rashiq and Dick, 2009).

In COPD patients pain can be more severe and impact in a more significant manner on quality of life compared to healthy, non-COPD patients: in a survey performed in both categories of subjects it was found that pain was more severe, with significantly stronger interference with their daily living, associated with a more severe pain-related fear of movement and impaired physical activities in terms of frequency and intensity in COPD patients compared to healthy controls. Pain severity correlated inversely with the physical component score of a quality of life questionnaire and was more commonly found in neck and trunk by these patients (HajGhanbari et al., 2012b)

Pain can be detected in patients with COPD in both exacerbated and stable state but during exacerbations its severity and impact on the underlying respiratory disease are more significant in fact in a study performed in patients hospitalized for an acute COPD exacerbation and in whom this symptom was evaluated with Short Form McGill Pain Questionnaire (SF-MPQ) and with Brief Pain Inventory, pain severity was assessed in both exacerbated and stable state. Pain was significantly more prevalent in exacerbated state compared to stable state (92% versus 58%, $p<0.001$), was significantly more severe during exacerbation compared to stabilized disease (SF-MPQ 29.7 versus 1.4, $p<0.001$) and was most commonly located in the chest and in the limbs. During exacerbation pain directly correlated with anxiety (Maignan et al., 2019).

Furthermore in a personal research which is below presented in more detail, I demonstrated that pain can also be associated with impairment in health status during COPD exacerbations (Antoniu et al., 2019).

In stable state the presence of pain can be associated with impairment of the health status and with an impairment of the level of activities of daily living. Often pain is associated with the cardinal respiratory symptom in COPD ie dyspnea and with fatigue and this triple "combination" of symptoms can exert a synergic effects on these two outcome measures mentioned above. In fact a clinical study evaluated this aspect and also quantified the prevalence, the severity and the interactions among such symptoms in COPD patients attending pulmonary rehabilitation programs. Tools used to assess these three symptoms were represented by the Brief Pain Inventory, by the Brief Fatigue Inventory and by Dyspnea Inventory, whereas health status was assessed with CCQ. As expected dyspnea was found to be the most prevalent symptom (93%), fatigue respectively pain being detected in 77% respectively 74% of patients. Severity scores for each of the three symptoms were found to be comparable across the whole sample analyzed. The three symptoms were found to correlate (strongly or moderately, $r=0.49$-to 0.78, $p<0.01$) among each other and dyspnea was found to impact more significantly on general activity than pain, whereas the latter interfered in a more significant manner with mood and sleep compared to dyspnea and fatigue. All three symptoms were associated with a significant impact on health status (Chen et al., 2018).

In terms of sites of pain which should be more specifically associated with COPD, there is no clear and sound evidence of such, virtually any or more parts of the body can present with pain in COPD patients and there might be also even generalized pain in such patients. Previous studies discussed

in this section demonstrated that neck, trunk or limb pain were more prevalent in COPD patients irrespective of the state of their background respiratory disease. In a cross-sectional study performed in a Spanish population recruited within European Health Interview Surveys framework, it was found that prevalence of migraine, chronic low back pain or chronic neck pain was higher in COPD patients than in matched controls. In the same study, COPD was found to be associated with a higher risk for each of these types (sites) of pain. Pain was more likely to be present in patients of younger age, female sex, poor self-rated health, high blood pressure, mental disorders, obesity or use of pain medication (de Miguel-Díez et al., 2018).

Presence of chronic pain might also be associated with a higher mortality risk on long-term basis: in fact, in a longitudinal study with a 5 year follow up duration it was investigated if chronic pain could be a predictor of 5-year mortality in patients with COPD and it was demonstrated that indeed higher pain interference with daily activities at the time of enrollment was an independent predictor along with older age and poorer lung function (Bentsen et al., 2020).

In conclusion, pain is a relevant extra-respiratory symptom in COPD and it impacts the functional status, contributes to an increased symptom burden, is associated with emotional distress, further impairs the health status and might be associated with an increased disease morbidity. Therefore, it is necessary that at least the chronic pain should be included as a therapeutic target in management guidelines (Lewthwaite et al., 2019).

Another group of extra-respiratory symptoms with relevance for COPD is represented by those of emotional distress such as anxiety or depression or both have been recognized in patients with chronic conditions, depression being more prevalent than anxiety: in fact, in a global study coordinated by the Word Health Organisation, The WHO World Health Survey, a cohort of over 245000 subjects was investigated for the prevalence of depression and it was found that this was present as a comorbidity in a up to 23% of those having a chronic disease. The likelihood to have depression in the subjects with chronic disease was significantly higher than that of subjects without a chronic disease ($p<0.0001$). Furthermore the same study demonstrated that the presence of comorbid depression worsened the health scores across all disease states (Moussavi et al., 2007)

In COPD emotional distress can manifest with anxiety, depression or both and these extra-respiratory symptoms are prevalent and need constant medical attention (Putman-Casdorph and McCrone, 2009).

In fact, a meta-analysis including 39857 COPD patients and 39431 controls found a prevalence of about 25% of depression in COPD population compared to less than 12% in the control population (Zhang et al., 2011).

Anxiety can also be a comorbidity in COPD patients who are at an increased risk of experiencing panic disorders. A systematic review estimated that the prevalence of anxiety and of related disorders variably ranged from 10-55% in COPD inpatients and from 13-46% in COPD outpatients and that females were at higher risk of developing such comorbidities (Willgoss and Yohannes, 2013).

The mechanism of development of anxiety and depression in COPD patients is complex and it can include inability to cope with the disease, the increased burden of respiratory symptoms, the

reduced exercise capacity, social and professional limitations and the last but not the least systemic inflammation or chronic hypoxemia (Panagioti et al., 2014). Another study postulated that smoking which is the classically recognized risk factor for COPD can be also involved in development of anxiety and depression in such patients (Goodwin et al., 2012).
Alike pain or fatigue, previously discussed in this section, comorbid depression and anxiety can worsen the health status in both exacerbated and stable state and their presence can be associated with an increased risk of mortality, with a more severe course of an exacerbation and with worse health status (Ng et al., 2007, Antoniu et al., 2019, Yohannes et al., 2005).
Therefore the clinical burden of extra-respiratory symptoms such as fatigue, pain symptoms of emotional distress etc can no longer be ignored, and is emerging based on the evidence from various clinical studies as:

- a relevant issue associated with progression of the disease,
- a marker of increased clinical burden
- a marker of increasing morbidity and of high risk for mortality
- an important determinant of the health status or of the quality of life
- a potential indicator of the necessity for palliative care if these symptoms are associated with a poor therapeutic control of the respiratory symptoms

This research direction is documented with the following papers:

Antoniu SA, Ungureanu D. Measuring fatigue as a symptom in COPD: From descriptors and questionnaires to the importance of the problem. *Chron Respir Dis* 2015; 12: 179-188, **IF=1.64 (reproduced with permission)**

Antoniu SA, Petrescu E, Stanescu R, Anisie E, Boiculese L. Impact of fatigue in patients with chronic obstructive pulmonary disease: results from an exploratory study. *Ther Adv Respir Dis* 2016; 10: 26-33. **IF=2.74 (reproduced with permission)**

Antoniu SA, Apostol A, Boiculese LV. Extra-respiratory symptoms in patients hospitalized for a COPD exacerbation: Prevalence, clinical burden and their impact on functional status. *Clin Respir J* 2019; 13: 735-740. **IF=1.51 (reproduced with permission)**

2.2 Fatigue in COPD : descriptors, questionnaires, pathogenic complexity and impact on health status

2.2.1 Introduction

In the previous section of this chapter I discussed in a more generic manner the current evidence related with fatigue in COPD. As mentioned above, the real dimension of the problem is still not known because of the fatigue is not appropriately considered in COPD in terms of diagnosis and treatment.

One of the reasons from which fatigue is often ignored in clinical daily practice is the fact that its description by the patient can be misleading with that of dyspnea. This behavior can make the healthcare professional to still focus on the latter symptom and not to consider the former as the real clinical manifestation explained by the patient. Other reasons might include the lack of an adequate knowledge on the importance of this symptom in COPD patients outside pulmonary rehabilitation setting or that on the potential tools to assess fatigue from a clinical point of view (Stridsman et al., 2014).

Being convinced that fatigue should deserve a closer attention in COPD especially from the perspective of palliative care (if to compare with "oncologic" fatigue) I focused some of my research on this symptom.

In the first paper, a review on the various aspects related to fatigue in COPD patients, I focused on potential descriptors, on potential pathogenic mechanisms and potential tools which can be used to assess severity or other features of this symptom (Antoniu and Ungureanu, 2015).

In the second paper, I performed a research in which I evaluated the prevalence of clinically significant fatigue and its correlations with other severe symptoms in patients with stable COPD (Antoniu et al., 2016)

Personal contribution

Antoniu SA, Ungureanu D. Measuring fatigue as a symptom in COPD: From descriptors and questionnaires to the importance of the problem. *Chron Respir Dis* 2015; 12: 179-188, **IF=1.51 (reproduced with permission)**

Antoniu SA, Petrescu E, Stanescu R, Anisie E, Boiculese L. Impact of fatigue in patients with chronic obstructive pulmonary disease: results from an exploratory study. *Ther Adv Respir Dis* 2016; 10: 26-33. **IF=2.74 (reproduced with permission)**

Fatigue was defined by Ream and Richardson as ''a subjective and unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity''(Ream and Richardson, 1996).

Fatigue is a common general symptom encountered in general (healthy) population and behaving episodically, or diagnosed in various chronic pathologies including cancer and exhibiting a progressive pattern (Breslin et al., 1998, Minton et al., 2013).

Fatigue episodes usually self-resume whereas progressive fatigue impacts significantly on the health status and often requires medical attention. Conventionally two main components of fatigue are widely recognized ie the physical and the mental ones. Fatigue as a symptom should be distinguished from the chronic fatigue syndrome which has different clinical criteria of definition(Evengård and Komaroff, 1999).

2.2.2 Fatigue: descriptors, pathogenic complexity and questionnaires

a. Descriptors

Previously in this section I mentioned that in the particular COPD setting fatigue can be confounded with dyspnea. In order to better differentiate them various descriptors can be used. One such study performed in patients with stable COPD identified five main attributes which can be used as descriptors for fatigue (Ream and Richardson, 1997):

1. Perceived physical exhaustion
2. Perceived mental exhaustion
3. Impairment of the daily activities due to fatigue
4. Emotional distress due to fatigue
5. Coping impairment due to fatigue

These attributes were analysed comparatively in patients with cancer and in patients with COPD: generally all these descriptors were found to correspond to a more severe state. In cancer patients, physical component of fatigue was found to manifest at rest and to be associated with a general malaise and with aching pain in the limbs; in COPD instead, physical fatigue was described as manifesting as a result of exercise and associated with dyspnea. Mental component of fatigue was similarly described in both populations, generally with impaired mental concentration. Fatigue impact of daily routine activities was found to be more affected in COPD patients than in cancer patients because the latter category reduced the range of them as a result of this symptom (energy saving approaches). Emotional distress as a result of fatigue was more constant in COPD whereas in cancer patients it has an episodic allure (occurring during and shortly after the chemotherapy courses). Coping was found to be similarly affected in both diseases as a result of the fact they did not understand the causes of this symptom and because this symptom made them feel overwhelmed and in poor control of their lives(Ream and Richardson, 1997).

b. Pathogenic mechanisms in COPD

In the same review I showed that in COPD fatigue can be due to anemia, sarcopenia, hypoxemia or systemic inflammation (Antoniu and Ungureanu, 2015). Usually there isn't only one such factor involved in the etiopathogenesis of fatigue and this symptom is rather the result of a complex interplay among them.

The link between fatigue and chronic hypoxemia was documented in COPD patients in whom it was found that oxygentherapy was able to reduce it and the lack of supplementary exogeneous oxygenation worsened it (Eaton et al., 2002, Eaton et al., 2004).

Anemia- related fatigue was inconstantly reported in COPD but this can probably be explained by the lack of a comprehensive approach for this symptom rather than by its inconstant identification (Yohannes and Ershler, 2011, Silverberg et al., 2014). Sarcopenia/skeletal muscle loss represents an important problem in COPD because this can be associated not only with fatigue but with impaired ventilation. Cachexia can also be associated with fatigue alike in cancer patients.

Systemic inflammation is recognized as one of the main pathogenic mechanisms for fatigue in cancer and in type 2 diabetes (Bower et al., 2002, Lasselin et al., 2012). In COPD elevated levels of biomarkers of systemic inflammation such as TNF-α were found to correlated with the severity of exertional fatigue (Al-shair et al., 2011a).
Fatigue was also found to be a predictor of frequent exacerbations and to predict mortality (Baghai-Ravary et al., 2009, Stridsman et al., 2015).
All these complex relationships between fatigue on the one hand and the above listed pathogenic factors on the other hand raise the hypothesis that fatigue can be considered as an attribute of more advanced (more severe) COPD. In fact one of the initial studies evaluating fatigue in COPD provided results which confirm such a hypothesis (Breukink et al., 1998). In this study the relationship between fatigue and physiological variables was assessed in a small sample (n=19) COPD patients with a mean FEV1%pred of 38% (SD17%). Fatigue was assessed with a questionnaire named the Fatigue Index MFI-20 which measures five attributes of fatigue, ie general fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue. It was found that lung function impairment (low FEV1) significantly correlated with reduced activity and with reduced motivation. Reduced motivation also correlated with the severity of exertion dyspnea and with various skeletal muscle forces(Breukink et al., 1998).
In a study in which fatigue was evaluated in terms of severity, duration, frequency with a specific questionnaire, it was found that COPD patients with fatigue demonstrated worse lung function than COPD patients without fatigue and that the former category of patients also had a more impaired exercise capacity(Tödt et al., 2013).

c. **Fatigue scales**

In clinical practice fatigue can be measured using a large range of instruments such as numerical scales or health status/quality of life questionnaires incorporating fatigue among their domains. Alike quality of life, fatigue can be measured in COPD patients using generic or using COPD-specific scales.
Generic instruments which can be used to assess fatigue can include unidimensional tools or multidimensional tools. The following discussion addresses the unidimensional (symptom) scales, the multidimensional (symptom) scales and the (multidimensional) assessment with quality of life/health status questionnaires.

Unidimensional fatigue scales

Unidimensional scales are also called rating scales because they are only able to evaluate fatigue severity: among them numerical rating scales and multi-symptom unidimensional scales are often use to measure fatigue severity in settings in which this symptom is routinely considered in the therapeutic plans such as oncology or palliative care. Numeric rating scale is the simplest instrument to assess severity of fatigue by giving to the perceived symptom a grade ranging from

0 (symptom is absent) to 10 (worst/most severe possible symptom). A "visual" version of this scale is represented by the Visual Analogue Scale (VAS) which can also be used to quantify fatigue severity. In COPD patients in whom exercise testing is performed for various purposes, Borg VAS for fatigue can be used to assess this symptom in a similar manner with dyspnea.
Multi-symptom unidimensional scales are also used in the setting of palliative care: Edmonton Symptom Assessment Scale (ESAS) is such a relevant example and also a popular instrument to evaluate symptom burden in terms of severity in a certain patient. ESAS was developed within the framework of the Regional Palliative Care Program in Edmonton Alberta and grades symptoms such as fatigue for example, using individual numeric rating scales (Bruera et al., 1991a).
ESAS is able to measure 9 symptom which are most often encountered in a palliative care setting such as pain, fatigue, dyspnea, anxiety, depression, nausea, lack of appetite, drowsiness and general well-being impairment and also includes an extra blank scale in case another symptom is reported by the patient.
ESAS can be easily filled in by the patient, caregiver or healthcare professional and has the biggest advantage of a rapid documentation of the presence of various symptoms and of their severity at various moments so that their dynamics under therapeutic intervention can be easily evaluated for example, in oncology patients undergoing radiotherapy for various types of cancers.
In COPD patients until recently ESAS scales was not used. However, a modified ESAS scale having 4 instead of 11 grades of severity was assessed in various chronic illnesses including COPD in one study and fatigue in particular was found to be a bothersome symptom associated with impaired quality of life or functional disability(Walke et al., 2006b, Walke et al., 2007).
Being particularly interested in the study of fatigue in COPD patients and in evaluating the burden and the consequences of extrarespiratory symptoms in such patients, I used ESAS scale in exacerbated patients and found that this tool was able to capture very well the burden of extra-respiratory symptoms in such patients.

Multidimensional fatigue scales

Such scales can measures not only the severity of the symptom but also its impact on daily functioning. Among the many tools which are reported in literature as valid instruments to measure fatigue in various chronic diseases including COPD FACIT scales are becoming more and more popular due to the fact that they are easy to use and able to capture various features of fatigue. FACIT (Functional Assessment of Chronic Illness Therapy) scales for fatigue (FACIT-F) are commonly used in research extended versions (for example that with 26 items used by my in one of my researches below presented) and a shortened one (13 items) being available(Webster et al., 2003).
In an original exploratory research performed in stable COPD patients and discussed in detail below, I demonstrated that the extended version can be used to document fatigue besides severity.

COPD-specific multidimensional fatigue scales

FACIT-F scale modified for COPD is a nine-item scale derived from FACIT-F shortened version which was used in a large cohort study Evaluation of COPD Longitudinally to Identify Predictive

Surrogate Endpoints (ECLIPSE) study performed on a sample of 2107 COPD patients and which was demonstrated to correlate with effort intolerance and with depression(Al-shair et al., 2012). Subsequently the same team of authors developed the Manchester COPD Fatigue scale which is another valid instrument to measure the severity and the impact of fatigue in COPD patients (Al-shair et al., 2009).

Quality of life and health status questionnaires with fatigue as a scoring domain

Fatigue can be measured with both generic and disease specific quality of life/health status questionnaires provided these tools have items which specifically investigate this symptom. The most relevant examples for fatigue in COPD are represented by SF-36 and by the Chronic Respiratory Disease Questionnaire is an example of generic questionnaire which is able to detect fatigue despite not have a domain score specifically devoted to this(Brazier et al., 1992). In the original study I performed in stable COPD patients and which I describe below I used a SF-36 method to detect clinically significant fatigue based on Vitality domain score, method which was previously validated in a clinical setting different from that of COPD and which was also found to be sound and valid in COPD –specific studies including in my research (Baltzan et al., 2011, Antoniu et al., 2016) .

Chronic Respiratory Disease Questionnaire is one of the disease specific questionnaires extensively used to evaluate health status in patients with COPD. Its item construction generating domain scores for fatigue, dyspnea, or emotional distress made this tool to be particularly useful for pulmonary rehabilitation. This questionnaire is also described on the section on health status evaluation (Guyatt et al., 1987a).

Conclusions

In conclusion, in COPD fatigue is the main extra-respiratory symptom and yet it often passes unrecognized or underdiagnosed. As demonstrated in the above presented review, fatigue can have a complex pathogenesis in COPD, chronic hypoxemia for example being considered as a prominent pathogenic pathway in end-stage disease for example. In COPD fatigue can be measured with a large range of scales and questionnaires, some of them being simply able to quantify the severity of the symptom (for example fatigue-related scale in the ESAS) whereas others can also measure various dimensions of this symptom or its impact on health-status quality of life. The latter aspect is below presented and exemplified with a research done in patients with stable COPD.

2.2.3 Fatigue as a determinant of health status impairment in COPD

Based on the data discussed earlier in this section it is demonstrated that fatigue is a debilitating symptom in patients with COPD, it can increase the mortality risk and it can increase disease morbidity. Fatigue is also recognized as a determinant of quality of life/health status impairment in such patients and therefore it is important to detect such a relationship between the two outcome measures in order to better tailor the management of COPD patients and in order to potentially

consider the need for palliative care should other markers of appropriateness are concomitantly identified in patients with more advanced COPD.

Personal contribution

Antoniu SA, Petrescu E, Stanescu R, Anisie E, Boiculese L. Impact of fatigue in patients with chronic obstructive pulmonary disease: results from an exploratory study. *Ther Adv Respir Dis* 2016; 10: 26-33. **IF=2.74 (reproduced with permission)**

The objectives of this exploratory study were to demonstrate that in patients with stable COPD fatigue is more severe than in healthy subjects and when clinically significant fatigue is a prevalent symptom, and associated with an increased disease burden (Antoniu et al., 2016).

Methods

The analysed sample included two populations, the stable COPD population (COPD group) and the healthy, non-COPD population (control group) who were enrolled after signing the informed consent form. Inclusion and exclusion criteria were applied to each of the two groups. Airways obstruction was measured according to standard methodology with post-bronchodilator forced expiratory volume in 1 second %predicted (FEV1%pred), exercise capacity with distance walked during the 6 minutes walking test and expressed in meters, the level of dyspnea related to exercise testing was measured with Borg dyspnea scale at the beginning respectively at the end of the exercise, health-related quality of life was measured in both COPD and non-COPD groups with SF-36 generic questionnaire, whereas in COPD group this was measured with Clinical COPD Questionnaire. Symptom burden was assessed with the Scores domain of the CCQ.
Fatigue was evaluated with two approaches: one was represented by Vitality domain score of the SF-36 and the other one was represented by one of the extended FACIT-F scales(Cho et al., 2013). The use of vitality score to document fatigue has been previously validated in the setting of chronic invalidating diseases such as multiple sclerosis or rheumatoid arthritis, clinically significant fatigue being established for Vitality scores of 50 or less. FACIT-F scale was used in order to back up the vitality score and in order to further analyse other attributes and impacts of fatigue. The FACIT-F scale used is a 26-item scale with four domain scores including physical fatigue (FACIT-PWB), emotional fatigue (FACIT-EWB), social fatigue (FACIT-SWB), and functional fatigue (FACIT-FWB) and a total score (FACIT-T).
Serum C reactive protein was measured as a marker of systemic inflammation in COPD.

Statistical analysis

Statistical analysis was performed with SPSS software and included:

- student's t test and non-parametric Mann-Whitney U test to compare mean values respectively median values in variables with normal respectively non-normal distribution with p values less than or equal to 0.05 to demonstrate statistical significance (p values

calculated with Student's t were labelled pT whereas p values calculated with Mann Whitney were labeled as pMW

- Spearman's correlation was used to evaluate the relationship between outcome measures of relevance described below

Results

Table 2.1 Descriptive data in COPD and in control groups

	Age, mean (SD)	Gender distribution	Post-bronchodilator forced expiratory volume in 1 s 1%predicted, mean (SD)	SpO2, median (interquartile range)	Vitality Short Form Health Survey 36 score, mean (SD)	Functional Assessment of Chronic Illness Therapy total score, median (interquartile range)
Patients with chronic obstructive pulmonary disease	66.3 (7.9)	19 males 1 female	55.34 (16.86)	95 (4)	45.62 (19.98)	74.5 (12.7)
Healthy subjects	61 (3.16)	4 males 1 female	102.51 (15.12)	96.5 (3)	76.25 (15.56)	9 (24.08)
Significance	*p*t = 0.16		*p*t = 0.001	*p*M = 0.21	*p*t = 0.004	*p*M = 0.03
***p*M, Mann–Whitney U test; *p*t, Student's *t*-test; SD, standard deviation; SpO2, amount of oxygenated haemoglobin in the blood**						

The analysed sample included 20 COPD patients and 5 healthy subjects. Age, gender distribution, airways obstruction, SpO2 and SF-36 Vitality score FACIT-F Total score were analysed comparatively and are presented in **Table 2.1**. Based on the fact that age was comparable between the groups (mean value 66.3 years in the COPD group and 61 years in the control group, p=0.16), the bias regarding the age-related influence on fatigue were practically excluded.

Analysis of fatigue severity

Mean vitality SF-36 score was found to be significantly lower in the COPD group compared to the control group (45±19.98 compared to 76.25±15.56, pT=0.004) (***Fig. 2.1***).

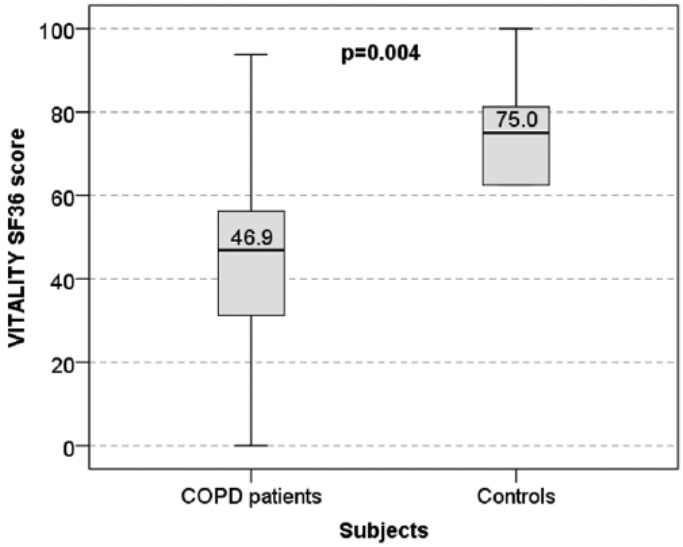


Fig. 2.1 Fatigue severity in COPD versus control group (Vitality SF-36scores)

The Physical Component Summary (SF-PCS) score of SF-36 was also significantly lower in COPD group compared to the control group (41.5± 7.15 versus 50.46± 3.08, pT=0.013, ***Fig. 2.2***).

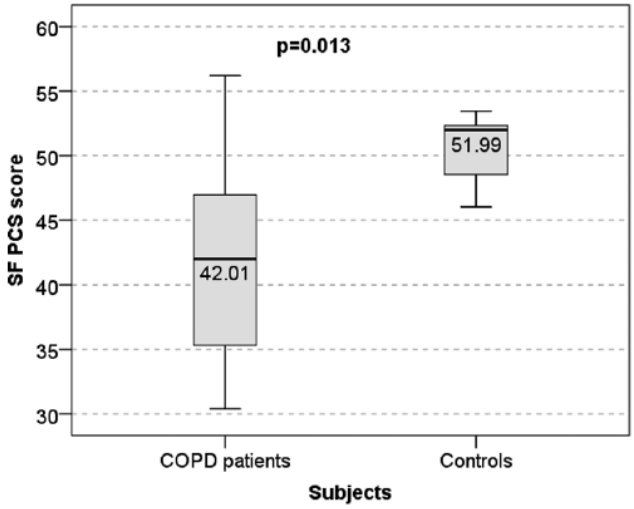


Fig. 2.2 SF-PCS scores in COPD respectively in healthy control groups

The Mental Component Summary (SF-MCS) score had a similar behavior (41.47±10.15 versus 52.91 ±7.51, pT=0.028). Fatigue severity was also analysed with FACIT-F scores: the scores which significantly differed between groups were the total score 74.5 versus 95 (pMW=003), FACIT-FWB (20 versus 23, pMW=0.026) and FACIT-PWB (20 versus 24, pMW=0.057).

Analysis of clinically significant fatigue

The prevalence of clinically significant fatigue was 60% in COPD group (seven ex-smokers and most of them,11, men). COPD patients with clinically significant fatigue did not differ in terms of age and smoking status from those without clinically significant fatigue. COPD patients with

clinically significant fatigue had significantly more impaired lung function (FEV1%pred 47.7% versus 65.82%, PT=0.016 (**Fig 2.3**).

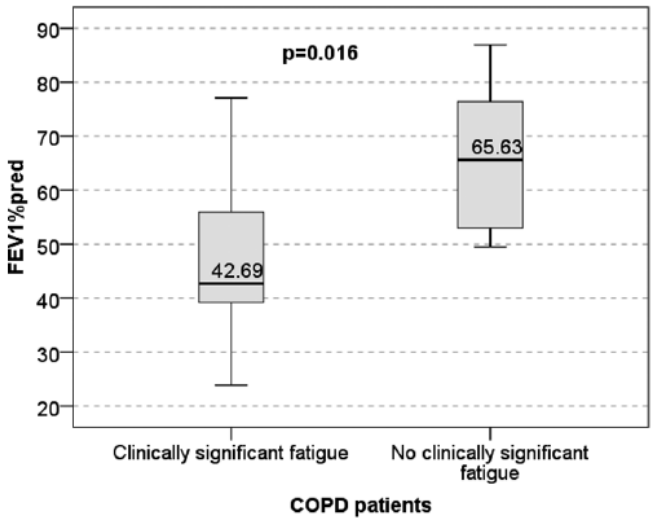


Fig. 2.3. Lung function impairment in COPD subsets (clinically significant , no clinically significant)

Likewise, SF-PCS score was also significantly more impaired in patients with COPD and clinically significant fatigue (39.67 versus 67.5, pT=0.002). Exercise capacity was not found to differ significantly between the two COPD subsets (340 versus 389, p=0.147). Social functioning score of SF-36 also differed significantly in patients with clinically significant fatigue compared to patients without (48.75 versus 79.68, p=0.006). Respiratory symptom burden was significantly heavier in COPD patients with clinically significant fatigue (3.75 versus 2.43, pT=0.019) unlike the functional and mental scores of CCQ which did not differ significantly. Severity of dyspnea at the end of exercise test was more severe but not significantly worse in COPD patients with clinically significant fatigue (3.3 versus 2.8, pMW=0.39). Health status measured with CCQ-T differed however in a significant manner (3.30 versus 2.11, pMW=0.011, ***Fig. 2.4***)

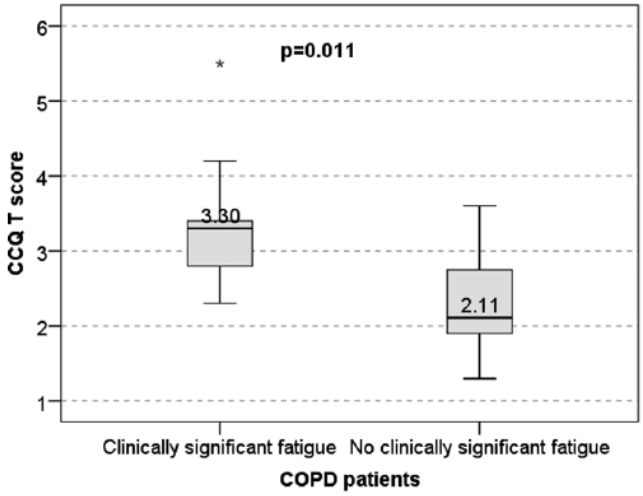


Fig. 2.4. CCQ-T scores in COPD subsets (clinically significant , no clinically significant)

SF-PCS score was found to correlate significantly with CCQ-T scores (r=-0.587, p=0.006)

Relationship between clinically significant fatigue and systemic inflammation

Comparisons of serum C reactive protein, TNF-α and monocytosis were all found to be higher in patients with clinically significant fatigue but without significant differences compared to COPD patients without clinically significant fatigue.

Discussion

In the analysis above presented we found that compared to healthy subjects fatigue severity was significantly higher in COPD patients. We also reported a high prevalence of clinically significant fatigue in COPD patients with stable disease. This was associated with worse lung function, health status, worse physical and social functioning and higher respiratory disease burden. In other studies focusing on evaluating fatigue, outcome measures similar with those used in our study such as systemic inflammation, airflow obstruction, and dyspnea, or differing from such as depression or BODE index. One such study examining the relationship between fatigue and systemic inflammation assessed with C reactive protein, TNF-alpha receptors 1 and 2 and interleukin-6 found no significant correlation between the symptom and each of these inflammation biomarkers. However that study did not considered health status as an outcome measure and did not compare fatigue with that of the healthy subjects (Al-shair et al., 2011b). In the ECLIPSE study, fatigue was evaluated with FACIT-F and health status with SGRQ: fatigue correlated with health status, and was more severe in patients with more severe dyspnea, more severe depression and with more impairment exercise capacity (Janssen et al., 2014). Another study the OLIN study also used SF-36 but defined clinically relevant fatigue with FACIT-F scale and evaluated this symptom dynamically: clinically relevant fatigue was associated with worse health-related quality of life and was identified as a predictor of mortality in COPD patients (Stridsman et al., 2015).Our study was not designed to examine fatigue in dynamics but found similar impact on health status/health related quality of life. In a subsequent analysis performed in the same OLIN cohort study, fatigue severity correlated well with the low level of physical activity (Andersson et al., 2015). In our study we also found that the exercise capacity was more impaired in patients with clinically significant fatigue but probably due to the small sample the difference was not statistically significant. Another limitation of our study apart from the small sample (appropriate though for the exploratory nature of the study) is the fact that prognostic index such as BODE was not considered as an outcome measure because the study involved only one examination and not the repeated measurements of the outcome measured described above.

Conclusions

To conclude, this study demonstrated that clinically significant fatigue can be also prevalent in less advanced COPD not only in advanced disease and that consequently deserve more attention in order to be appropriately addressed from a therapeutic point of view.

2.2.4 Conclusions

In COPD fatigue is prevalent and its severity increases with respiratory disease progression and the same trend is also followed by health status. Fatigue also affects health-related quality of life and correlates with a higher burden of respiratory symptoms which is another indicator of disease severity. Fatigue can also be found in patients with less advanced COPD and probably it is this latter population the one in which this symptom is often not acknowledged.

2.3 Other extra-respiratory symptoms with clinical relevance in COPD

2.3.1 Introduction

In the introductory part of this section I mentioned that apart from fatigue, pain and emotional distress symptoms are often reported by COPD patients irrespective of the severity of respiratory disease. Fortunately, frequently such extra respiratory symptoms are transient and are more manifest during exacerbations. However if they are associated (clusters) they can significantly increase the disease burden and can be associated with more impaired health status.

2.3.2 Burden of extra respiratory symptoms in COPD

In an attempt to document the prevalent extra-respiratory symptoms and their impact on health status I performed a clinical study in which these symptoms were "captured" with ESAS scale and assessed for their individual prevalence and for the impact on health status when clustered amongst them.

Personal contribution

Antoniu SA, Apostol A, Boiculese LV. Extra-respiratory symptoms in patients hospitalized for a COPD exacerbation: Prevalence, clinical burden and their impact on functional status. Clin Respir J 2019 13(12):735-40 **IF=1,51 (reproduced with permission)**

In chronic obstructive pulmonary disease (COPD) it was demonstrated that the impairment of health status and that of the functional status are mainly due to the presence and to the progressive pattern of respiratory symptoms such as dyspnea, or cough with sputum production (Jones, 2001). Consequently, the aim of most therapeutic interventions has been to improve such symptoms, expecting a parallel increase in health status ((NG115), 2018). However, not always a decrease in the severity of respiratory symptoms is associated with a significant amelioration of the health status. This might be explained by the fact that other factors such as extra respiratory symptoms might be significant determinants of health status worsening. For example, fatigue which is the main extra respiratory symptom found in COPD was demonstrated to be associated with an impaired health status (Antoniu et al., 2016). During exacerbated COPD health and functional statuses are also deeply altered. However, little is known on this matter probably because of the

reticence in measuring during exacerbations these PROs especially as far as the health status was concerned. Existing questionnaires such as Clinical COPD Questionnaire or COPD Assessment Test were demonstrated to be reliable tools to measure health status during COPD exacerbations (Antoniu et al., 2014, Spencer, 2009). In COPD exacerbations also extra respiratory symptoms can be bothersome, can negatively impact both health and functional statuses, and can contribute significantly to the clinical burden of (exacerbated) illness. However little is known on this topic especially because the available studies rather focused on the relationship between respiratory symptoms and health status and because the interest in measuring functional status during an exacerbation was limited. The analysis presented below tries to fill this gap by evaluating the prevalence of extra respiratory symptoms as well as their clinical burden and their impact on functional status in patients with severe COPD exacerbations (hospitalisations).

Materials and methods

The analysis described below was performed in patients hospitalized for a COPD exacerbation between February and July 2017 and who agreed to participate in this study after signing the informed consent. Included were subjects with known COPD diagnosis**.** Excluded were subjects hospitalized for other conditions, patients unable to understand the questions related to data collection, patients with cognitive deficits, patients who were too ill or who did not agree to participate to this study. The study received approval of the institutional ethics committee. Severity of the extra respiratory symptoms was measured with the Edmonton Symptom Assessment Scale (ESAS). ESAS is a tool developed in order to document in a rapid and reliable manner the symptom burden in patients requiring palliative care. It is a numerical multiscale symptom scale evaluating the severity of various symptoms such as pain, fatigue, breathlessness, lack of appetite, anxiety, depression, drowsiness, nausea on a scale ranging from 0 (no symptom) to 10 (maximum severity symptom)(Bruera et al., 1991b). Extra respiratory symptoms were considered as clinically significant (bothersome for the patient if scored at least 4) (Selby et al., 2010). The use of ESAS in COPD is of more recent date and in studies evaluating rather a cluster of chronic diseases than a specific condition (Wajnberg et al., 2013). ESAS gains more terrain in COPD as a reliable symptom tool, and we report in this study its use in patients with exacerbated COPD. Health status was evaluated with COPD Assessment Test (CAT) test which is an 8 item disease specific questionnaire which measures the impact of the disease on various routine activities of daily living: scores range from 0 to 40 with higher scores corresponding to a more impaired health status (Jones et al., 2011). Functional status was assessed with Karnofsky Performance Status Scale (KPSS) named briefly Karnofsky index.This is a tool initially developed to predict survival in cancer patients undergoing chemotherapy (Karnofsky DA, 1948). KPSS measures functional status corresponding to various health states ranging from 100% "no evidence of disease" to 0 death. Currently KPSS is a recognized measure of functional status outside oncology setting, being extensively used in various chronic conditions such as COPD (Weingaertner et al., 2014). Clinical burden of (clinically significant) extra respiratory symptoms was evaluated with two indexes, a quantitative more objective index consisting of the number of clinically significant symptoms in

the same patient, and a more subjective index measuring the degree of impaired health status associated with concomitant presence of various such symptoms in an individual. Airways obstruction was measured with post-bronchodilator FEV1%predicted , this outcome measure being only used to characterize the analysed sample from the perspective of the severity of lung function impairment (Miller et al., 2005). Statistical analysis was performed with the IBM SPSS version 18 and with MedCalc version 15 softwares. Between group comparisons were made with student t test. To describe the association between score data the Spearman correlation was performed. To find the linear dependency the Pearson correlation was computed. Linear regression was also performed if both correlation coefficients were comparable, in order to further study the effect of the increase in the number of extra respiratory symptoms on the outcome (health respectively functional status). The decision on the significance of the statistical hypothesis was according to standard significance of 0.05.

Results

Population characteristics are featured with relevant variables and parameters in **Table 2.1**. A total number of 47 COPD was included in the analysis.

Table 2.1 Characteristics of the sample analysed

Variable/parameter	Number of patients observed	Value
Age (mean, SD)	47	68.4(5.6)
Gender Female Male	47	 9 38
Smoking status Ex smokers Current smokers Non smokers	44	 31 7 6
FEV1%pred(mean,SD)	46	34%(14.3)
ESAS-PAIN(mean, SD)	47	4.7(2.28)
ESAS-FATIGUE(mean, SD)	47	7.23(1.78)
ESAS-BREATHLESNESS(mean, SD)	47	6.4(1.96)
ESAS-LACK OF APETITE(mean, SD)	47	4.95(2.17)
ESAS-DEPRESSION(mean, SD)	47	4.98(2.2)
ESAS-ANXIETY(mean, SD)	47	4.87(2.21)
ESAS-DROWSINESS(mean, SD)	47	4.13(2.24)
ESAS-NAUSEA(mean, SD)	47	2.12(2.32)
CAT score(mean, SD)	47	27.46(5.66)
Karnofsky index (mean, SD)	47	61.27(13.7)

Prevalence of extra respiratory symptoms

The most prevalent clinically significant extra respiratory symptom was found to be fatigue which was detected in 45 (95.7%, ***Fig 2.5***). The next prevalent clinically symptom was represented by

pain which was detected in 35 (74.5%) of patients severe pain (ESAS score of pain at least 7) in particular being f found in 11(23.4%) patients. Figure 1 presents the prevalences of all extra respiratory symptoms measured.

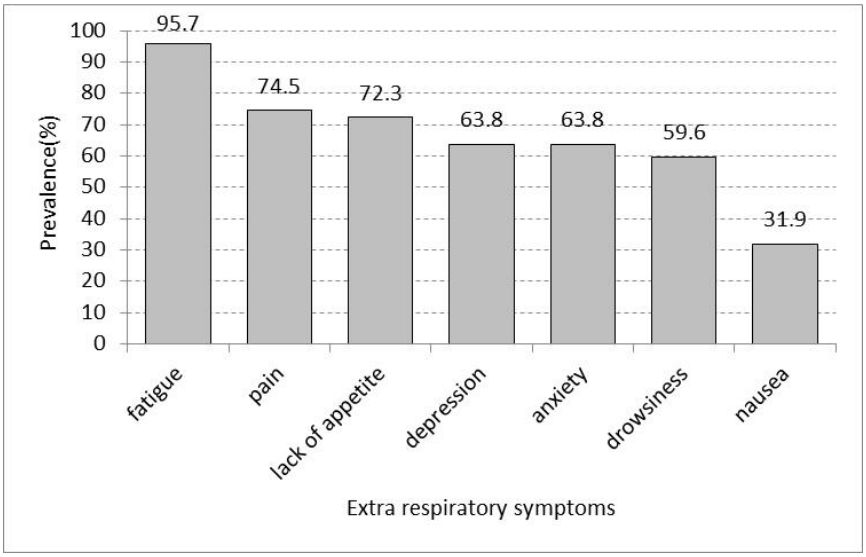


Fig. 2.5 Prevalences of clinically significant extra respiratory symptoms

Burden of extra respiratory symptoms

The first three most prevalent clinically significant symptoms were detected concomitantly in 25 (53.2%) patients, the first four /five each in 15 (31.9%), the first six in 15 (31.9%) and all seven symptoms were present in 7 (14.9%) COPD patients.

The concomitant presence of the first three most prevalent symptoms ie fatigue, pain and lack of appetite, was associated with a significantly worse mean CAT score compared with that of patients without them, 29.6 versus 25.1, p=0006. When clinically significant depression was present concomitantly with the first three most prevalent symptoms, mean CAT score was more impaired 31.6 versus 25.5, p<0.001. Addition of anxiety to the first four most prevalent symptoms was associated with a persistent and comparable worsening of CAT score 31.4 versus 25.8, p=0.001 and an identical effect was detected in patients exhibiting also drowsiness. Finally in patients with all seven clinically significantly extra respiratory symptoms CAT score was still worse than in patients without all these symptoms 31.3 versus 26.8 p=0.05.

The increase in the number of concomitant clinically significant extra respiratory symptoms was associated with a directly proportional significant increase in CAT scores (ie worsening of health status), Spearman's rho 0.49, p<0.001. Pearson's correlation coefficient was 0.46 (p=0.001), demonstrating a linear (proportional) relationship between the number of symptoms and the increase in CAT score. A linear regression was further applied in order to compute to further analyze the effect of progressive increase in number and the "increase per symptom" added in CAT score: we found that for each extra respiratory symptom the increase in CAT score was 1.7 (p=0.001, ***Fig.2.6***).

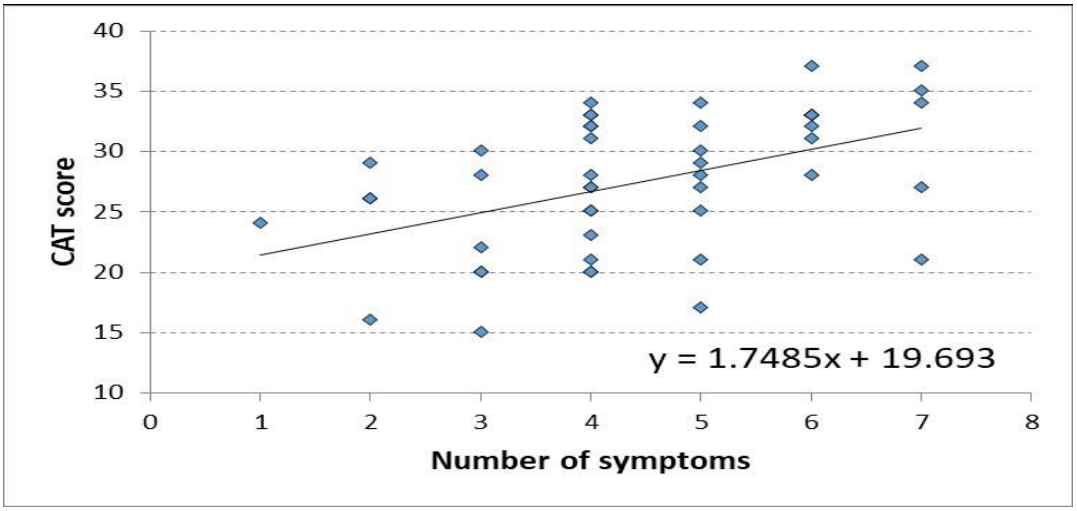


Fig2.6 Correlation between the increase in number of the concomitant extra-respiratory symptoms and the worsening of the health status (CAT scores)

Impact of the number of clinically significant extra respiratory symptoms on functional status

The concomitant presence of the first three extra respiratory symptoms did not have a significant impact on functional status. However, the presence of the first four most prevalent symptoms was associated with a significantly worse functional status, KPSS 52 versus 65.6, p=0.001. Presence of first five symptoms respectively first six had a similar effect KPSS 52.1 versus 65.1, p=0.002. Surprisingly, patients with all seven symptoms, even if exhibiting worse functional status, did not differ significantly as far as this was concerned, when compared to patients without all these symptoms(52.8 versus 62.8, p=0.07). Correlation analyses were done in a similar manner with that done with CAT scores, and again, significant (inversely proportional) correlations between the increase in the number of symptoms and worsening (decrease) of KPSS were found: Spearman's rho= -0.39, p=0.006, Pearson's coefficient =-0.41, p=0.004). Linear regression yielded a decrease in KPSS of 3.63 units of score (%) for each added symptom (p=0.006, ***Fig 2.7***).
Both health status and functional status significantly correlated, a worsening of the former (ie increase in CAT score) being associated with a worsening of the latter (ie decrease in KPSS): Spearman's rho =-0.57, p<0.001, Pearson's coefficient =-0.58, p<0.001.

Impact of symptoms clustering on length of hospital stay

Length of hospital stay (LoS) is known to be a marker of exacerbation severity respectively disease morbidity. LoS was compared in patients with highest extra respiratory symptom burden in terms of number ie in those having all 7 extra respiratory symptoms with that in those not having them and it was found that the former category tended to have larger LoS than the latter although probably due to the limited sample size this difference was not statistically significant (11 versus 10.3 days, p=0.7).

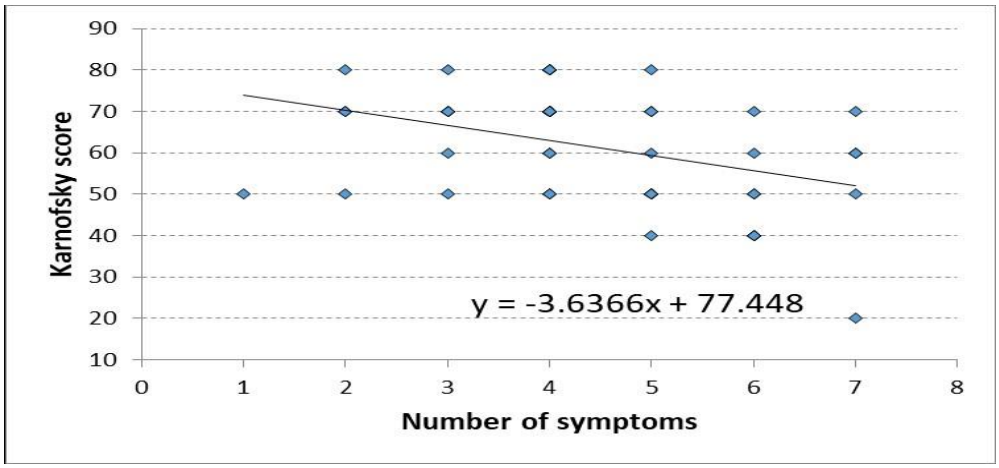


Fig.2.7 The correlation between the number of concomitant extra-respiratory symptoms and the worsening of the functional status (measured with the Karnofsky index)

Discussion

In COPD patients hospitalized for an exacerbation, extra-respiratory symptoms were prevalent, and the higher their number the worse the respiratory health status and functional disability were. Most of the existing studies focused on fatigue and more recently on pain. In these studies fatigue was demonstrated to individually impact on health status, and to be a marker of disease severity, mortality and morbidity but in patients with stable disease (Stridsman et al., 2015, Antoniu et al., 2016, Paddison et al., 2013). However none of the existing studies examined the prognostic value of other individual or clusters of extra respiratory symptoms on these outcome measures in both stable or exacerbated COPD.

Pain was also investigated in patients with COPD in terms of site involved, severity and its impact on health status, and compared to that found in matched normal controls: it was found that impairment of health status (Physical Functioning domain of the SF-36) as a result of pain was more consistent in patients with COPD than in controls (HajGhanbari et al., 2012a). The same team also demonstrated that in COPD pain severity was inversely correlated with exercise capacity and with health status scores (SF-36)(HajGhanbari et al., 2013). A prognostic value of chronic pain in COPD patients was not yet demonstrated.

The evaluation of extra respiratory symptoms in COPD beyond fatigue and pain is still not considered as worthwhile because little is known on the effects of such symptoms on relevant outcome measures such as health status for example. A further barrier against such an approach might be represented by the difficulty in finding appropriate tools to simultaneously assess such symptoms. ESAS scale address this limitation, being demonstrated as an easy and reliable tool to rapidly gather a comprehensive picture regarding the symptom burden in each patient across various chronic conditions including COPD (Walke et al., 2006a).

Health status is well known as prognostic factor for COPD mortality and morbidity in stable state and in the light of this evidence can be assimilated as a measure of clinical burden of the disease (Carone et al., 2016). It might be expected that the impairment of the health status can be due

exclusively to the severity of respiratory symptoms and to their impact on the individual ability to perform daily routine activities. In fact several studies focused on outcome measures related to the respiratory disability such as breathlessness, impaired exercise capacity, and found them to be significant determinants of the health status along with the illness perception, depression or disease coping (Brien et al., 2018, Ketelaars et al., 1996).

However, our data demonstrate that other determinants such as the number and the severity of extra respiratory symptoms can also contribute to the worsening of the health status and that the same clinical burden of extra respiratory symptoms can also explain the worsening of functional status.

It would be interesting to find out how this happens for each of these two patient reported outcomes. A clinical explanation of these results would be the fact that for example extra respiratory symptoms such as fatigue, or pain can further limit the performance of daily activities. Another explanation would be the self-perceived severity of respiratory symptoms such as dyspnea might be accentuated by the association of these extra respiratory symptoms leading to a worsening of the health status.

Previous studies outlined the fact that a poor functional status was an independent risk factor for the subsequent disease morbidity (COPD exacerbations) but it was the respiratory disability mainly producing this worsening (Fan et al., 2007, Pitta et al., 2006).

Our study demonstrates that extra respiratory symptoms can also contribute to an impaired functional status during a severe COPD exacerbations and therefore their burden (the concomitant occurrence of several such symptoms, their severity) might also indirectly predict the impaired functional status.

Therefore occurrence of extra respiratory symptoms in severe COPD exacerbations could not only explain the worse health and functional status in patients with comparably severe respiratory symptoms but might also be the reason for their slower or their lack of full recovery after exacerbation. As functional status is the main element in establishing disease trajectory, the issue of the prognostic value of such extra respiratory symptoms starts to take shape and investigative value. In our study we evaluated the extra respiratory symptoms in patients with severe COPD exacerbation and found that their clustering might be associated with prolonged length of stay. This particular aspect needs however further studies in larger cohorts in order to better ascertain this relationship and in order to find out if this clustering might not also be a predictor of in hospital or short-term(post discharge) mortality.In this study, the health status and the severity of the symptoms were not assessed for their dynamics during hospitalization for COPD exacerbation.

This would be an interesting issue beyond our analysis because it may offer information on the potential role of such symptoms as “unexpected” factors of severity for a particular hospitalization episode.

Conclusions

To conclude, the data presented in this paper demonstrate the importance of extra respiratory symptoms in patients with severe COPD exacerbations and offers preliminary evidence on the

rationale to evaluate them in this clinical setting. Apart from fatigue, other extra-respiratory symptoms are more and more relevant in COPD patients, due to their individual severity, due to the fact that if they occur concomitantly they increase the burden of symptoms and due to the fact that they further impair health respectively functional statuses. Depression is one such symptom and the best is to prevent it by acting on potential risk factors. One such modifiable risk factor is smoking. Further evaluation of these extrarespiratory symptoms is needed in order to better integrate their therapy in the frame of COPD management.

2.3.3 Conclusions

In COPD patients extra-respiratory symptoms are present and bothersome. Among them, fatigue remains the most prevalent and yet underdiagnosed extra-respiratory symptom. Fatigue can be evaluated with a large range of tools their choice depending on the purpose of measurement. Edmonton Symptom Assessment Scale for example can be used for rapidly quantifying the severity of fatigue along with that of other symptoms most of them considered as extrarespiratory in the COPD setting. Extra-respiratory symptoms are gaining relevance in the setting of COPD due to various reasons. One of these reasons is represented by the fact that they further impair the health status/health-related quality of life and the other is represented by the fact that they increase the disease burden. They can also impair functional status and can contribute to a suboptimal control of the disease in COPD patients. Therefore extrarespiratory symptoms have an emerging relevance in the current management of this disease.

CHAPTER 3: OUTCOME MEASURES IN PALLIATIVE CARE FOR END STAGE COPD

3.1 State of the art

Virtually any chronic disease reaching an end-stage (of the diseased organ/tissue functioning) can benefit from palliative care in order to ensure a better health status/health-related quality of life.
Palliative care is a holistic approach aiming at covering all the unmet care needs of a patient in whom the conventional therapy used up to that point is no longer able to result in an acceptable control of the underlying disease.
Palliative care concept is to relieve the suffering by addressing not only the medical needs but also the social and/or spiritual needs of the patients and of his/her caregivers.
In this respect, the definition developed by the World Health Organisation for palliative care offer the most complete picture of what this approach aims to: "An approach that improves the quality of life of patients and their families facing problems 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" (WHO, 2002).
The same organization set up the operational principles for palliative care in early '2000. Thus, palliative care should:

- Provide relief from pain and other distressing symptoms
- Affirm life and regard dying as normal processes
- Intend neither to hasten or postpone death
- Integrate the psychological and spiritual aspects of the patient care
- Offer a support system to help patients live as actively as possible until death
- Offer a support system to help the family cope during the patient's illness and their own bereavement
- Use a team approach to address to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life ad may also positively influence the course of illness
- Be 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 include those investigations needed to better understand and manage distressing clinical complications

In its beginnings, palliative care developed mainly as a terminal (end-of-life) care an approach which today is still retained by some palliative care services offered in the USA. In Europe, palliative care evolved dramatically starting from early '60s in United Kingdom, as a result of revolutionary thinking of Dame Cicely Saunders who understood the complex need of the dying patient and of the related family, coined the term "total pain" and outlined the need for a dedicated palliative care team to address all these physical, psychologic, social and spiritual needs of the patient/family.

Later it became clear that in many chronic illnesses the need for palliative care can be documented earlier than the end-of-life stage and this was acknowledged by the WHO who advocated the need for earlier palliative care in these diseases including in cancer.

Canadian Hospice Palliative Care Association exemplified a model which tries to integrate palliative care at various stages of a chronic disease and which includes the following approaches:

- First discussion of the availability of a palliative care service should be done with a patient in relationship with the prognosis of its illness at the moment of its first diagnosis
- Throughout disease progression the psychosocial and spiritual needs should be considered and if necessary addressed in the care plan
- Identification of an increasing symptom burden including pain as the disease advances is another potential indication of palliative care need
- The progressive loss of disease therapeutic control under the conventional therapy indicates the potential need for specialized palliative care interventions able to improve the quality of life of such patients.
- Documentation of end-of life stage of the disease requires terminal care

The figure reproduced with permission from Murray et al 2005 presents comparatively the old versus the "modern" view of the continuum palliative care approach:

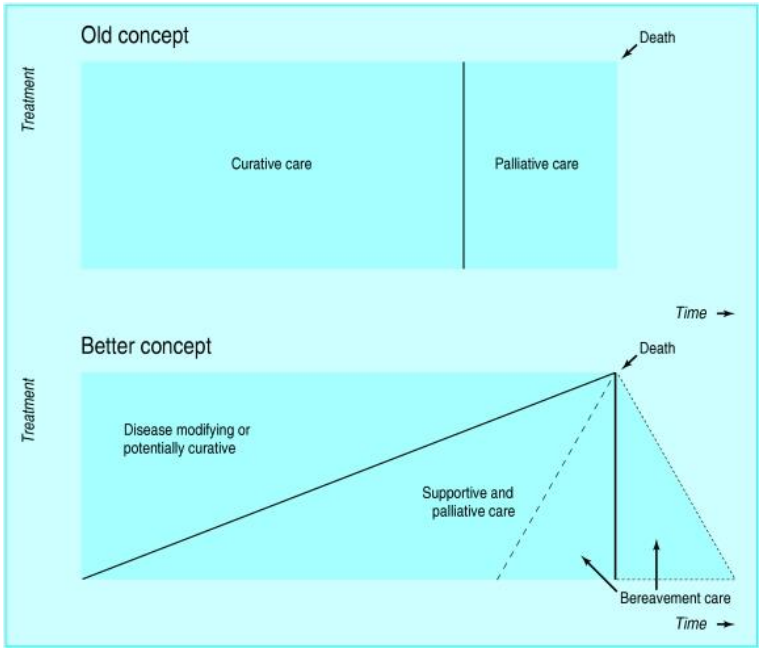


Fig 3.1 Continuum of palliative care approach old versus modern (reproduced with permission)

According to the modern view, palliative care should be considered much earlier than the end-of life of the patient, in order to allow patient/family to benefit to the most especially regarding symptom relief, reduction of psychological distress and improvement of quality of life. Furthermore, late palliative care referral can result in a less appropriate understanding of the

beneficial effects of this approach in the patient if applied earlier, less appropriate coping with the disease and poor understanding of the disease course and of the increase in patient's symptom burden. This is supported for example by the results of a multicenter questionnaire survey which was done in 318 family members who lost cared patients due to cancer. Half of these persons considered that the cared patient was referred late or very late, and only a minority (5%) of family members reported early palliative care referral. The study also identified determinants of the family-perceived late referral to palliative care which were represented by family belief that palliative care shortens the survival of the care patient, insufficient discussion of the preferred end-of life care approach between family members and healthcare professionals, hospital admission before referral and insufficient understanding of disease trajectory leading to inappropriate preparation for changes in patient conditions (Morita et al., 2005)

On the contrary, early palliative care in patients with metastatic non-small lung cancer was found to be associated with better quality of life, less severe depression and better survival and were able to better understand the prognosis of their disease and to retain an adequate perception on it until the end of life (Temel et al., 2011, Temel et al., 2010)

In another study performed in the Netherlands general practitioners were trained to identify the early palliative care needs and to deliver specific interventions in patients with various chronic conditions such as chronic obstructive pulmonary disease, congestive heart failure and cancer etc. Patients who benefited from this approach were more frequently in touch with their GPs for palliative care-related issues, were less often hospitalized, were more likely to die at home and less likely to die in the hospital (Thoonsen et al., 2011, Thoonsen et al., 2015). Furthemore GPs trained to early identify palliative care needs were more likely to actually detect them in the seen patients compared to untrained GPs (Thoonsen et al., 2015).

In COPD palliative care is still a challenge because the survival is more difficult to predict and because it is not currently very well known when this palliation should be started in these patients. This uncertainty is also backed up by the fact that the effectiveness of a potential palliative care intervention in reducing COPD-related morbidity and in improving the health status are not very substantially documented.

In a study comparing cost and healthcare utilization in patients with various end-stage diseases addressed to palliative care it was demonstrated that this kind of care was associated with a lower likelihood of ICU admission, better medical care provision and lower inpatient care costs compared to that of patients who only received usual care (Penrod et al., 2006).

Since in COPD the number of severe exacerbations requiring hospitalization or even ICU admission is increasing with disease progression and since this behavior is a source of emotional distress and since physical frailty increases in such patients, then the need of palliative care is justified even before end-of life is documented in such patients.

Which would be the main benefits of palliative care in COPD patients?

According to Yohannes and colab, palliative care can offer the most appropriate framework for a better communication between the medical team and the patient/family, can give the latter to better

understand the available treatment strategies and to choose the most appropriate options including those related to the advance care planning, the patient can make a choice on the end of life withholding and withdrawing of life support therapies can make a choice on the place he/she wants to die. Another major benefit of palliative care according to the same author is represented by the fact that being multidisciplinary in its operating principle, palliative care will focus on all problems such a patient faces and not only on those related to the severe respiratory symptoms. Such problems might also be represented by social distress, emotional distress or spiritual issues. Palliative care also gives the patient the opportunity to actively engage in the own management and this helps him to better cope with the disease and to understand the fact that even at such advanced stages he can still mastery his respiratory disease. The most recent meta-analysis focusing on the effectiveness of palliative care in patients with non-oncologic illnesses evaluated data coming from 28 randomized clinical trials comparing addition of palliative care to the usual care in patients with various forms of end-stage disease (Quinn et al., 2020). The main outcome measures were represented by acute health care use (hospitalisations or emergency department visits) quality of life assessed with both generic and disease-specific quality of life and symptoms. Data from 13664 patients were included in the analysis most of the patients having heart failure (10 trials 4068 patients) whereas COPD data came from 3 studies and 441 patients. The authors concluded that compared to the usual care palliative care was associated with significantly less emergency department visits, less hospitalisations and to a lesser extent with lower symptom burden. Palliative care did not result in a significant effect on quality of life(Quinn et al., 2020). However in these studies there was no differentiation between early palliative care and end—of-life care and consequently the data pool analysed considered altogether these two approaches.
Unfortunately in COPD setting, development and delivery of palliative care services still encounter various barriers. Those barriers which are related to the development of palliative care services specialized for COPD patients are mainly represented by:Insufficient knowledge and consideration for functional status as a prognostic factor of poor survival in COPD patients

a) Inappropriate differentiation of an early (pro-active) versus an end-of-life palliative care approach in COPD patients
b) The lack of adequate comprehensive criteria for referral to a proactive palliative care service for COPD patients

a. Functional status as a prognostic factor in COPD

Functional status represent the major element used for prognostication in palliative care or in other medical specialties. Its dynamics over time can have particular pattern in cancer, in the group of organ specific chronic diseases and in frail elderly/dementia and is used to define disease trajectory.
Murray et collaborators (fig 3.2, from ref Murray et a 2005) (Murray et al., 2005) found that in patients with progressive chronic illnesses (including COPD) the disease trajectory has a pattern similar to the second curve presented in the figure below. This trajectory is characteristic for a

disease in which functional status decreases progressively and constantly as the underlying disease advances and o this descending trend there are episodes of steep transitory deteriorations characteristic for the disease severe exacerbations (leading to hospitalisations). Although usually as a result of care during hospital, initial such episodes are associated with a recovery of functional status, this is usually partial and to a level which is worse than that found before each hospitalization. Death can virtually occur during each such episode but it is more likely to occur in associated with a deteriorated functional status (see figure 3.2 below).

Unlike the trajectory of chronic illnesses that of cancer is associated with a rather constant functional status for a period of time during which it is assumed the curative therapy is efficient, and after a variable period of time, a steep decrease in functional status which is associated with loss of therapeutic control occurs (first trajectory in the fig 3.2 below). In the case of frail elderly/patients with dementia, the trajectory has a dwindling allure.

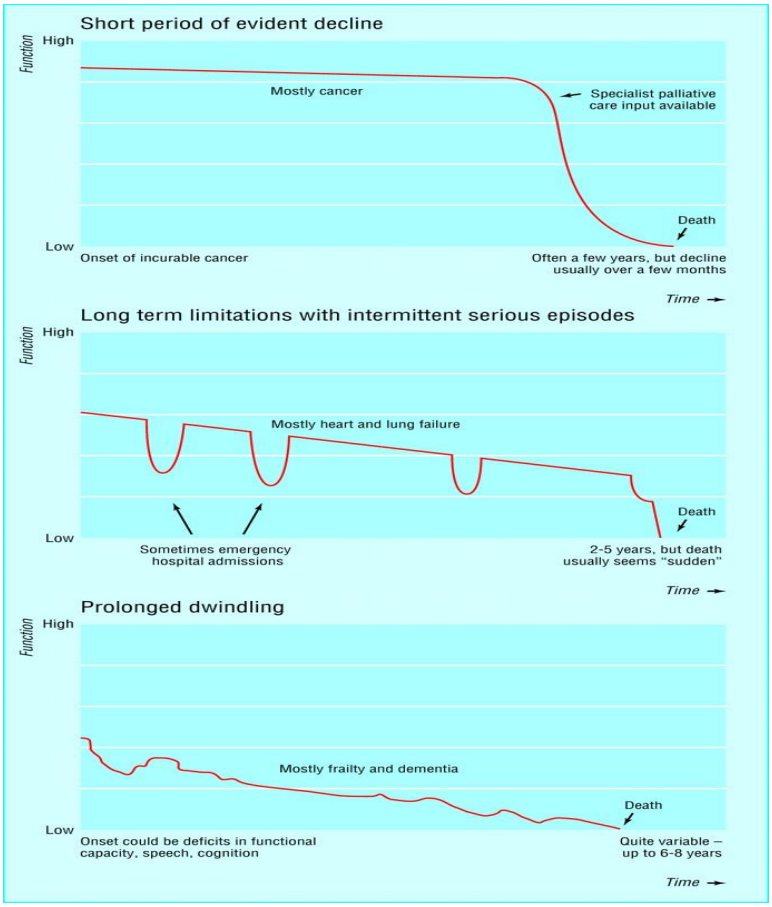


Fig 3.2 Patterns of disease trajectories (reproduced with permission)

Such trajectories are useful to predict the palliative care needs of such patients. For example Murray et colab hypothesized in 2017 that the physical, psychological, and social well- being follow a similar dynamics with that of the functional status (see Fig 3.3 below from ref Murray et al 2017). Interestingly enough, according to this diagram, social well-being exhibits an accelerated

reduction even at stages when physical respectively psychological well-being could still be considered as being acceptable, whereas the spiritual well-being has a rather constant course even at the end-of life(Murray et al., 2017). Usually spiritual distress increases with the decrease in survival and is rather dominant at the end-of life stage.

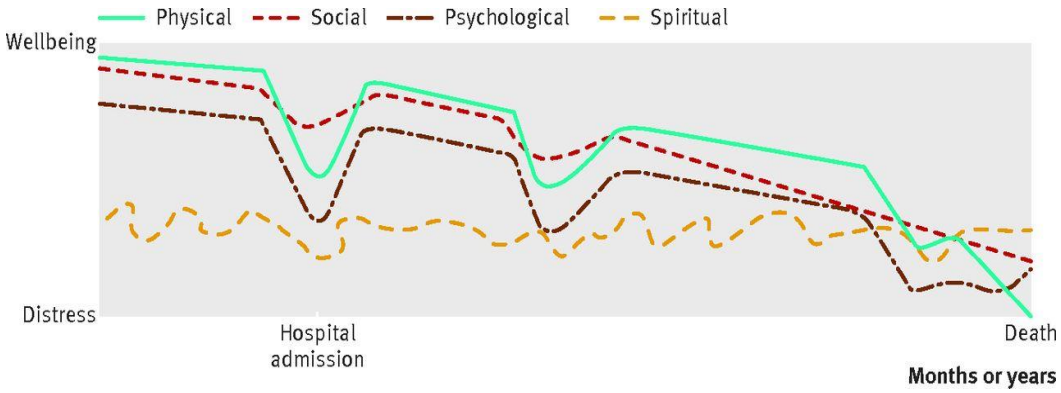


Fig 3.3. Disease trajectory in organ dysfunction (most chronic diseases) and the dynamics of the four types of wellbeing (reproduced with permission)

b. Inappropriate differentiation of an early (pro-active) versus an end-of-life palliative care approach in COPD patients

As mentioned in the beginning of this section, earlier palliative care comprises a larger range of interventions which can improve the quality of life whereas the end-of-life (terminal) palliative care includes a rather limited number of measure able to induce comfort in patient.
There is a need to identify the eligibility for palliative care as early as possible in COPD patients in order for them to really benefit from this type of care. This also involves an appropriate prognostication of the disease because if terminal state is wrongly diagnosed, the patient is refrained for a while (until reassessment and invalidation of the initial diagnosis of an end-of-life) from the benefits of proactive palliative care, ie there are needs which remain unmet for a variable period of time. If indeed it is end of life but the assessment wrongly classifies the patient as eligible for early palliative care, many of these interventions are going to be (soon) proved to be futile. Then when this assessment for early palliative care eligibility should start in COPD patients? There are studies which suggest that at the end of a hospitalization for a COPD exacerbation it is important to foresee the subsequent disease-related morbidity and to consider in certain patients the referral to a palliative care specialist. One such study was performed in order to assess palliative care needs of patients with COPD with or without cancer from an epidemiological point of view. This study enrolled 1455 inpatients with COPD and found that 132(9.1%) of them had at discharge palliative care needs. COPD patients with palliative care needs at discharge had significantly longer hospital stays, were at higher risk to die during the analysed hospitalization and were less likely to be discharged at home. In the same study possible predictors for palliative care needs were analysed in the same patients and the presence of COPD as a main diagnosis the association

of metastases in a COPD patient, association of depression and the lack of a relative were identified as the main outcome measures(Meffert et al., 2015).
According to Curtis et all, the following features should trigger the end-of-life discussion with a patient with severe COPD (Curtis, 2008):

- Age>70 years
- FEV1%predicted <30%
- Oxygen dependence
- At least one hospitalization for a COPD exacerbation during the last year
- Left heart failure or other comorbidities
- Weight loss or cachexia
- Decreased functional status
- Increased dependence on the others

Some of these criteria are also considered as criteria for referral to palliative care services for a patients with COPD (**Table 3.1**).

Table 3.1. Criteria for palliative care need assessment (Antoniu and Boiculese, 2016 reproduced with permission)

● Estimated survival of no more than 12 months
● Very severe airway obstruction: post-bronchodilator FEV1% predicted <30%
● Resting dyspnea (mMRC score 4) despite optimal therapy
● At least two severe COPD exacerbations requiring hospitalization over the last 12 months, reduction in time to next severe exacerbation
● Domiciliary oxygen therapy
● Association of comorbid conditions: congestive heart failure, psychiatric disorders, etc.
● Reduction in functional status with total dependency on a caregiver for at least two daily activities
● Social deprivation

The access to early palliative care services to COPD patients is more reduced compared to that of patients with lung cancer for example.
In a study in which included were patients with COPD and patients with inoperable no-small cell lung cancer it was found that quality of life measured with SF-36 was significantly better in the latter category of patients (see Fig 3.5 below) (Gore et al., 2000). Furthermore depression respectively anxiety risks analyzed with hospital anxiety and depression scale was significantly higher in COPD patients compared to non-small cell lung cancer counter parts. More COPD

patients were housebound compared to non-small cell lung cancer (82% compared to 36%), whereas 36% compared to 10% were chair bound.

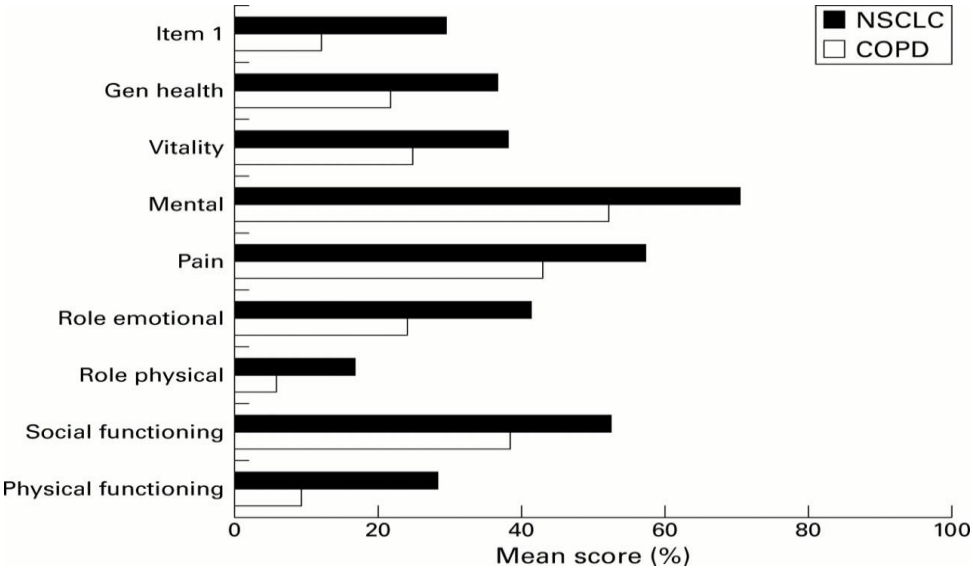


Fig.3.5 Domain scores of SF-36 in COPD respectively lung cancer(higher values mean better quality of life, reproduced with permission)

Cancer patients were also more likely to appropriately cope with their disease and to retain an optimistic outlook, compared to COPD patients who were anxious and not educated to accept and to self-manage exacerbations of dyspnea. In terms of healthcare utilization the number of GP visits per year were significantly higher with non-small cell lung cancer patients and were for emerging symptoms, whereas COPD patients had a higher emergency room visit rate and this was usually done because of an exacerbation. Both categories of patients received financial support for the underlying disease in comparable proportions but more COPD patients complained that this was delayed and perceived it as coming too late in the disease course. The most surprising finding of this study which perhaps explain the findings presented in Fig 18 were represented by the fact that none of COPD patients had access to palliative care compared to about 30% of patients with inoperable lung cancer (Gore et al., 2000).

One possible explanation of the limited access to palliative care by patients with chronic disease such as COPD is the fact that compared to oncology setting, non-oncological palliative care still encounters numerous barriers against its implementation. They are related to the limited availability of dedicated units which are able to deliver palliative care services for COPD patients, they are related to the patients/their families and to the limited involvement of the primary care in the palliative care continuum.

Most of the implementation barriers related to the patients and to the primary care are mostly in the field of communication.

According to a review performed by Yohannes and colab some of the communication barriers related to patients are represented by:

- Unwillingness of the patient/family to find out and discuss about his/her diagnosis of end-stage COPD
- Lack of communication with primary care team
- Inappropriate importance given to the end-stage pulmonary disease
- Lack of information that such a service is available
- Lack of hope in better health status

On the primary care physicians these barriers are mainly represented by

- Inadequate preparation to tackle such a topic with the own patients
- Busy practice (lack of time)
- Not familiar with provision of palliative care at primary care level
- Lack of appropriate resources and facilities

All these evidence discussed above strongly support an integrated early palliative care approach should be made available for patients with COPD. This is as also backed up by the World Health Organization resolution on early palliative care adopted in 2014 and according to which this type of care should be considered even at the time of diagnosis in a prospective manner so that people suffering from chronic illnesses such as COPD can foresee what types of therapies are available throughout the disease course, can understand the disease better and at the end of the day can learn gradually how to cope with disease and with what its progressions involves.

c. The lack of adequate comprehensive criteria for referral to a proactive palliative care service for COPD patients

In the concept paper discussed below I listed some of the orientative criteria for palliative care referral which can be used in COPD patients. These criteria do not fully cover all the areas of a palliative care assessment procedure, do not entirely apply for an early approach but still can be effectively used.
This should prompt further validation of relevant criteria for early/pro-active palliative care services referral and also a more appropriate definition of disease-related criteria for end-of-life (terminal) care in COPD patients. Such revised criteria should be able to better detect disease burden, deteriorating functional status and various unmet care needs (Rajnoveanu et al., 2020).
This research direction is described by the following papers:

Antoniu SA. Outpatient palliative care effectiveness: both patients and caregivers can gain. Expert Rev Pharmacoecon Outcomes Res. 2013 Oct;13(5):575-7. **IF=1.87 (reproduced with permission)**

Antoniu SA, Boiculese LV. Palliative care outcome measure in COPD patients: a conceptual review. Expert Rev Pharmacoecon Outcome Res 2016;16(2): 267-74, **IF=1.78**, ISSN: 1473-7167 **(reproduced with permission)**
Carone M, **Antoniu S**, Baiardi P, Digilio VS, Jones PW, Bertolotti G; QuESS Group. Predictors of Mortality in Patients with COPD and Chronic Respiratory Failure: The Quality-of-Life Evaluation and Survival Study (QuESS): A Three-Year Study. COPD. 2016;13(2):130-8**, IF=2.47,** ISSN: 1541-2555 **(reproduced with permission)**.
Antoniu SA, Mihaltan F. Outcome measures for palliative oxygen therapy: relevance and practical utility. Expert Rev Pharmacoecon Outcomes Res. 2014 Jun;14(3):417-23, **IF=1.66**, ISSN: 1473-7167 **(reproduced with permission)**

3.2 Models of palliative care: the effectiveness of the outpatient model

As mentioned earlier in this chapter, in COPD palliative care is not as developed as that related to the oncological diseases. Considering that an outpatient palliative care service would appropriate for end-stage COPD, I evaluated the results of a study on the impact of an outpatient palliative care service on both patients and their caregivers (Antoniu, 2013). The advantages of such a service would be the fact that they allow the patient to spend as much time as possible with the family and in an active manner. The study analysed included both non-oncological and oncological pathologies and involved both patients and their informal caregivers (Groh et al., 2013).

Personal contribution

Antoniu SA. Outpatient palliative care effectiveness: both patients and caregivers can gain. Expert Rev Pharmacoecon Outcomes Res. 2013 Oct;13(5):575-7. **IF=1.87 (reproduced with permission)**

Methods and results

This was a prospective study performed by a specialized outpatient palliative care (SOPC) interdisciplinary team, which analyzed the effectiveness of the delivered healthcare services on patients and on their caregivers. Included were patients requiring and receiving palliative care as outpatients and their primary (not paid) caregivers who consented to participate to the study. Patients who were willing and able to fill in questionnaires, were given two satisfaction with care tools that were under development, as well as other (already validated) questionnaires or tools such as the McGill Quality of Life Questionnaire, the Minimal Documentations System for Palliative Medicine (MIDOS) and the Palliative Outcome Scale, which had to be completed before and after receiving the SOPC team.
Caregivers were asked to fill in the caregiver versions of the questionnaire under development, the Quality of Life in Life-Threatening Illness-Caregiver version (QOLLTI-F), the Hospital Anxiety and Depression scale (HADS) and the Home Care scale before and after the interaction with the SOPC team.

Of the 100 patients visited over the study period, 60 patients were considered eligible, but 23 (38%) were ill or refused to fill in the questionnaires and five more died before the second assessment took place.

Most of the patients 33 (55%) were males and the median age was 67.5 years, most of the patients had a malignancy (n = 52; 87%) and most of them had a cancer in the gastrointestinal tract (n = 21; 35%).

The median duration between the two assessments was 2.5 weeks (few days to 7 weeks range). A total of 53 caregivers were included in the study, 41 (77%) being females, the median age being 58 (29–91 years range), most of them being spouse/partners (64%) or parents (20%). The effectiveness of the care provided by the SOPC was assessed with satisfaction with care, care burden relief (reduction) as perceived by the patients, respectively, by the caregivers and by a more complex outcome measure defined as patients' and caregivers' adjustment after the interventions delivered by the SOPC which included for the patients quality of life, symptoms' control, respectively, for the caregivers quality of life, related stress and burden.

SOPC interventions were able to increase significantly the satisfaction with care for both patients and caregivers as demonstrated by the tested questionnaires' scores.

The burden of care was significantly diminished by the same interventions as perceived by both patients and caregivers themselves and expressed by the scores of numerical scales.

The main strengths were represented by the psychological support, by the interventions related to the activities of daily living, by the information on the disease status and trajectory delivered to both patients and care givers.

The delivered interventions, however, were not able to improve the quality of the spiritual care and that of communication with general practitioners and other healthcare providers, for both tested parties. SOPC team interventions were also able to improve both patients' and carers' adjustments: in patients, this was demonstrated by the significant improvement in the MCQ questionnaire score (interquartile range [IQR]: 4.5 before and 6 afterwards; $p < 0.001$), in the Palliative Outcome Scale, the total score (IQR: 25 before, 14.5 afterwards; $p < 0.001$) and by the significant improvement in pain, nausea, vomiting, anorexia, depression and well-being scores (as assessed by MIDOS).

In caregivers, this was demonstrated by the significant improvements in satisfaction quantified with a numerical scale and by the improvement in the QOLLTI-F (IQR: 6.1 before, 7.3 afterwards; $p < 0.001$), HADS scores (IQR: 22 before and 16 afterwards; $p < 0.001$) and HPS scores (IQR: 13 before and 9 afterwards; $p < 0.001$).

Discussions

This analysis demonstrates that the intervention of an outpatient palliative care team is able to reduce both the disease and the care-related burdens.

In terms of disease burden, the interventions provided by such a team could reduce or make to disappear major symptoms such as pain or nausea, although no significant effects were found on others such as fatigue or dyspnea.

Such results can be partially explained by the fact that among the analyzed patients, a significant proportion had digestive malignancies and that at least in the case of dyspnea, based on the results discussed by the authors, the severity of this symptom did not seem to be very significant.

Conclusions

The fact that the major symptoms such as fatigue, depression or dyspnea could not be significantly improved by an unique intervention of an outpatient palliative care team that however was able to improve the pain or nausea, for example, raise the question of the need to repeat such interventions and to tailor the next episodes of these activities to address what the previous interventions were not able to correct.

Overall, the results of this study encouraged the expansion of such teams thatare extremely useful especially at the both extremes of palliative interventions: early palliation in patients requiring it and mainly aimed to improve the quality of life and to prevent hospitalizations, and end-of-life patients in whom the interventions are no longer able to improve the quality of life in such a sustained manner as the early palliation, but are mainly targeting the well-being and the comfort of the patients as well the reduction of the distress of the caregivers.

3.3 Palliative care outcome measures in COPD

Palliative care in COPD is currently at a developmental stage in terms of outcome measures for effectiveness in research as well as in clinical practice. Therefore I tried to develop a conceptual framework able to include outcome measures able to evaluate the dimension of the various needs (physical, psychologic, social, spiritual) and the effects of various palliative care interventions in patients with COPD.

Personal contribution

Antoniu SA, Boiculese LV. Palliative care outcome measure in COPD patients: a conceptual review. Expert Rev Pharmacoecon Outcome Res 2016;16(2): 267-74, **IF=1.78**, ISSN: 1473-7167 **(reproduced with permission)**

In COPD patients, palliation need assessment should include health status/health-related quality of life, functional status, fatigue, severity of respiratory symptoms, and the number and severity of hospitalizations for COPD exacerbations as main outcome measures. Frailty must also be considered as an important outcome measure in palliation of COPD as the condition itself is a disease of the aging population (**Table 3.1**).

Other elements that are also related to disease pathogenesis and/or mortality such as severe airway obstruction (post-bronchodilator FEV1% predicted <30%), presence of resting hypoxemia/hypercapnia, and oxygen dependence should also be considered as additional elements given their prognostic importance, especially at the initial evaluation for palliation; however, these are outcome measures that palliation is not able to influence significantly, and therefore, given its scope, this review does not go beyond their listing.

Table 3.1. Meaningful outcome measures in COPD palliative care

1. Physical outcome measures
a. Dyspnea
b. Fatigue
c. Other non-respiratory symptoms (mainly pain)
d. Functional status
e. Health status
f. Frailty
g. Disease-related morbidity: exacerbations
2. Psychological outcomes
a. Anxiety
b. Depression
c. Delirium and other cognitive deficits
3. Social outcome measures
a. Social support
b. Caregiver burden
4. Spiritual outcome measures
a. Hope
b. Meaning in life
c. Dignity
d. Religious beliefs

The other three categories of outcome measures, psychological, social, and spiritual, are also important in documenting the need for proactive or end-of-life palliation in COPD patients.

3.3.1 Health status and other physical outcome measures

- **Health status**

Health status and health-related quality of life are outcome measures commonly used in COPD to document the efficacy of various interventions, such as inhaled therapies, or to assess the deterioration caused by exacerbations. In COPD, health status can be measured with various disease-specific questionnaires such as the Saint George's Respiratory Questionnaire, Clinical COPD Questionnaire, and COPD Assessment Test. The scores generated by each of these three instruments demonstrate valid predictors of mortality in COPD patients and in those with end-stage disease in particular(Carone et al., 2016, Casanova et al., 2015). On the other hand, health-related quality of life can be measured with generic questionnaires that are able to capture the overall negative impact of the disease irrespective of existing symptoms and instead as a result of impaired health. COPD questionnaires such as SF-36 and EuroQoL-5D were successfully used for this purpose(Miravitlles et al., 2011). Both health status and health-related quality of life are complementary measures of patient disease experience and, therefore, it is recommended that in COPD they are used in combination for the reasons discussed above; however, generic

questionnaires such as SF-36 are lengthy and the completion of such a questionnaire by a patient with advanced COPD receiving palliative care can be a real challenge. Health-status measurement, on the other hand, can be done with shorter questionnaires and can be more useful in evaluating disease dynamics, for example, it can help with foreseeing an exacerbation before respiratory symptoms worsen significantly (van der Molen et al., 2014). Indeed health status/health-related quality of life also include psychological dimensions but because in COPD the focus is on physical traits this outcome measure was reviewed under this label.

- **Functional status**

Functional status is defined as the ability to perform routine daily activities including physical tasks and is used in various chronic diseases as a prognostic outcome measure. This was assessed most commonly for disease morbidity as both short and long-term predictor: in a cohort of 4596 patients, most of them at older ages (mean age 72.3 years), lower levels of physical activity before first hospitalization was associated with an increased risk of hospital readmission in the first 30 days following discharge due to a COPD exacerbation (Nguyen et al., 2014). Furthermore, when the functional status was evaluated in a subset of the same cohort at discharge, it was demonstrated that those unable to walk at hospital discharge had a twofold risk of being readmitted within the next 30 days as compared to those able to walk (Nguyen et al., 2015). Functional status was also found to be a prognostic factor for mortality in older patients with COPD, when evaluated with the Manchester Respiratory Activities of Daily Living questionnaire after an exacerbation of the underlying disease(Yohannes et al., 2002, Yohannes et al., 2005). Functional status has also been used as a major criterion for the evaluation of palliative care needs in different diseases due to the fact that significantly impaired functional status is a common feature of advanced diseases or advanced diseases reaching end-of-life stage, and these are usually the settings in which palliative care is needed. In oncology, functional status is one of the main outcome measures used to estimate survival and can be documented via different scales such as the Eastern Cooperative Oncology Group (ECOG), Karnofsky index, and Palliative Performance Scale. For example, ECOG score was identified as a predictor of mortality in a recent study performed in patients with advanced lung cancer (O'Mahony et al., 2016), and functional status was found to be significantly more impaired in an outpatient oncologic population seeking palliative care as compared to a community population of comparable age (Schuit et al., 1998).

In COPD, the use of functional status as a marker of palliative care need was not studied in detail. This is due to the fact that the need for palliative care in this disease has only recently been recognized, not only for end-of-life but also for end-stage disease with longer survival, and, unlike cancer, COPD does not have a functional status measurement tool which appropriately considers the impact of the condition on performance status. Tools such as the London Chest Activity of Daily Living scale are excellent instruments that are able to document the impairment of functional status as a result of disease (respiratory) symptoms, or to evaluate how much help is needed to perform basic daily activities, but no tools are able to capture both dimensions of this impairment, which is essential in documenting the overall need of palliative care (Miravitlles et al., 2014a).

Despite the existing limitations, however, functional status should be considered when evaluating the need for palliative care in COPD patients with advanced airway obstruction.

Another aspect related to functional status measurement that should be taken into consideration is the dynamics of disease impairment. This parallels the trajectory of the disease itself and means that for COPD the decline rate is significantly slower than that for cancers; however, it is not clear which monitoring intervals are appropriate in order to link this rate with a certain prognosis(Murray et al., 2005). Even under such circumstances, disease trajectory can be a very useful tool to predict, for example, the end-of-life stage in COPD patients if its decline rate increases over a relatively short period of time. Determinants of functional studies should be further assessed; attempts to identify factors associated with poor physical activity have been made in patients with various degrees of disease severity with poor quality of life and depression identified as main determinants (Miravitlles et al., 2014a). However, the picture of functional status and of its determinants should be more detailed in the particular setting of 'palliated COPD'; it would be important to see if there are interventions able to interfere significantly with its decline, especially during the early phase of palliation.

- **Fatigue**

Fatigue is a common complaint of COPD patients, being present even at earlier stages of the disease when conventional inhaled therapy is still able to slow disease progression(Antoniu et al., 2016); however, little attention is usually given to this symptom, which is usually addressed when disease is more advanced and presents other symptoms or signs of a chronic systemic disease(Andersson et al., 2015, Antoniu and Ungureanu, 2015). If earlier in the disease history fatigue is mainly a manifestation of skeletal muscle deconditioning, in more advanced stages and at the end-of-life stage fatigue has both physical and mental components and has foundations in chronic hypoxemia, poor exercise capacity, systemic inflammation, and so on (Andersson et al., 2015). In COPD, the evaluation of fatigue has so far been done in heterogeneous populations including patients with various degrees of disease severity and at single points, in an attempt to document correlations with other outcome measures and impact on quality of life.

In such a study, fatigue was found to be associated with impaired quality of life, and more severe symptoms were associated with a more impaired quality of life predicting mortality in COPD patients (odds ratio for fatigue 1.06; 95% CI: 1.02–1.10) (Stridsman et al., 2015).

Despite fatigue not being given equal importance as for that detected in cancers, it remains an important symptom in COPD that deserves further study and more appropriate consideration in palliative care of COPD patients. In particular, it would be interesting and purposeful to find out if its steep aggravation, which parallels that of the functional status, could be a marker of approaching end-of-life in such patients.

- **Dyspnea**

In COPD, respiratory symptoms are mainly represented by dyspnea, which in certain patients can be associated with productive cough. These symptoms worsen with disease progression and further aggravate during disease exacerbations. Dyspnea severity is the main subjective outcome measure

used in COPD as such or as a component of prognostic indexes such as BODE (B = body mass index, O = obstruction, D = dyspnea, and E = exercise capacity).
The scale most commonly used to document the so-called 'patient-reported dyspnea' is the modified Medical Research Council (mMRC) dyspnea scale that quantifies dyspnea severity against the amount of physical effort tolerated [2]. Dyspnea severity has been documented in many studies as a predictor of mortality in COPD patients and, for example, in a recent study performed on a cohort of 768 patients, it was demonstrated that an mMRC dyspnea score of at least 2 had a stronger predictive power for all-cause mortality than health status scores.
When dyspnea was incorporated into the BODE index, a 10-point scale, in order to predict mortality in a cohort of 207 patients, it was demonstrated that higher BODE scores were associated with higher risk of death; a one-point increase in the BODE index score being associated with 1.34 hazard ratio for all-cause mortality and 1.62 for mortality or respiratory causes (Celli et al., 2004, Cote et al., 2008).

- **Other extrarespiratory symptoms**

Apart from fatigue, the non-respiratory symptoms most commonly diagnosed in patients with advanced COPD are represented by pain, delirium, depression, and anxiety (Claessens et al., 2000, Lynn et al., 2000). The latter three symptoms are going to be discussed with the psychological outcomes below. Pain was found to be commonly detected in patients with COPD irrespective of the degree of airflow limitation and is currently considered as a comorbid symptom. Some studies using the Brief Pain Inventory to evaluate various features of this symptom, including its severity under specified circumstances, found that pain intensity paralleled that of respiratory symptoms such as dyspnea, fatigue, and worsening quality of life (van Dam van Isselt et al., 2014, Lee et al., 2015). The major problem associated with dyspnea and with other symptom measurement in palliative care is represented by the difficulties in its qualitative (e.g. impact on health status, descriptors) or quantitative assessment in a population of patients with advanced disease, most commonly with advanced age and a high probability of having a certain degree of cognitive function deficit.
However, what is important in palliative care for practical (management) purposes is the severity of the symptom, and therefore the use of numerical rating scales is opportune and appropriate in this setting. A more comprehensive picture of all existing symptoms inventoried for presence and severity can be gained with palliative care multi-symptom scales such as Edmonton Symptom Assessment Scale (ESAS), which can be a very useful instrument not only for initial evaluation but also for follow-up purposes.
This scale was developed for use in palliative care of oncological patients and includes the 10 most commonly encountered symptoms in such populations, among them pain, fatigue, dyspnea, anxiety, and depression.
Despite its documented reliability and validity, the ESAS was not frequently used in advanced chronic diseases and few studies report its successful use in patients with various conditions including COPD (Wajnberg et al., 2013).

- **Frailty**

Frailty is an attribute of the geriatric population that is associated with increased morbidity and/or disability.

In geriatrics, it was initially described as a phenotype and nowadays it is defined as a syndrome that includes several criteria, among them involuntary body weight loss, impaired grip strength, gait speed, self-reported exhaustion, and low physical activity(Fried et al., 2001b).

Some other authors went beyond physical frailty and, still considering this syndrome a phenotype, or better, a cluster of phenotypes, identified other entities such as mental frailty and social frailty (Garre-Olmo et al., 2013).

Frailty has been documented not only as an additional source of disability but also as a risk factor for mortality irrespective of the chronic diseases present in the noninstitutionalized elderly (Graham et al., 2009, Chang and Lin, 2015).

Interestingly, a mutual relationship between respiratory impairments and frailty was previously described in a cardiovascular health study including 3578 participants aged 65–80 years.

There were 5.8% frail subjects, 13.8% had previously undiagnosed airway obstruction and frail subjects had a higher risk of having airway obstruction (odds ratio 1.88; 95% CI: 1.15–3.09).

Frail patients with impaired respiratory status had the highest mortality risk in the studied population (hazard ratio 3.91; 95% CI: 2.93–5.22) (Vaz Fragoso et al., 2012); however, the mortality risk was calculated taking into account other types of lung function alterations, not only airway obstruction and hence a definitive conclusion on the relationship between frailty and mortality in COPD patients needs to be validated with further studies.

An initial attempt to clarify this aspect came from the National Health and Nutrition Examination Survey cohort that included 20,470 participants in which a subset aged at least 55 with an emphysema diagnosis, chronic bronchitis, or both was subsequently analyzed for the presence of frailty and for its effects on their underlying disease status.

In this subset of 211 patients, mean age 70.6 years, frailty had a prevalence of 57.8% and was more likely to be diagnosed in patients with more severe respiratory symptoms with dyspnea being the strongest predictor of frailty (odds ratio 3.98; 95% CI: 1.7–8.88)(Park et al., 2013). However, in this cohort, the presence of COPD was not confirmed with spirometry and a mixed population with chronic bronchitis (normal lung function) and COPD (airway obstruction) was included and hence the results have a limited validity.

In the more recent Rotterdam study, the risk of frailty in older COPD patients was evaluated in a population-based study including 2142 patients with a mean age of 74.7 years and with the presence of COPD certified with spirometry.

Frailty was more commonly diagnosed in patients with COPD as compared to non-COPD patients (10.2% vs 3.4%; $p < 0.001$), the former category exhibiting a significantly higher risk of developing frailty (odds ratio 2.2; $p = 0.02$) as compared to the latter.

Frailty prevalence increased with the severity of airway obstruction, presence of dyspnea, and number of exacerbations. In COPD patients, the presence of frailty as defined with Fried criteria was reported to be associated with poor survival (Park et al., 2013).

- **COPD-related morbidity**

In the natural history of COPD, there are disease exacerbations, in particular exacerbations of respiratory symptoms and airway obstruction/inflammation, usually due to infections.
They can be of varying severity with some only requiring additional therapy at home yet some others resulting in hospital referral. Less severe COPD exacerbations are not usually associated with an increased risk of mortality, especially for the earlier stage of the disease; however, they contribute to the sustained decline of lung function and health status, which are the most important determinants of accelerated progression of the disease.
Furthermore, hospitalizations for COPD exacerbations were demonstrated to bear an increased risk of short- and long-term mortality in older patients with advanced COPD, worse dyspnea outside exacerbation, or undergoing domiciliary oxygen therapy (Gudmundsson et al., 2006, Marin et al., 2013b). On the other hand, if the number and severity of exacerbations increases despite appropriate therapy, this becomes an indicator of loss-of-disease control and increases the impact of the disease on the daily functioning (Alvarez-Gutiérrez et al., 2007). If this is associated with a large decline in lung function and other features of advanced disease (reduced exercise capacity, poor health status), this means that palliative care is needed. In fact, hospitalization rate in the previous year is among the criteria for referral for palliative care for patients with COPD (O'Kelly and Smith, 2007, Murray et al., 2006).

3.3.2 Psychological outcomes

In patients with COPD, depression is a common comorbid symptom and can be detected virtually at any disease stage; however, it is more severe in more advanced disease. It correlates with severity of other symptoms such as fatigue or dyspnea and can significantly impair health status (Miravitlles et al., 2014b, Antoniu and Ungureanu, 2015). In particular, as depression is a relevant outcome measure at the end of life, especially in COPD patients, it should be always considered in the care plan of such patients; it can still be effectively treated even at this stage and its alleviation improves overall patient comfort and also indirectly effects spiritual comfort.
Another reason for considering depression as an outcome measure is its relationship with disease morbidity and in particular with hospitalizations or COPD exacerbations; previous studies recognize depression as a major risk factor for hospital readmission (Pooler and Beech, 2014, Iyer et al., 2016, Gonzalez-Gutierrez et al., 2016, Laurin et al., 2011).
Anxiety has also been recognized as a comorbid symptom of COPD, even if commonly in combination with depression.
Similarly to depression, anxiety can be present in COPD irrespective of the degree of airflow limitation; however, it was found to be more commonly associated with a worse functional and health status and with more frequent disease exacerbations(Mohapatra and Janmeja, 2010). The presence of anxiety was also found to exert a significant impact on disease burden with the use of long-acting beta-2 agonists as a monotherapy and poor health status being documented (Soler et al., 2004).

Cognitive deficit has been reported in COPD in various forms, the most common being the milder form of impaired executive and attention functions (Villeneuve et al., 2012). It can fluctuate according to the exacerbated or stable phase of the disease and this means that it can improve during recovery stages following an exacerbation, especially in patients without resting hypoxemia in the stable phase (López-Torres et al., 2016). In patients with COPD and domiciliary oxygen therapy, this cognitive deficit is more complex, more severe, and has been associated with a higher hospitalization burden (Karamanli et al., 2015). Delirium is a common symptom of end of life, present not only in cancer patients but also in patients with end-stage chronic diseases such as COPD. Delirium can be hypo- or hyperactive, and episodes can initially be of limited duration with longer delirium-free periods. Toward the active dying phase, these symptom-free intervals shorten and hyperactivity dominates. In COPD patients, older age, the presence of comorbid psychiatric disorders, suboptimally treated hypercapnia, and hypoxemia represent risk factors for delirium (Wilkinson et al., 2014).
Delirium in such circumstances requires palliative sedation and should be considered as an outcome measure in patients with COPD requiring end-of-life palliative care (Hoek et al., 2015).

3.3.3 Social outcomes

It is recognized that chronic diseases have been associated with a negative social impact at various levels such as financial, social interaction, community insertion, and caregiver burden. Such findings were demonstrated with multiple sclerosis and diabetes, but in COPD these aspects are less well studied (Airlie et al., 2001).
Social support has been demonstrated as a reliable outcome measure not only for the social impact of the disease but also for the effectiveness of various social interventions (George et al., 1989). In patients with congestive heart failure, social support correlated well with self-care and in other chronic diseases, studies demonstrated that improvements in social support were associated with better understanding of, and better coping with, the underlying disease (Sayers et al., 2008, Gallant, 2003).
In COPD, social support was previously evaluated in patients with various degrees of airway obstruction and disease severity in relation to daily functioning, self-efficacy, and depression, and it was found that along with the self-efficacy, social support was the major determinant of daily functioning (Marino et al., 2008).
Another important dimension of social burden also relevant in COPD is caregivers' burden. In a study evaluating caregivers' burden in a mixed population of patients with advanced COPD, health failure, and chronic renal failure, most of the caregivers included in the study were females and the amount of the care related distress was found to be influenced by disease itself (being the highest with COPD), by marital relationship (i.e. if the caregiver was a spouse), by the presence of psychological symptoms, and of other comorbidities (Janssen et al., 2012). When this burden was analyzed after 1 year, caregiver burden was found to be influenced by the survival of the patients being higher in those who died during this period (Nakken et al., 2015).

A nationwide study performed in Spain found that caregiving was associated with a high incidence of health and social problems in persons informally caring for COPD patients and that the severity of these problems was inversely related to the degree of self-efficacy of cared persons (Miravitlles et al., 2015) . Further studies defined various dimensions of this burden with deterioration of the caregiver–patient relationship, emotional strain, and impaired coping with the patients (Simpson et al., 2010).
In palliative care of COPD patients, both social support and caregiver burden are relevant and should be considered as outcome measures able to detect the presence of social sufferance and to measure how this changes as a result of targeted social interventions.

3.3.4 Spiritual outcomes

In palliative care, 'spirituality' is an important component of care because spiritual distress is often present early in the course of disease and is dominant toward the end of life. Lack of hope, feelings of meaningless, or lack of dignity were the commonly identified features of spiritual distress and better spiritual wellbeing was demonstrated to predict better quality of life in patients with oncological conditions (Brown et al., 2015, Bai and Lazenby, 2015). In COPD as well as in the other chronic conditions, the spiritual dimension of quality of life has only recently been considered and this is reflected by the paucity of the research results supporting the need to integrate this dimension within the multidisciplinary, holistic care plan when the patient reaches a palliative care stage.
Spiritual well-being was evaluated in patients with COPD as such, in a global manner or with some of its components mentioned above. Similarly to patients with cancer, COPD patients experience an impairment of their spiritual well-being with the progression of the disease and this can worsen with perception of the disease burden by the patient themselves (Strada et al., 2013).
Hope is another measurable spiritual trait that is significantly impaired in patients requiring palliative care and frequently reported by the end-of life patients. There are various tools to assess the depth of its impairment and they help better identify areas of intervention that can improve terminal comfort or quality of life (Kennedy and Lloyd-Williams, 2006).
Dignity was also evaluated in COPD patients with advanced disease and it was found that from a sample of 195 patients, about 13% had a significant loss of dignity irrespective of the presence of end-of-life stage, and that this was related to psychological distress such as depression and anxiety and not to severity of the underlying disease itself (Solomon et al., 2016). Furthermore, spiritual interventions tailored to improve dignity were demonstrated to improve spiritual well-being across various end-stage pathologies (Chochinov et al., 2011).

3.3.5 Conclusions

In COPD palliative care is an approach reserved for the end-stage disease and has the aim of improving quality of life or in case of end-of-life stage to ensure a comfort state till death. Unlike

the oncological conditions, in COPD palliative care is not very developed and not very well known for what it is able to do by both healthcare professional and patients/families.
In COPD palliation should be approached in a similar manner as that of oncological conditions. Given that the overall aim of palliative care is represented by the improvement in the quality of life, all its impairments as a result of the disease itself should be documented. This is why in assessing the needs for palliative care in a COPD patient four categories of outcomes should be considered ie physical (including health status which mostly focus on physical problems), psychological, social and spiritual. This approach is needed in order to obtain a full image regarding the needs of a particular patient with end-stage COPD. Functional status is a physical outcome which is also very important in palliative care because it can be a very useful prognostication tool for survival in both prognostic models or in the trajectory analysis. Therefore a very good knowledge of the meaningful outcomes in palliation for COPD is needed in order to do an appropriate assessment of the palliative care needs.

3.4 Outcome measures for palliative oxygen therapy: relevance and practical utility

3.4.1 Introduction

Chronic oxygen therapy is a method which is commonly used in patients with end-stage chronic pulmonary disease and chronic respiratory failure. In this setting supplemental oxygen is given in order to correct hypoxemia, to improve survival and to reduce the risk of development of hypoxemia-related complications such as pulmonary hypertension, cor pulmonale or secondary polycythemia. This therapy is also called long-term oxygen therapy or domiciliary oxygen therapy and in patients with COPD and chronic respiratory failure in particular, the clinical evidence supporting this indication came from two ancillary studies, the Medical Research Council, respectively the NOTT studies which were discussed in a previous section.
Palliative oxygen therapy on the other hand is a supplemental oxygen therapy which has narrower applicability and which is indicated as a therapeutic method to correct refractory dyspnea. Palliative oxygen therapy is more recently advocated as a therapeutic method in various palliative care settings and probably this is why the clinical evidence supporting its use is very limited. In recognition of the fact that there is a need to document or even to identify appropriate outcome measure of effectiveness for this method, and being interested in finding out which of the patient reported outcomes currently validated to document the effectiveness of other methods can be also reliably be used in the setting of the palliative care oxygen therapy, I performed and published a review of the literature in which I identified health status/health-related quality of life, respiratory symptom burden and emotional distress as the main patient reported outcomes which can be further studied and refined for this purpose.

3.4.2 Health-related quality of life/health status/quality of life

In a study performed to assess the effects of a 7-day course of palliative oxygen therapy in patients with various advanced non-malignant diseases or cancer, the quality of life was evaluated using a generic questionnaire, the McGill Quality of Life Questionnaire, which failed to show any significant improvement in its scores in patients with oxygen therapy as compared to those on room air (Abernethy et al., 2010).

In the setting of palliative oxygen therapy, the quality-of-life evaluation raises some methodological aspects; these are mainly related to the choice of the tool(s), which is crucial for the practical relevance of such an assessment. If the relief of the dyspnea is firstly considered, then a disease-specific questionnaire should be used. In the case of diseases such as COPD, congestive heart failure or lung cancer, the oxygen therapy is the most commonly prescribed therapy. However, apart from dyspnea, other symptoms such as fatigue and other components
of the quality of life such as psychological or social domains are important for patients who are prescribed for palliative oxygen therapy. If these aspects are to be considered, they are best assessed by a generic questionnaire, that is, a tool that can be applied irrespective of the underlying pathology. A combined generic and disease-specific questionnaire could be feasible to evaluate most if not all possible aspects of the quality of life.

However, the amount of data supporting the beneficial effects of palliative oxygen therapy on HRQoL is very low, probably because most of the prospective studies evaluating the outcomes of palliative oxygen therapy focused mainly on dyspnea burden and only marginally assessed the quality of life.

3.4.3. Respiratory symptom burden: palliative oxygen therapy & refractory dyspnea

The hospice movement has become increasingly involved in the management of life-threatening, both malignant and nonmalignant diseases, which is currently approached in a multidisciplinary manner. Dyspnea is the final, tragic symptom of COPD and many other respiratory diseases but can become severe and distressing even before the end-of-life stage and can represent a therapeutic challenge. Dyspnea is one of the most distressing symptoms experienced by patients. It is a combination of a ‘sensation’ (neural activation resulting from stimulation of a receptor) and a ‘perception’ (reaction of the individual to that sensation) (ATS 1999). Dyspnea refractory to the usual therapy represents an indication for palliative care that should be provided either in the pulmonary disease unit or in the palliative care unit. Currently, the majority of the patients are more likely to be treated for this symptom in the former than in the latter units. The main aims of palliative care oxygen therapy are to reduce the severity of respiratory symptoms and especially that of dyspnea and to improve the functional status (Uronis et al., 2011).

However, the overall effects of this therapeutic method in relieving dyspnea are rather modest and surpassed by those of opioids and benzodiazepines(Mahler, 2013). This might be explained by the fact that the recommendations do not take into account the degree of hypoxemia in indicating the necessity for palliative oxygen therapy.

The precursor of palliative oxygen therapy, the non-continuous oxygen therapy COT (NCOT), was defined as a daily regimen of less than 12–15 h administered regularly or on an intermittent basis and was designed to reduce dyspnea and to improve the quality of sleep in patients with COPD or with chronic heart failure.

The previous studies evaluating NCOT effects in smaller samples demonstrated a minimal effect of the nocturnal regimen and a clear beneficial effect only in the case of hypoxemia-related dyspnea in COPD (NOTT, 1980, Chaouat et al., 1999, 1980, Restrick et al., 1992, Waterhouse and Howard, 1983).

The most supportive data subsequently came from a study performed within the Danish Registry evaluating the effects of NCOT on breathlessness, well-being, sleep quality and quality of life in 174 patients, 82 receiving regular nocturnal oxygen therapy and 92 receiving it on demand. The overall mean age of the patients was 68.9 years, 25.4% were hypoxemic, the average time spent on oxygen was 5.1 and the diseases for which the oxygen therapy was recommended were COPD (51.1%), cancer (23.4%), cardiac disease (9.9%) or neuromuscular disorders (5%). Dyspnea was evaluated using a 0–10 visual analogue scale (VAS). The most beneficial effects of NCOT were detected on dyspnea and quality of life. The proportion of patients with dyspnea VAS score of at least 5 was 89% before the start of oxygen therapy, and this decreased to 50% under oxygen. The proportion of patients with a dyspnea reduction of at least the minimal clinically important difference (0.5 units of score) was 76.3%. In 43.2% of patients, dyspnea improvement was associated with a similar effect on physical activity. The largest therapeutic effect was detected in patients who were ex- or non-smokers and who had a more severe dyspnea at baseline (Ringbaek et al., 2001).

It is currently accepted that the NCOT can be given during rest or during exercise. The latter is called ambulatory oxygen therapy and was found to decrease dyspnea severity in patients with exertional mild hypoxemia (McDonald et al., 1995, Eaton et al., 2002).

Palliative oxygen therapy is aimed (at least in theory) at reducing dyspnea irrespective of if it is related or not related to the physical activity, and therefore, both continuous and non-continuous regimens can be used for symptom alleviation.

However, little is known which of these regimens is appropriate for which dyspnea characteristics. The severity of this symptom was actually considered to be the main reason for prescribing palliative oxygen therapy in a study performed in Australia and including 5203 patients, finding that oxygen therapy was more likely to be prescribed for patients with more severe dyspnea with a VAS score of 7.6 (on oxygen) than for those with a VAS score of 4.2 (without oxygen) ($p < 0.01$) (Currow et al., 2008).

In a prospective 4-year cohort study performed in Australia, palliative home oxygen therapy was prescribed in about 21.1% ($n = 1239$) of a population of 5862 patients covered by a community palliative care service. The impact of oxygen therapy on dyspnea was assessed via a VAS (ranging from 0 to 10) at baseline (before oxygen initiation) and 1 or 2 weeks afterward in 413 subjects, and it was found that the mean baseline dyspnea score was 5.3 and that the home oxygen therapy had no significant impact on dyspnea severity irrespective of the underlying disease or

demographic factors. Particularly in patients with oncological conditions receiving home oxygen therapy, it was found that this therapeutic method had no significant impact.

Therapy responders were patients who at 1 or at 2 weeks exhibited a dyspnea improvement of at least 20%, and 115 fell in this category (Currow et al., 2009).

However, in this study, the analysis was not performed according to the hypoxemia degree, the type of oxygen regimen used was not clearly mentioned (i.e., continuous or burst) and the scale used was only a quantitative visual scale and not a dyspnea questionnaire.In a most recent study 239 patients with refractory dyspnea caused by various diseases such as COPD, lung cancer and other respiratory or cardiac diseases were enrolled and were randomized to receive oxygen therapy (120) or to breath room air (119), and dyspnea was assessed using two different scales and with a diary covering various symptom dimensions and quality of life was also evaluated. Oxygen therapy failed to improve dyspnea significantly compared to the room air irrespective of the time of the day when it was measured (morning, evening) and the largest effect was detected in patients with moderate to-severe symptoms (Abernethy et al., 2010).

The above-mentioned studies all included a mixed population of patients with both oncological and non-oncological conditions, and their results were rather concordant and not supporting the use of palliative oxygen therapy as a therapy for refractory dyspnea.

If COPD is taken into consideration, the existing data might be in favor of the effectiveness of palliative oxygen therapy even in patients with mild or no hypoxemia and who consequently do not qualify for domiciliary oxygen therapy. In fact, a meta-analysis performed on 18 trials that included 702 patients reported that oxygen therapy was able to significantly reduce the dyspnea level (Uronis et al., 2011). Such results support the use of palliative oxygen therapy beyond the current indications of home oxygen therapy, but still further studies should be carried out in order to support this approach.

The same reasoning might also apply for patients with dyspnea due to end-stage heart diseases; however, in this population, there were only few studies evaluated the effectiveness of palliative home oxygen therapy and therefore more studies should be carried out to obtain conclusive and reliable results (Clark et al., 2011).

In patients with oncological conditions and mainly with lung cancer dyspnea irrespective if transient or persistent can occur in 20–70% of them. However, the more episodic character of dyspnea, the higher the likelihood of normoxemia and the more common association of dyspnea with pain might make the oxygen therapy for palliative purposes to be less appropriate.

In fact, in patients (n = 134) with cancer who were normoxemic or with mild hypoxemia while experiencing dyspnea refractory to other therapies, palliative oxygen was not able to improve significantly the symptom severity (Uronis et al., 2015).

Therefore, the role of oxygen in the management of dyspnea in non-hypoxemic oncological patients is questionable despite its wide clinical use.

In such patients, opioids should be used as the first-line therapy, whereas in patients with dyspnea and hypoxemia, the initial use of oxygen seems to be more plausible (Ben-Aharon et al., 2012, Qaseem et al., 2008).

3.4.4 Effort tolerance & functional status

Ambulatory oxygen was evaluated for its ability to improve not only dyspnea and quality of life but also for its effects on effort tolerance and functional status (Criner, 2013, Moore et al., 2011)

3.4.5 Emotional distress and cognitive impairment

People with severe progressive disorders are often subjected to a high risk of psychological distress that has a complex etiology.
The most commonly encountered disorders are represented by anxiety and depression; their prevalence increases toward the end-of-life stage, and their management usually requires a multidisciplinary approach involving physicians, social workers and spiritual assistants (van Laarhoven et al., 2011, Kramer, 2013). In the case of patients with COPD, for example, the prevalence of anxiety is three times higher than that in the normal population and depression is also commonly encountered, and both have a negative impact on quality of life and disease-related morbidity (Brenes, 2003, Wilson, 2006).
In patients with hypoxemic COPD, such symptoms are directly related to the underlying hypoxemia and it is expected that domiciliary oxygen therapy is able to reduce their severity in an indirect manner. However, the data on this specific disease population are scarce: for example, in the NOTT study, the neuropsychological status was evaluated in both nocturnal and continuous oxygen arms (n = 150 patients in total), and it was found that at 6 months, it improved the mood status in a comparable manner in both study subsets. At 1 year follow-up, patients who underwent COT had significantly improved mood status as compared to patients under nocturnal oxygen therapy (Heaton et al., 1983).
In a subsequent study performed only in 10 patients, the therapeutic effects of home oxygen therapy were apparent although there was no statistical significance after the first 3 months (Hjalmarsen et al., 1999).
Cognitive impairment was detected in patients with COPD and is considered to be related to hypoxemia, and home oxygen therapy was reported to reduce the risk of its development (Thakur et al., 2010).
In the case of palliative oxygen therapy, however, it is not known whether the therapy can improve the mood status significantly.
Therefore this aspect should be further evaluated and in case of a demonstrated therapeutic benefit, this should be used as an argument for a wider use in palliative care setting.

Conclusions
It should be mentioned that palliative care oxygen therapy still lacks definite criteria of indication such as those in force for long-term/domiciliary oxygen therapy. As I previously mentioned the generic indication is the treatment of refractory dyspnea in palliative care setting but the few studies available demonstrated that this method was not universally effective: patients who were normoxemic or who presented with milder hypoxemia during the episode of refractory dyspnea,

or (those having continuous refractory dyspnea) were less likely to benefit from this method. Therefore it can be concluded that further studies are needed in order to find out which is the threshold value for hypoxemia beyond which this method is really effective. This approach is similar to that used to define the current criteria for long-term/domiciliary oxygen therapy.

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3.4.6 Conclusions

In end-stage COPD, palliative care is still seen as end of life care only whereas the benefits of the early palliative care are less well known. This is due to the fact that currently there are no validated criteria for referring COPD patients to the palliation, to the inappropriate knowledge of palliation at both specialist and family medicine levels and to the reticence of patients and their caregivers in accessing this type of medical service.

There are many outcome measures which are worth being considered when evaluating a COPD patient as a potential candidate for palliation and these includes not only physical outcomes but also social or spiritual outcomes for example.

As far as the palliative oxygen therapy is concerned there is a need to better characterize it in terms of indications in end-stage COPD respectively in comorbid COPD. There are various outcome measures which can be used to document the efficacy of this method and this can include health status/health-related quality of life but further studies are needed in order to document their relevance and their practical applicability.

Some of the issues related to palliative oxygen therapy and discussed in the above mentioned review are also found in the latest version of the American Thoracic Society guidelines on home oxygen therapy for adults with chronic lung disease. According to them palliative oxygen therapy should be prescribed as I mentioned above for dyspnea relief and it can be done using nocturnal, continuous, ambulatory or short-burst regimens (Jacobs et al., 2020).

SECTION II. FUTURE PROJECTS IN THE ACADEMIC, PROFESSIONAL AND RESEARCH FIELD

The habilitation is going to open new horizons in academic, clinical and research fields. They are summarized below in this section, the largest elaboration being done for research field where I plan to take over the research findings previously obtained to further use them and to integrate them in the setting of early palliative care.

II.1 Future projects in academic field

As an academic physician with habilitation certificate I plan to further advance my career by developing the main activities related to the teaching. I am currently an Associate Professor and I teach Palliative Care to nursing student. I plan to promote to Professor and to continue to teach on this topic. In order to fulfill this desiderate I plan to use some of the findings and approaches described in the previous section in order to improve the quality and the practical applicability and in order to diversify the range of topics included in the teaching curriculum. It is very well known that in Romania palliation is rather developed for oncological conditions whereas some of the non-oncological conditions such as COPD are practically not specifically considered. I plan to integrate in the teaching approach some of the aspects which are relevant for the future nurses and which are discussed in Section I. I have already applied this procedure with the Edmonton Symptom Assessment Scale (ESAS) which is used by my student at the bedside and this tool proved to be very interesting and very useful to assess the palliative care needs in patients with end-stage COPD hospitalized in the clinic where I am currently working. Therefore I am convinced that this experience can be further fructified to translate in novel teaching topics methods or findings previously discussed.

II.2 Future projects in professional (clinical) field

As mentioned in Section I, I am currently a Consultant in Pulmonary Disease at the University Hospital of Pulmonary Disease in Iasi. I also hold a supra-specialty certificate in Palliative Care. Given the fact that the need for palliative care in COPD is recognized in this thesis based on the characteristics of the patients hospitalized in the clinic where I work and given my interest in better defining early palliative care in COPD, I pla to start developing a clinical framework which should be able to identify the patients in need for palliative care. For this exercise the knowledge described in this thesis is very useful as it allow me to focus on identifying the needs and on developing simple interventions which should be effective on both short- and long-term basis.

II.3 Future projects in research field

In section I elaborated on the importance of health status as an outcome measure in COPD describing its potential applications with various evidence coming from the literature and from the own research and in the end of this section I started to discuss the current knowledge regarding

palliative care for end-stage COPD. I considered this approach in order to better introduce the future research projects:

- Validation of criteria for early (proactive) palliative care in end-stage COPD
- Identification of symptom (respiratory and extra respiratory) clusters as indicators of necessity for early palliative care in end-stage COPD
- Frailty as a patient-reported outcome measure in early palliative care in end-stage COPD

II.3.1 Early palliative care in end-stage COPD

In oncology there is no current border between curative and palliative care as once considered as being appropriate. The diagram presented in Fig 14 demonstrates that the effective palliative care starts nowadays to add on to the curative therapy even when the disease is still considered to be curable based on the criteria of good prognosis identified at that certain moment.
Earlier palliative care is able to improve health status/health-related quality of life in various forms of cancer and there is also growing evidence that early palliative care can significantly increase survival duration (Temel et al., 2010).
This evidence and the other coming from future studies can seriously challenge the current definition and operational framework set up by the World Health Organisation according to which palliative care is not able to prolong survival but to improve the suffering and the quality of life. Early palliative care therefore can have the potential to become that component of palliative care which is actually able to improve survival.
In chronic disease setting the early palliative care is also needed, but much less is known on how early palliative care should be and therefore in prevalent diseases such as COPD the moment of considering palliative care is not clearly delineated. It cannot be said that the criteria for palliative care referral in COPD are missing but in the current form they are rather able to be used in the end of life frame, ie for comfort therapy and not for proactive therapy.
Therefore I plan to undertake research in which I attempt to:

- Evaluate validity and the practical applicability of patient-reported outcomes other than health status/health-related quality of life/quality of life in early detection of palliative care needs in patients with end-stage COPD
- Elaborate and validate in routine clinical practice a set of palliative care criteria which should be able to validly be applied when early palliative care is also contemplated I end-stage COPD
- Elaborate and evaluate the effectiveness of a set of minimal interventions of early palliative care which can be done in hospital by the palliative care specalised mobile team. This team can be functional and effective in healthcare units in which there are no palliative care sections but there is a lot of palliative care need

With these overarching objectives I therefore plan to apply to the bedside the results of the planned research.

II.3.2 Symptom clusters as a clinical marker of the need for palliative care in end-stage COPD

The modern concept of symptom cluster was coined about two decades ago as a potential model for a better more integrated management (Dodd et al., 2001). Symptom cluster in its original version was defined as a group of two or more symptoms which are correlated and which can share or not the same etiology (Kim et al., 2005, Barsevick, 2007). However the clustering of symptoms to characterise a certain disease is much older and represented the foundation for learning of medicine. The relationship among the symptoms in a cluster was defined by Williams and collaborators as one of the following (Williams, 2007):

- The symptoms of a cluster share a common etiology
- In a cluster of symptoms there is an "index" symptom which can trigger or can exacerbate other symptoms
- Treatment of a symptom can cause side-effects represented by other symptoms

Such an approach towards understanding the intra-cluster relationships is very helpful in identifying common mechanisms such as those of biological, psychological or social which ones outlined, can become therapeutic targets for cluster management.
Oncology was the first medical specialty in which the science of symptom clusters found the most immediate applicability.
The Symptom Cluster in Children and Adolescents with Cancer was the first theoretical model which conceptualized symptom cluster model based on three components:

- Antecedent component including personal, environmental or disease-related factors
- Symptom cluster of three most prevalent and correlated symptoms represented by pain, sleep disturbances and fatigue
- Outcome component refers to the impact on functional and health status, on child growth and development, and on the relationship between symptom cluster and disease course

The main limitations of this model were represented by the fact that in that incipient form this model was found not be appropriate for the adults and also by the fact that it strictly referred to one cluster of only three symptoms (Xiao, 2010).
Subsequently further refinements of the definition of symptom clusters evolved in the same oncological setting: three or more concomitant symptoms related to each other or two or more symptoms that occurred together. Two main approaches were described to identify such symptoms: most common symptoms and all possible symptoms and whereas the first method is generally able to detect one cluster, the second one generates several clusters (Xiao, 2010).
Subsequently Tsai and collaborators evaluated the relevance of symptom cluster approach in patients with advanced cancers referred to a palliative care service: in prospective study which included 427 patients hospitalized for advanced cancer having a median age of 66 year, and with lung respectively liver respectively colorectal cancers the most prevalent in the sample studied, a median survival of 13 days was demonstrated. Most of the patients (>75%) had a functional status

measured with ECOG scale score of 3 or 4 and as far as the symptom prevalence was concerned, the analysis demonstrated that fatigue was found in almost all patients (94.2%), followed by weakness (93.9%), anorexia (87.1%), and pain (83.8%). In the same study the severity of symptoms was also measured via Symptom Reporting Form, a tool previously validated by the same team: severity analysis found that anorexia was the most severe symptom (1.75) and fatigue (1.73), weakness (1.72), pain (1.35), and constipation (1.19) followed. Further analysis of the symptom clusters identified four such associations which were named "loss of energy" (LE: fatigue and weakness), "poor intake" (PI: anorexia, taste impairment, xerostomia, dysphagia and constipation), "autonomic dysfunction"(AD: restlessness, heat episodes, dizziness, insomnia and night sweats) and "aerodigestive impairment"(AI: nausea and/or vomiting, abdominal bloating and dyspnea). In terms of severity of the symptom cluster, LE was found to be the most severe one, followed by PC and AD. Furthermore symptom clusters were found to correlate with survival duration or with functional status impairment and this is among the first indirect evidence of relevance of symptom cluster approach in palliative care (Tsai et al., 2010).

A subsequent analysis reviewed the data from several studies evaluating the management based on symptom cluster (Kwekkeboom, 2016).

According to this author finding a common pathogenic pathway for a symptom cluster was the easiest manner to manage it: for example in oncology chemotherapy induced neuro-inflammation may result in symptom clusters represented by fatigue, sleep disturbances, impaired appetite, mood or cognitive disturbances and their impact on health status for example might be reduced by approaches which aim at severing the common pathogenic pathway.

In terms of management approaches for such clusters, there are two main types of interventions: interventions which are aimed to target several/all symptoms in the cluster and interventions that are focused on a single symptom which is the one best correlated with the others in the cluster. Multiple symptom interventions were mainly educational and behavioral interventions directed towards a better understanding by the patient and the family of cancer course under treatment and of potential symptoms which can appear. In this manner the ability of the patient to cope with the disease and to engage himself in self-management of such symptoms is expected (Kwekkeboom, 2016, Given et al., 2004) .

The other approach is aimed at reducing the symptom burden (secondary outcome) as a result of targeting and decreasing a single symptom (primary symptom). One such example is represented by an intervention which was done on cancer patients receiving chemotherapy and consisting of behavioral therapy to reduce the impact on insomnia: it was found that this intervention was also able to reduce fatigue and depression levels(Fleming et al., 2014).

Some other interventions are multimodal and might target effectively various symptom clusters whereas others target a certain symptom cluster : for example in a study performed in patients who underwent hematopoietic stem cell transplant, an intervention combining exercise training with relaxation techniques and with psychosocial support was found to be effective on reducing the burdens of gastrointestinal, cognitive, physical functioning and oral symptom clusters (Jarden et al., 2009).

Single symptom cluster interventions were also found to be effective: for example in a study evaluating the effectiveness of a psychotherapeutic intervention developed to target a cluster comprising pain fatigue and sleep disturbance in patients with advanced cancer, demonstrated a reduction in the burden of the whole cluster as a results of this intervention (Kwekkeboom et al., 2012).

Finally symptom clusters were also identified in patients with advanced cancer attending a hospice: the first cluster was represented by physical related symptom(pain, cough, dry mouth, difficulty in swallowing, and lack of appetite), the second was represented by gastrointestinal-related symptom (nausea and vomiting), the third respiratory-related symptom (dyspnea) and the fourth by psychological-related symptom(difficulty in concentrating, sadness irritability, sweating, dizziness, drowsiness, worrying and lack of energy. The first and the last clusters were found to be strong predictors of the quality of life (Omran et al., 2017).

Symptom clusters and their impact on quality of life were also studied outside oncological setting: for example in a study performed in patients with heart failure identified three main clusters sickness impact behavior represented by anxiety, depression, fatigue, daytime sleepiness and cognitive impairment, discomfort of illness including dyspnea, edema and pain and gastrointestinal symptom clusters. Quality of life was generically defined as life satisfaction and was found to be the most negatively impacted by the sickness impact behavior (Salyer et al., 2019).

Symptom cluster science was also applied in COPD for various purposes, one of them being related to the ability of such clusters to predict exacerbations and especially those severe and leading to hospitalization (Sanchez-Morillo et al., 2015).

Another study performed in COPD patients focused on anxiety-related clusters and identified four such clusters: general somatic distress, fear, nervousness, respiration-related distress and a greater fear was associated with a more impaired disease mastery (Breland et al., 2015).

Respiratory as well as extra-respiratory symptoms were assessed in COPD patients in another study and three distinct clusters were identified: respiratory-functional cluster (dyspnea, physical functional status and dry mouth), mood cluster (anxiety and depression) and fatigue sleep cluster (sleep disturbance and fatigue). These clusters were found to depend on the age, educational level and monthly income and their burden significantly influenced health status measured with CCQ, ie the more severe the symptoms in a clusters were, the more impaired the health status was (Lim et al., 2017).

Symptom clusters might be an important therapeutic target in early palliative care for COPD. Some of the studies which are briefly discussed below demonstrated that in patients with advanced cancer for example the attempt to approach each symptom individually might be associated with useless polypharmacy and with increased risk of medication related side-effects.

Some of these clusters might be directly related to a sustained impaired of the functional status and therefore might be indicative of the need for early palliative care.

Symptom clusters might also have a prognostic value and might help in the same setting once the need for palliative care is identified, to better estimate survival and consequently to tailor in an

appropriate manner the whole management approach (more complex if improvement of quality of life is still envisaged, or developed to induce comfort as end of life palliative care).
As mentioned in various sections of this thesis, in patients with advanced diseases including cancers, the number of symptoms can increase with the decrease of survival and towards the end of life these symptoms can be really difficult to control and a source of major discomfort for the patient and for the family.
In my previous original research presented in section 1, I demonstrated that in patients hospitalized for a COPD exacerbation the number of concomitant extra-respiratory symptoms can significantly impact on health status respectively on functional status. I plan to further expand this research direction in order to:

- find out which are the symptom clusters which can be associated with the worst functional status respectively health status in end-stage COPD patients
- to test such clusters in another prospective study in which to also see the relationship with frailty and with disease morbidity in end-stage COPD patients
- to document which symptom clusters are the easiest to be diagnosed and managed in such patients
- to perform a subset analysis in patients with end-stage COPD in order to identify symptom clusters which are clinical markers/sentinels for the need of early palliative care respectively terminal care

Documentation of symptom clusters is not difficult in clinical practice and therefore the results of the above described research has good premises of clinical applicability after validation.

II.3.3 Outcomes of frailty in pro-active palliative care in end-stage COPD

In my conceptual paper discussing potential outcome measures for palliative care in patients with COPD I mentioned that functional status could be an important outcome measure in palliative care for COPD.
Frailty is currently seen as an aging-related phenotype encompassing several major traits such as "shrinking", low activity or weakness(Fried et al., 2001a). At the first glance many of the defining traits of the frail phenotype are also items used to characterize an impaired functional status. Frailty is currently considered among the outcome measure in many chronic conditions of the aging but little is still known on the importance frailty in COPD patients and more importantly if this can be used to characterize in more comprehensive manner the impairment of functional status in COPD. Previous studies discussed above, clearly delineated a relationship between frailty and increased risk of morbidity or mortality. In COPD frailty is scarcely studied, more data being available for defining criteria for frailty such as sarcopenia, weight loss or fatigue than for frailty itself.
In other chronic progressive diseases such as heart diseases, frailty itself was found to be associated with a more adverse prognosis. In COPD such relationship has not been investigated yet but might be of particular interest in elderly patients who belong to the frequent exacerbator phenotype. This COPD phenotype has received a particular interest over the last few years since its identification

due to the fact that it is associated with increased mortality and with increased utilization of healthcare resources. Therefore attempts to document what makes such patients more prone to exacerbations and to severe exacerbations in particular identified various factors related to etiology (smoking exposure), pathogenesis of the disease (inflammation more prominent at bronchial level), pathogenic epiphenomena (chronic infections of the airways), nutritional status or presence of comorbidities. Physical deconditioning is also thought to play a role in this disease outcome but few data are available to strongly support this.

Most importantly frailty in itself still unrecognized in COPD despite its demonstrated relevance in other populations of patients. In COPD in particular the predictive capacity of frailty for mortality is going to be of particular interest in the subsequent years in the elderly subset of the patients and in a similar manner it might be both interesting and useful to study frailty as a potential predictor of frequent hospitalisations in aged frequent exacerbators. Such supportive data are not only useful for research purposes but are important for the routine care of frail COPD patients who might benefit from a more integrated, multidisciplinary approach of their disease targeting major unmet medical needs including frailty.

The relevance of frailty in COPD is not only based on consideration that many of patients with this disease can develop it when they become older than 65 years of age but also by the fact that both the state (frailty) and the disease (COPD) negatively influence each other: frailty can increase the disease morbidity and the mortality risk whereas COPD can accelerate the progression of pre-frail state to frailty or the aggravation of the latter. By identifying COPD patients at risk of becoming frail can trigger therapeutic measures which by reversing pre-frailty or by improving frailty have the potential to indirectly improve the outcome of the underlying disease.

The identification of frailty in COPD patients and especially the so called “irreversible” frailty is particularly important in advanced COPD because this has to trigger the assessment for palliative care needs in such persons. As the functional status is a key outcome measure of prognosis in palliative care and as frailty, based on the data discussed above can be considered a measure of severely impaired functional status, then it is now clear why frailty should be considered in COPD requiring this type of care and should be taken into consideration when evaluating the prognosis of the disease.

Furthermore the current definition of frailty still focuses on physical frailty not taking into account yet that in chronic advanced diseases what makes the patient to be frail cannot be limited to the functional status ie to the ability of performing daily activities.

More recently, however, psychological frailty (emotional and cognitive) has been advocated as being relevant for the definition of frailty: this was due to the growing evidence that this is also a marker of disability, morbidity or mortality: for example in a cohort of patients with coronary artery disease the combined physical+psychological frailty index was able to predict disability and the subsequent decline in health-related quality of life in these patients (Freiheit et al., 2010).

Such patients with advanced chronic disease can be considered frail from other points of view, for example can be socially or spiritually frail and these traits should be also taken into account if to include frailty as an outcome measure for palliative care (Teo et al., 2017, Kirby et al., 2004).

The fact that palliative care addresses the physical, psychologic, social and spiritual impairments and that in the disease course the impairment progresses often rapidly to disability qualifies frailty to be considered with all its four potential features as an outcome measure of disability in palliative care in general and in COPD in particular. Furthermore it is necessary to study if the current age threshold of 65 which is considered when measuring physical frailty should be kept in palliative care.

In the light of the evidence above discussed I plan to do clinical studies which should address the following hypotheses:

- Frailty is an important outcome measure and a criterion for the first referral to palliative care
- In palliative care frailty cannot be evaluated only for its physical features but a more comprehensive frailty model should be developed and validated
- To develop and validate a questionnaire able to identify the multidimensional frailty in COPD patients who need palliative care; by the means of this tool frailty can be used as a patient reported outcome measure to complement the so called objective measures of frailty
- In patients with advanced COPD frailty can be detected more often in elderly but also at younger ages

It is also necessary to document the pre-frailty criteria in order to anticipate the need for palliative care. The results of these researches described above can also have clinical applicability especially because they can speed up the identification of COPD patients with palliative care needs.

If we are able to identify appropriate criteria for early palliative care in COPD, if we are able to identify symptom clusters as early signs of the potential appropriateness for palliative care and if are able to evaluate more often pre-frail patients in an attempt to anticipate the needs for palliative care, then this type of care has all good auspices to be timely, effectively and proactively implemented in COPD patients.

I plan to do this research with undergraduate students and with PhD students. Working with motivated undergraduate students was very productive for me, two of my original articles, the one on health status during hospitalisations for COPD exacerbations and that on the prevalence and the number of extra-respiratory symptoms being actually parts of the graduation projects of them and addressing very interesting and actual topics.

With the PhD students I am going to further use my experience but to bring the research to a next (superior) level by considering novel research methods which require more time to become "mature" and by refining and expanding the existing ones.

I also plan to consider various competitive funding sources and to try to test my research ideas in powerful national or international consortia which are able to offer the opportunity of addressing an issue from different points of view.

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