Tampere University

HEIDI RANTALA

Symptoms and Survival in Patients with Chronic Respiratory Insufficiency

Tampere University Dissertations 523

Tampere University Dissertations 523

HEIDI RANTALA

Symptoms and Survival in Patients with Chronic Respiratory Insufficiency

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the auditorium F115
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 14th January 2022, at 12 o'clock.

ACADEMIC DISSERTATION

Tampere University, Faculty of Medicine and Health Technology
Tampere University Hospital, Department of Respiratory Medicine
Finland

Responsible supervisor and Custos	Professor Lauri Lehtimäki Tampere University Finland	
Supervisor	Professor Juho Lehto Tampere University Finland	
Pre-examiners	Docent Terttu Harju University of Oulu Finland	MD, PhD Annamari Rouhos University of Helsinki Finland
Opponent	Professor Tarja Saaresranta University of Turku Finland	

The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Copyright ©2022 author

Cover design: Roihu Inc.

ISBN 978-952-03-2214-4 (print)
ISBN 978-952-03-2215-1 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-2215-1

PunaMusta Oy – Yliopistopaino
Joensuu 2021

ACKNOWLEDGEMENTS

This study was carried out at the Department of Pulmonology of Tampere University Hospital and the Faculty of Medicine and Health Technology of Tampere University, Finland, from 2015 to 2021. This has been a long journey with different leaves on the line. This thesis would not have been possible without the help and support of the wonderful people around me.

First, I would like to express my deepest gratitude to my inspiring and supportive supervisors. Professor Lauri Lehtimäki, you have always given me constant support and helped me to get through difficult times. It was a great advantage to have your expertise and comprehension on this project. Professor Juho Lehto, you have been an encouraging mentor and always believed me, even when I did not believe in myself. You have always pushed me forwards; otherwise, this thesis would not have been finished at this time. Working with you both has always been easy and fast, as you have always found time for all my questions. With good humour, we survived all the adversities.

Sirpa Leivo-Korpela, MD, PhD, I have always considered you to be my third supervisor. Thank you for all the support and help you have given me along the way. Your expertise has been valuable. You have taught me many things about treating patients with chronic respiratory insufficiency. You also helped me to associate clinical work and study.

Thank you to the official reviewers of my thesis, docent Terttu Harju, MD, PhD, and Annamari Rouhos, MD, PhD, for their valuable comments and feedback, which markedly improved the final version of this thesis. I appreciate your time and efforts for my manuscript. I am highly honoured to have Professor Tarja Saaresranta as my opponent.

Sirpa Valonen, specialized nurse, for her valuable help with the patients requiring noninvasive ventilation. I truly appreciate your valuable comments and your expertise. It has been rewarding to discuss all the difficult cases with you. I would also like to thank all the other nurses who treat patients in the respiratory insufficiency unit of Tampere University Hospital, as well as in our acute pulmonary wards. Without your great efforts, this study would not have been possible.

Docent Seppo Saarelainen, Kirsi Laasonen, MD, PhD, and Hannele Hasala MD, PhD, for enabling me to perform research by arranging some occasional leave from clinical duties. Thank you to Kirsi for getting me interested in this study and for your guidance with respiratory insufficiency, as well as encouraging the development of practices for treating patients with chronic respiratory insufficiency. Thank you to Hannele for co-operating in the different respiratory insufficiency projects.

I also warmly thank the doctoral studies follow-up group. I would also like to thank Anni Hanhimäki, MD, and Siiri Kettunen, MD, for helping with the data collection. Thank you to Erja Kiviharju for arranging all the papers for the leaves from the clinical work for this study.

Mika Helminen, MSc, for his help and guidance with the statistical analyses. I would not have been able to perform all the analyses without your help.

I want to thank all my wonderful colleagues and coworkers in the Department of Pulmonology at Tampere University Hospital. You all have played an enormous role in the treatment of these patients and thus are part of this study. I appreciate your help and support during all these years. Thanks especially to my colleagues Johanna Pakkasela, MD and Virve Korhonen, MD, PhD, for their friendship; it has been rewarding having discussions with you. We also have had a great respiratory insufficiency team treating patients with chronic respiratory insufficiency. Many new ideas have come as a result of this great multiprofessional team.

My godfather, Voitto Kotti, MD, for being always a role model for me and showing me the world of study concerning our earlier common study. Thank you for all the support and guidance you have given me during all these years.

Thank you to all my friends and relatives for their relaxing company and giving me other things to think about. These last 6 years have kept me busy, but I am glad you all have understood. Elina Lahnaoja for our precious talks, even though we currently live far away from each other. My cousin Elina Kotti for always being there. I have always considered you as almost my sister. Annukka and Eugén Bergman, as well as Kai Vilevaara for giving me other things to think about in our band trainings.

I want to express my gratitude for my family, especially my parents, Merja and Kalevi Toivonen, for your endless understanding and support, as well as your love throughout my life. You have always pushed me forwards and believed in me. Thank you for making this project possible by taking care of our children and giving them wonderful time with their grandparents. I also want to thank my

mother-in-law, Hilkka Rantala, and father-in-law, Aarne Rantala, for the great help and understanding you have given and for taking care of our children when I had to work. Thank you my godmother, Marjo Kotti, for taking care of our children and being a close friend to me. My brother, Antti Toivonen; you have influenced me throughout my life.

Finally, and most importantly, I want to thank my husband, Mikko Rantala. Without you, this study would not have been possible in many ways. Thank you for making me a clinical record form for recording data and giving me endless IT help. You have supported me through hard times and also been there in times of success. Thank you for your patience and understanding, even with long working hours. Thank you to my lovely daughters, Sofia and Sara. You are the joy of my life and bring happiness and activities in our lives.

This thesis was financially supported by grants from the Medical Research Fund of Tampere University Hospital, the Graduate Program of University of Tampere Medical School and the Faculty of Medicine and Life Sciences, the Väinö and Laina Kivi Foundation, the Tampere Tuberculosis Foundation, the Research Foundation of the Pulmonary Diseases and the Finnish Anti-Tuberculosis Foundation.

Pirkkala, November 5th, 2021

Heidi Rantala

ABSTRACT

Chronic respiratory insufficiency affects patients with diverse underlying diseases with varying progression and prognosis. Chronic respiratory insufficiency can derive from diffusion impairment or hypoventilation and is treated with long-term oxygen therapy or noninvasive ventilation. Many patients have advanced respiratory disease, with severe symptoms and impaired functional capacity affecting their everyday lives. It is important to recognize the total symptom burden and factors associated with poor survival to be able to provide comprehensive treatment and to make well-timed end-of-life plans for patients with chronic respiratory insufficiency.

The aim of this thesis was to describe the symptom burden in patients with chronic respiratory insufficiency and the symptoms associated with depression and dyspnoea upon exercise. The factors associated with survival and end-of-life characteristics were studied in patients with chronic respiratory insufficiency and the need for long-term oxygen therapy (LTOT) or noninvasive ventilation (NIV).

This retrospective study was based on the evaluation of medical records and death certificates. All the patients who visited the respiratory insufficiency clinic of Tampere University Hospital from 1.10.2016 to 31.10.2017 with completed Edmonton Symptom Assessment System (ESAS) questionnaires (n = 226) and modified Medical Research Council dyspnoea scale (mMRC) questionnaires (n = 101) were studied for symptom prevalence and severity. In the studies concerning survival and end-of-life characteristics, all patients with newly initiated devices for respiratory support (LTOT n = 195 or NIV n = 205) from 1.1.2012 to 31.12.2015 were included and followed up until 31.12.2017 or death.

The most common diseases causing the need for LTOT were chronic obstructive pulmonary disease (COPD) and interstitial lung diseases (ILDs) and the most frequent reasons for the need for NIV were COPD and obesity hypoventilation syndrome (OHS). Patients with chronic respiratory insufficiency suffered from many symptoms, of which dyspnoea, dry mouth, tiredness and pain upon movement were the most common. Depressive symptoms and severe dyspnoea upon exercise (mMRC score of 4) were associated with higher scores in all the ESAS categories compared with no depressive symptoms and milder

dyspnoea, respectively. The depression scores on the ESAS questionnaire correlated well with the scores on the Depression Scale (DEPS) questionnaire.

Altogether, 68.2% and 43.9% of the patients on LTOT and NIV died during the follow-up, respectively. The overall survival varied greatly among patients as a consequence of the heterogeneous underlying diseases, being shortest in patients with ILD and the need for LTOT (0.9 years). The survival of patients needing help in activities of daily living was shorter than that of those who were independent. Most of the deceased patients had a decision not to be resuscitated, but only a few had end-of-life care decisions, including ruling out intensive care and invasive ventilation. Nevertheless, these patients mostly died in the hospital and not at home.

In conclusion, patients with chronic respiratory insufficiency suffer from many severe and heterogeneous symptoms. Systematic symptom screening should be implemented in patients who are treated in respiratory insufficiency clinics. The timing of end-of-life decisions and advance care planning is difficult because of the heterogeneous underlying diseases and varying disease progression. However, even though many patients with chronic respiratory insufficiency have advanced disease with poor survival, end-of-life care decisions were made for only a few patients, as most of the patients died in the hospital. The discussion of end-of-life care, paying attention to patients' own wishes, should be part of the treatment plan of patients with chronic respiratory insufficiency at the time of initiation of LTOT or NIV unless lung transplantation is not an option. This is especially true in patients with interstitial lung disease as opposed to patients with COPD as the disease progression is more variable.

TIIVISTELMÄ

Useat vaihtelevasti etenevät ja ennusteeltaan erilaiset sairaudet voivat johtaa pitkäaikaiseen hengityksen vajaatoimintaan. Krooninen hengityksen vajaatoiminta voi johtua keuhkokudoksen kaasujen diffuusiohäiriöstä tai keuhkojen vähentyneestä tuuletuksesta, joita voidaan hoitaa pitkäaikaisella happihoidolla tai kaksoispaineventilaatiohoidolla (2PV-hoito). Monilla potilailla pitkälle edennyt keuhkosairaus vaikuttaa jokapäiväiseen elämään vaikeiden oireiden ja alentuneen toiminnallisen suorituskyvyn myötä. On tärkeää tunnistaa pitkäaikaista hengityksen vajaatoimintaa sairastavien kokonaisoirekuorma ja huonoon ennusteeseen vaikuttavat tekijät, jotta voidaan kohdistaa kokonaisvaltainen hoito ja tehdä hyvin suunniteltuja elämän loppuvaiheen hoitosuunnitelmia.

Tämän väitöskirjan tavoitteena oli kuvata pitkäaikaista hengityksen vajaatoimintaa sairastavien potilaiden oirekuorma sekä masennukseen ja liikkuessa tulevaan rasitushengenahdistukseen yhteydessä olevat oireet. Lisäksi tutkittiin pitkäaikaista hengityksen vajaatoimintaa sairastavien ja 2PV- tai happihoitoa käyttävien potilaiden ennusteeseen vaikuttavia tekijöitä ja elämän loppuvaihetta.

Tähän takautuvaan tutkimukseen kerättiin tiedot sairaskertomuksista ja kuolintodistuksista. Ensimmäisessä osatutkimuksessa selvitettiin oireiden esiintyvyyttä ja vaikeutta niillä potilailla, jotka olivat käyneet Tampereen Yliopistollisen sairaalan Hengitysvajausyksikössä ajanjaksolla 1.10.2016-31.10.2017 ja olivat täyttäneet Edmonton Symptom Assessment System (ESAS) kyselyn (n = 226) sekä muunnellun Medical Research Council (mMRC) hengenahdistuskyselyn (n = 101). Toinen osatutkimus koski ennusteeseen vaikuttavia tekijöitä, mihin otettiin mukaan ne potilaat, joille oli aloitettu aikavälillä 1.1.2012-31.12.2015 uusi laite pitkäaikaiseen hengityksen vajaatoimintaan (happihoito n = 195 tai 2PV-hoito n = 205). Potilaiden kuolleisuutta seurattiin 31.12.2017 asti tai mahdolliseen kuolemaan.

Yleisimmät sairaudet, jotka johtivat pitkäaikaiseen happihoitoon, olivat keuhkoahtaumatauti ja interstitiaaliset keuhkosairaudet ja yleisimmät sairaudet, jotka johtivat pitkäaikaiseen 2PV-hoitoon, olivat keuhkoahtaumatauti ja

obesiteetti-hypoventilaatio oireyhtymä. Pitkäaikaista hengitysvajausta sairastavat potilaat kärsivät monenlaisista oireista, joista yleisimmät olivat hengenahdistus, kuiva suu, väsymys ja kipu liikkuessa. Masennusoireet ja vaikea hengenahdistus liikkuessa (mMRC 4) olivat yhteydessä vaikeampiin muihin oireisiin kaikissa ESAS kyselyn arvioimissa oireissa verrattuna niihin potilaisiin, joilla ei ollut masennusoireita tai joilla oli lievempi hengenahdistus. Masennuspisteet ESAS kyselyssä olivat yhteydessä Depression Scale (DEPS) kyselyn masennusrajat täyttäviin arvoihin.

Yhteensä 68.2% happihoitopotilaista ja 43.9% 2PV-hoitoa saavista potilaista kuoli seuranta-aikana. Yleisesti ennuste vaihteli suuresti eri pitkäaikaista hengitysvajausta aiheuttavien sairauksien välillä, ollen lyhyin happihoitoa tarvitsevilla interstitiaalista keuhkosairautta sairastavilla potilailla (0.9 vuotta). Päivittäisissä toiminnoissa apua tarvitsevien potilaiden ennuste oli lyhyempi kuin niiden, jotka olivat itsenäisiä näissä toiminnoissa. Suurimmalla osalla kuolleista pitkäaikaista hengityksen vajaatoimintaa sairastavista potilaista oli ei elvytetä -päätös, käsittäen myös rajaamisen tehohoidon ja kajoavan hengityslaitehoidon ulkopuolelle, mutta selvästi harvemmalla oli oireenmukainen hoitopäätös ja valtaosa heistä kuoli sairaalassa.

Pitkäaikaista hengitysvajausta sairastavat potilaat kärsivät monista vaikeista ja vaihtelevista oireista. Potilaiden oireita pitäisi järjestelmällisesti seuloa vastaanottokäyntien yhteydessä. Oireenmukaisen hoitopäätöksen ja elämän loppuvaiheen suunnitelmien tekeminen on usein vaikeaa sairauksien vaihtelevan kuvan ja etenemisen vuoksi. Vaikka monella pitkäaikaista hengityksen vajaatoimintaa sairastavalla potilaalla on pitkälle edennyt sairaus ja huono ennuste, elämän loppuvaiheen suunnitelmia oli tehty harvalle, sillä suurin osa potilaista kuoli sairaalassa. Elämän loppuvaiheen hoidosta keskustelu huomioiden potilaan omat toiveet, pitäisi olla aina osana pitkäaikaista hengityksen vajaatoimintaa sairastavien potilaiden hoitoa siinä kohtaa, kun heille aloitetaan pitkäaikainen happihoito tai kaksoispaineventilaatiohoito, mikäli keuhkonsiirto ei ole heille mahdollinen. Erityisesti keuhkofibroosipotilaiden kohdalla keskustelut täytyy käydä heti laitehoidon aloituksessa, toisin kuin keuhkoahtaumataudissa taudinkulku on vaihtelevampaa.

CONTENTS

ABBREVIATIONS

ACP	Advance Care Planning
ADL	Activities of Daily Living
AHI	Apnoea-Hypopnoea Index
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
ATS	American Thoracic Society
AUC	Area Under the Curve
BDI	Beck Depression Inventory
BMI	Body Mass Index
BTS	British Thoracic Society
CAT	COPD Assessment Test
CCI	Charlson Comorbidity Index
CHF	Chronic Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
DALS-15	Dyspnoea-ALS-Scale
DEPS	Depression Scale
DMD	Duchenne Muscle Dystrophy
DNH	Do Not Hospitalize
DNR	Do Not Resuscitate
EOL	End-of-Life
EPAP	Expiratory Positive Airway Pressure
ERS	European Respiratory Society
ESAS	Edmonton Symptom Assessment Scale
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Hazard Ratio
ILD	Interstitial Lung Disease

IPF	Idiopathic Pulmonary Fibrosis
IPAP	Inspiratory Positive Airway Pressure
IQR	Interquartile Range
LTOT	Long-Term Oxygen Therapy
MIP	Maximal Inspiratory Pressure
mMRC	Modified Medical Research Council dyspnoea scale
MND-DS	Motor Neuron Disease Dyspnoea Scale
MRF-26	Maugeri Respiratory Failure Questionnaire
MSAS	Memorial Symptom Assessment Scale
NA	Not Available
ND	No Data
NIV	Noninvasive Ventilation
NPV	Negative Predictive Value
NRS	Numeric Rating Scale
OHS	Obesity Hypoventilation Syndrome
PAH	Pulmonary Arterial Hypertension
PaO_2	Partial Pressure of Oxygen in arterial blood gases
$PaCO_2$	Partial Pressure of Carbon Dioxide in arterial blood gases
pCO_2	Partial Pressure of Carbon Dioxide in blood gases
PPV	Positive Predictive Value
Ref.	Reference
ROC	Receiver Operating Characteristic
SGRQ	St. George's Respiratory Questionnaire
SNIP	Sniff Nasal Inspiratory Pressure
SRI	Severe Respiratory Insufficiency
VAS	Visual Analogue Scale
VC	Vital Capacity
15-D	15-Dimensional health-related quality of life
2PV-hoito	Kaksoispaineventilaatiohoito
6MWT	6 Minute Walk Test
95% CI	95% Confidence Interval

ORIGINAL COMMUNICATIONS

Publication I Rantala HA, Leivo-Korpela S, Lehtimäki L, Lehto JT. Assessing symptom burden and depression in subjects with chronic respiratory insufficiency. Journal of Palliative Care. Nov 2021.

Publication II Rantala HA, Leivo-Korpela S, Lehto JT, Lehtimäki L. Dyspnea on exercise is associated with overall symptom burden in patients with chronic respiratory insufficiency. Palliative Medicine Reports. 2021; 2:1, 1-6

Publication III Rantala HA, Leivo-Korpela S, Lehtimäki L, Lehto JT. Predictors of impaired survival in subjects with long-term oxygen therapy. Respiratory Care. 2019 Nov; 64(11):1401-9

Publication IV Rantala HA, Leivo-Korpela S, Kettunen S, Lehto JT, Lehtimäki L. Survival and end-of-life aspects among subjects on long-term noninvasive ventilation. European Clinical Respiratory Journal. 2020 Nov; 8(1):1840494

AUTHOR'S CONTRIBUTION

The study design in Studies I-IV was made by the author with the help of supervisors and other authors. The author did most of data collection from medical records and death certificates. The author analysed the data of all the studies with the help of supervisors and a statistician. The author wrote first drafts and was the primary author on all the papers with the support from other authors. The author submitted the papers to the journals and contributed the final version of the papers.

1 INTRODUCTION

Respiratory insufficiency can be caused by either a gas exchange disturbance in pulmonary alveoli, leading to a reduced level of oxygen in arterial blood, or hypoventilation, resulting in an increased level of carbon dioxide in arterial blood. The most common diseases underlying respiratory insufficiency are obesity hypoventilation syndrome (OHS) and advanced pulmonary diseases. The prevalence of chronic respiratory insufficiency seems to be increasing due to the increasing prevalence of obesity and chronic lung diseases, such as chronic obstructive pulmonary disease (COPD) (Cantero et al., 2020; Kotanen et al., 2019; Ng et al., 2014).

Most patients with chronic respiratory insufficiency live with severe chronic disease that is often undiagnosed and untreated. They thereby suffer from various symptoms that impair their quality of life (Janssen et al., 2011; Morris & Galicia-Castillo, 2015). Shortness of breath, also known as dyspnoea, is the most common symptom perceived by patients with respiratory diseases or chronic respiratory insufficiency (Carvajalino et al., 2018; Moens et al., 2014; Mokhlesi et al., 2008). Dyspnoea is also common in patients with chronic heart failure or chronic respiratory insufficiency due to neurological diseases (Janssen et al., 2011; Raghu et al., 2018). In addition to dyspnoea, patients with chronic respiratory insufficiency suffer from many other symptoms, which are derived from the underlying disease process, comorbidities and medication or treatment. Some symptoms, such as depression, may increase the perceived symptom burden even further and increase the need for hospitalization (Blakemore et al., 2019; Delgado-Guay et al., 2009; Miravitlles & Ribera, 2017; Rajala et al., 2017). Therefore, being aware of the overall symptom burden in patients with chronic respiratory insufficiency enables better targeted symptom management to reduce individual suffering.

Palliative care focuses on relieving symptoms in association with psychosocial support instead of treating the underlying disease at the point where the disease cannot be cured or the disease process cannot be slowed down (Lanken et al., 2008; WHO & WHPCA, 2020). Advance care planning (ACP), including the possibility for an individual to define and discuss preferences for care with health-

care professionals and family, is recommended if the risk of dying is within the following year (Boyd & Murray, 2010; Rietjens et al., 2017). Palliative and supportive care has been implemented in patients with advanced cancer, but it is still underused in patients with respiratory diseases, even though it is strongly recommended ("GOLD," 2021; Jabbarian et al., 2018; NICE, 2016; Raghu et al., 2011; WHO & WHPCA, 2020). The most important barrier for the lack of ACP is the absence of trigger points to initiate ACP conversations, which is understandable, as the underlying diseases are diverse with varying disease progression, thus making it difficult to estimate individual survival (Jabbarian et al., 2018). Due to the heterogeneity of underlying diseases, chronic respiratory insufficiency cannot be systematically used as an indicator of poor survival.

The quality of life should be the best possible in the last days of a person's life, and the hopes of the individual should be respected concerning the medication used and the preferred place of care (Lanken et al., 2008). Early integrated palliative care and ACP may also have a positive effect on end-of-life quality (Brinkman-Stoppelenburg et al., 2014; Detering et al., 2010; Temel et al., 2010). Furthermore, patients with chronic respiratory insufficiency place a burden on the health-care system due to acute exacerbations with hospitalizations and multidimensional symptoms.

Adequate symptom screening in patients with chronic respiratory insufficiency is needed to obtain sufficient palliative care. The identification of the factors associated with survival is relevant in identifying patients at risk of dying in approximately a year. These two factors allow comprehensive and symptom-centred treatment for patients, together with timely ACP, leading to high-quality end-of-life care. The aim of this thesis was to study symptom burden and factors associated with survival as well as end-of-life characteristics in patients with chronic respiratory insufficiency.

2 REVIEW OF THE LITERATURE

2.1 Chronic respiratory insufficiency

Respiratory insufficiency is defined as a disturbance in gas exchange between pulmonary alveoli and circulation due to pulmonary failure or as ventilatory insufficiency due to a failure of the ventilatory pump. The ventilatory pump consists of the chest wall, pleura and respiratory muscles, which are controlled by the central nervous system through spinal and peripheral nerves. Gas exchange failure causes hypoxaemia, with arterial partial pressure of oxygen (PaO_2) < 8.0 kPa and ventilatory failure causes hypercapnia, with arterial partial pressure of carbon dioxide ($PaCO_2$) > 6.0 kPa (Roussos & Koutsoukou, 2003).

Hypoxaemic respiratory failure can be caused by ventilation-perfusion inequality, alveolar hypoventilation, increased shunt (i.e., blood circulates from the right to the left side of the heart without passing through alveoli, e.g., in pulmonary oedema) or diffusion limitation (e.g. due to disease, which increases the diffusion distance from the alveolar space to the pulmonary capillaries, such as in pulmonary fibrosis) (Roussos & Koutsoukou, 2003; Wagner, 2012).

Hypercapnic respiratory insufficiency develops when the respiratory system is unable to maintain the balance between the production and the ventilation of carbon dioxide and is thus unable to maintain normal $PaCO_2$ levels (Adler & Janssens, 2019). Respiratory insufficiency causes various symptoms, such as daytime somnolence, fatigue, dyspnoea, orthopnoea, morning headache, cognitive dysfunction and exertional dyspnoea (Goldberg et al., 1999). Most commonly, the original problem is in the respiratory system, but in some diseases, such as amyotrophic lateral sclerosis (ALS), the disease is neurological at the time of diagnosis, but as the disease progresses, the respiratory system also becomes involved, leading to chronic respiratory insufficiency.

2.1.1 Epidemiology

Chronic respiratory insufficiency with hypoxaemia or hypercapnia affects many patients, especially those with advanced respiratory diseases. There are no specific studies on how many people worldwide suffer from chronic respiratory insufficiency due to the heterogeneity of the underlying diseases. However, some disease-specific studies have been performed, including studies on patients with COPD and interstitial lung diseases (ILDs). The most common diseases causing chronic respiratory insufficiency are COPD and OHS. Over the years, the proportion of patients with COPD or OHS has markedly increased among patients needing noninvasive ventilation (NIV), while the number of patients with other diseases has remained unchanged (Janssens et al., 2003).

According to the Swedevox register, the prevalence of long-term oxygen therapy (LTOT) usage was 31.6/100 000 in 2015, and the incidence increased from 3.9 to 14.7/100 000 from 1987 to 2015 (Ekström et al., 2017). In this study, the most common (69%) diagnosis was reported to be airway disease, of which 62% had COPD.

The Eurovent study previously estimated the prevalence of home mechanical ventilation use to be 6.6/100 000 in 2002, including patients using NIV through a face mask or invasive ventilation through a tracheostomy (Lloyd-Owen et al., 2005). The prevalence widely varied in this study between countries involved (0.1-17/100 000), being 8.7/100 000 in Finland. However, a recent study in the Geneva area reported that the prevalence of NIV usage increased from 15.1/100 000 to 37.9/100 000 from 2000 to 2017, a 2.5-fold increase (Cantero et al., 2020). In a recent study from Finland, the prevalence of home mechanical ventilation usage, 98% of which was NIV, was also reported to be 39.5/100 000 in 2018 (Kotanen et al., 2019).

2.1.2 Underlying diseases

The proportions of patients on NIV according to different underlying diseases have varied over the years, with an increasing number of patients with OHS and COPD over the years (Cantero et al., 2020; Laub & Midgren, 2007; Swedevox, 2020). The proportions of patients on NIV according to underlying diseases reported in a recent study by Cantero et al. are shown in Table 1 (Cantero et al., 2020). In a study concerning deceased patients who were on home mechanical ventilation, the underlying diagnoses were COPD in 36%, ALS in 16%, other

neuromuscular diseases in 18%, chest wall disease in 18% and other diseases in 13% of the patients (Vitacca et al., 2010).

Table 1. Diseases underlying noninvasive ventilation usage according to Swedish nationwide register study (Cantero et al., 2020)

Diseases underlying home mechanical ventilation usage	
COPD	38.9%
OHS	26.0%
Neuromuscular diseases*	15.7%
Kyphoscoliosis	5.9%
Restrictive lung diseases	4.5%
Sleeping relating breathing disorders	9.0%

* Of which 19% had Amyotrophic Lateral Sclerosis (ALS) (being 3.0% of the total population)
COPD, Chronic Obstructive Pulmonary Disease; OHS, Obesity Hypoventilation Syndrome

Chronic obstructive pulmonary disease

COPD is characterized by persistent respiratory symptoms and airflow limitation due to exposure to noxious particles ("GOLD," 2021). According to the international Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, COPD is diagnosed with post-bronchodilator ratio of forced expiratory volume in one second and forced vital capacity (FEV_1/FVC) < 0.7 in spirometry and sufficient exposure to the risk factors for the disease (e.g. tobacco smoke or other noxious particles) and typical symptoms such as progressive dyspnoea, especially upon exercise, cough and sputum production ("GOLD," 2021).

The pathophysiology of COPD consists of an inflammation and narrowing of the peripheral airways, which leads to small airway obstruction and a decline in forced expiratory volume in one second (FEV_1) ("GOLD," 2021; MacNee, 2012). Systemic inflammation is considered to be involved in comorbidities of COPD ("GOLD," 2021). Parenchymal destruction due to emphysema eventually leads to gas exchange abnormalities as the disease progresses. Patients with COPD may develop hypoxaemic respiratory insufficiency, hypoventilation, or both. Ventilation-perfusion inequality is the main cause of gas exchange abnormalities; other causes (such as decreased alveolar-capillary exchange) are less significant (MacNee, 2012). Oxygen transfer is unstable due to the

disturbance in diffusion as a result of emphysema. Gas transfer for carbon dioxide can be reduced due to deficits in ventilation, with increased breathing effort resulting from hyperinflation and the impairment of the muscles involved in ventilation ("GOLD," 2021; MacNee, 2012). Hyperinflation is due to emphysema and airway obstruction in addition to diaphragmatic dysfunction (Ferguson, 2006; Ottenheijm et al., 2007). Furthermore, dynamic hyperinflation in exercise reduces the inspiratory capacity in COPD and is the main mechanism of exertional dyspnoea with reduced exercise capacity ("GOLD," 2021; MacNee, 2012).

In the current guidelines, the severity of airway limitation is classified as mild ($FEV_1 \leq 80\%$), moderate ($50\% \leq FEV_1 < 80\%$), severe ($30\% \leq FEV_1 < 50\%$) and very severe ($FEV_1 < 30\%$ of predicted) according to FEV_1 ("GOLD," 2021). The guidelines also outline an A-D classification of COPD based on symptoms and the history of exacerbations. Group A is for COPD with low risk of exacerbations and fewer symptoms, and group D is for COPD with a high risk of exacerbations and more symptoms.

COPD is the fourth leading cause of death worldwide, but studies have still shown it to be underdiagnosed worldwide (Buist et al., 2007; Ruparel et al., 2020; Vos et al., 2020). Altogether, 3.2 million people died of COPD globally in 2015, an increase of 11.6% compared with 1990 (Soriano et al., 2017). The global prevalence of COPD in adults over 30 years of age increased from 10.7% to 11.7% between 1990 and 2010, showing a growing prevalence regionally and globally (Adeloye et al., 2015). In the Finnish general population aged over 30 years, the prevalence of COPD in general has been estimated to be 5.9%, and the prevalence of more severe COPD with GOLD stages II-IV was 3.6% (Kainu et al., 2013). In some Nordic countries, the prevalence of COPD has decreased as a result of a decline in smoking habits; however, in Finland, the prevalence of COPD has remained unchanged (Backman et al., 2020; Vasankari et al., 2010).

It has been estimated that 25% of patients with COPD with stable severe or very severe obstruction (GOLD category III-IV) have chronic hypercapnia ($PaCO_2 \geq 6.0$ kPa) (Dreher et al., 2019). Of the patients with moderate or severe obstruction (GOLD II-III), 7% have been reported to develop hypoxaemia, with saturation $\leq 88\%$ (Wells et al., 2016). A previous study by Sundh and Ekström reported the highest risk of developing hypoxaemic respiratory failure to be in patients with GOLD stage IV and patients in groups C and D (Sundh & Ekström, 2017). Additionally, higher body mass index (BMI) and lower forced vital capacity (FVC) have been described to be predictors of hypercapnia (Dreher et al., 2019).

The most important part of the treatment of COPD is the discontinuation of smoking ("GOLD," 2021). The pharmacological treatment of COPD consists of anti-inflammatory drugs for treating inflammation and bronchodilating medication to widen the airways, thus reducing symptoms and exacerbations and improving exercise tolerance. Non-pharmacological therapies include exercise training, vaccinations and nutritional evaluation, with supplementary nutrition for individuals who are malnourished ("GOLD," 2021; Katajisto et al., 2012). Comprehensive treatment should also include the management of comorbidities (Smith & Wrobel, 2014; Vanfleteren et al., 2016).

Obesity hypoventilation syndrome

OHS is defined as BMI $\geq$ 30 kg/m^2, chronic hypoventilation causing daytime hypercapnia $\geq$ 6.0 kPa, hypoxaemia PaO_2 < 9.3 kPa and sleep-disordered breathing (Burwell et al., 1956; Flemons et al., 1999; Mokhlesi et al., 2008). Approximately 90% of patients with OHS have concurrent obstructive sleep apnoea (apnoea-hypopnoea index, AHI $\geq$ 5/h), and the remaining 10% have nocturnal hypoventilation, with $PaCO_2$ rising at least 1.3 kPa during sleep versus the daytime $PaCO_2$ level, or nocturnal hypoxia, which is not due to obstructive apnoeas or hypopnoeas (Kessler et al., 2001; Littleton & Mokhlesi, 2009).

The main mechanisms behind OHS are disordered breathing while sleeping and a failure to respond to hypercapnia and hypoxia (Mokhlesi, 2010). Several specific mechanisms are described to be part of the process leading to hypoventilation, such as reduced lung volumes and respiratory muscle strength, leptin resistance and increased resistance in the upper airways (Littleton & Mokhlesi, 2009; Mokhlesi, 2010; Piper & Grunstein, 2010). Symptoms such as morning headache, morning drowsiness, dyspnoea, daytime sleepiness, nocturia and unrefreshing sleep are derived from disordered sleeping and chronic respiratory insufficiency (Masa et al., 2001).

OHS has been estimated to affect, on average, 0.15-0.4% of the general population (Littleton & Mokhlesi, 2009; Masa, et al., 2019a). Overweight and obesity have been estimated to have caused approximately 3.4 million deaths worldwide in 2010 (Lim et al., 2012). In a global systematic analysis by Ng et al., the proportion of adults (aged $\geq$ 20 years of age) with a BMI of at least 25 increased by 27.5% between 1980 and 2013 globally (Ng et al., 2014). Therefore, the number of patients with obesity-associated chronic hypoventilation should have further increased. In that study, the prevalence of obesity (BMI $\geq$ 30) in

Finnish adults over 20 years of age in 2013 was reported to be 20.9% in men and 22.3% in women (Ng et al., 2014). In a study by Nowbar et al., the prevalence of severe obesity (BMI ≥ 35) was 6% in hospitalized patients, of whom 31% had hypercapnia without other underlying causes (Nowbar et al., 2004). Furthermore, the prevalence of people with BMI over 40 has been reported to be increasing faster than that of people with BMI over 30 (Sturm, 2007).

The first-line therapy for OHS is weight loss through dietary changes or, in some cases, bariatric surgery (Kakazu et al., 2020; Masa et al., 2001; Masa, et al., 2019a; Mokhlesi et al., 2008). If obstructive sleep apnoea is involved, the first-line treatment is continuous positive airway pressure (CPAP), and the second-line treatment is NIV (Masa et al., 2001). OHS is also accompanied by multimorbidity, and the overall treatment should also include the management of comorbidities (Masa et al., 2015).

Interstitial lung diseases

Interstitial lung diseases (ILDs) are a heterogeneous group of diseases affecting mainly the gas exchanging portions of the lung. Several predisposing factors may cause ILD, such as connective tissue diseases, drugs, occupational or environmental exposures and granulomatous processes in sarcoidosis, in addition to unknown processes that cause idiopathic interstitial pneumonias (King & Nathan, 2013). Idiopathic interstitial pneumonias comprise idiopathic pulmonary fibrosis (IPF), cryptogenic organizing pneumonia, acute interstitial pneumonia, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, lymphocytic interstitial pneumonia and respiratory bronchiolitis (Travis & King, 2002). The disease process in ILD causes impaired gas exchange, with hypoxaemia, restriction in pulmonary function tests and bilateral infiltrates in chest radiography (King & Nathan, 2013).

The most common ILD is IPF, which has a poor prognosis and progressive clinical picture (Lederer & Martinez, 2018). IPF is a chronic, fibrosing interstitial pneumonia of unknown cause (Raghu et al., 2018). IPF usually appears at an older age (approximately ≥ 60 years) and with slowly progressive symptoms such as dry cough and exertional dyspnoea (Raghu et al., 2006, 2018). Disease progression is heterogeneous, with possible acute exacerbations, progression being slow or rapid and some patients having stable disease (Raghu et al., 2011). IPF affects the peripheral parts of the lungs, with heterogeneous distribution of affected and non-affected regions. The pathogenesis is thought to consist of

recurrent epithelial injuries in alveoli that activate abnormal interactions between epithelial and mesenchymal cells (Fernandez & Eickelberg, 2012; Kim et al., 2015; Lederer & Martinez, 2018). These abnormal interactions cause excessive accumulation of extracellular matrix, leading to the scarring of normal lung tissue, which results in a disturbance in gas exchange, reduced diffusion capacity and eventually hypoxaemic respiratory insufficiency (Rockey et al., 2015).

The prevalence of IPF has been shown to vary between 0.5 and 27.9/100 000 in different studies (Kaunisto et al., 2013). The prevalence of IPF in Finland has been estimated to be 16-18/100 000 (Hodgson, 2002). In a study concerning the European IPF Registry, the prevalence of LTOT and NIV users was 25.7% and 2.9%, respectively (Guenther et al., 2018). The role of long-term oxygen therapy or exertional oxygen is still not established without positive evidence on outcomes (Bell et al., 2017).

There are some medications (pirfenidone and nintedanib) that slow the decline in lung function, but there is no cure for IPF other than lung transplantation; thus, the disease often progresses to chronic respiratory insufficiency and death in patients with a progressive disease course (Raghu et al., 2015; Raghu & Richeldi, 2017).

Other diseases

Several diseases that cause restriction can lead to chronic hypoventilation. The mechanisms include chest wall abnormalities (e.g. kyphoscoliosis, thoracoplasty, post-tuberculotic sequelae), a disturbance in neural or neuromuscular transmission (e.g. spinal cord injury, ALS, poliomyelitis, myasthenia gravis, Guillain-Barré syndrome) or muscle abnormalities (e.g. muscular dystrophy, such as Duchenne muscle dystrophy) (Roussos & Koutsoukou, 2003).

Duchenne muscle dystrophy (DMD) is a progressive neuromuscular disease occurring in childhood that causes muscular weakness, with motor delays, a loss of ambulation, respiratory insufficiency and cardiomyopathy (Birnkrant et al., 2018). The vital capacity declines gradually after the age of 10 due to muscle weakness as well as thoracic scoliosis, which leads to chronic respiratory insufficiency on average at the age of 18-20 when vital capacity (VC) falls below 1.0 litres (Phillips et al., 1999; Rideau et al., 1983; Simonds et al., 1998; Simonds, 2006). The estimated prevalence of DMD has been reported to be 5.0/100 000 in Europe (Orphanet Report Series, 2020).

Amyotrophic lateral sclerosis (ALS) is a gradually progressive disease that damages the upper and lower motor neurons and leads to muscle impairment and defects in mobility, communication, swallowing and breathing due to paresis of all voluntarily innervated muscles (Dorst & Ludolph, 2019; Magnussen & Glass, 2017). The average age at the onset of disease is 63 years (Westeneng et al., 2018). The prevalence of ALS has been estimated to be 5.2/100 000 in Europe (Orphanet Report Series, 2020).

2.1.3 Treatment of chronic respiratory insufficiency

Long-term oxygen therapy

Long-term oxygen therapy (LTOT) is used to treat chronic hypoxaemia. The oxygen concentrator generates 100% oxygen, which is breathed in mainly via a nasal cannula in homecare settings (Figure 1). The flow of oxygen can be adjusted according to individual needs.

Figure 1. Oxygen concentrator with an oxygen tube and nasal cannula (Philips Respironics®)

The benefits of LTOT have been shown only in patients with COPD and severe hypoxaemia, in whom LTOT leads to longer survival when used at least 15 hours per day (Gulbas et al., 2012; Medical Research Council Working Party, 1981; Nocturnal Oxygen Therapy Trial Group, 1980). However, usage for 24 hours vs. 15 hours per day did not lead to a significant difference in the effect of LTOT on survival (Ahmadi et al., 2016a).

According to the current guidelines, the criteria for the long-term use of oxygen therapy in patients with COPD who have stable disease with optimal medication are $PaO_2 \leq 7.3$ kPa or saturation < 88% at rest or moderate hypoxaemia $PaO_2 \leq 8.0$ kPa with coexisting peripheral oedema, polycythaemia (haematocrit ≥ 55%) or pulmonary hypertension ("GOLD," 2021; Hardinge et al., 2015; Jacobs et al., 2020). It has been shown previously that there is no significant survival benefit of using LTOT in patients with COPD and moderate hypoxaemia without complicating factors, as specified earlier (COPD Working Group, 2012; Ekström & Ringbaek, 2018; Gorecka et al., 1997; Jacobs et al., 2020; Long-Term Oxygen Treatment Trial Research Group et al., 2016). The target saturation at rest with supplemental oxygen is ≥ 90% and $PaO_2 \geq 8.0$ kPa in arterial blood ("GOLD," 2021; Hardinge et al., 2015).

A recently published study concerning patients with COPD suffering only from exertional desaturation (< 90%), reported that there was no significant difference in exercise tolerance or health-related quality of life between patients using supplementary oxygen during exercise and patients who used medical air (Alison et al., 2019). However, British Thoracic Society (BTS) guideline for the use of home oxygen states that portable oxygen can be used in patients who are mobile outdoors and qualify for LTOT usage, and in some cases in mobile patients with advanced disease with an exertional desaturation drop ≥ 4% below 90% and at least 10% improvement in exercise capacity with ambulatory oxygen even if the criteria for LTOT are not met (Hardinge et al., 2015). The guideline also states that the use of oxygen during exertion has not been shown to have significant impact on a patient's quality of life or symptoms even it may help a patient to leave home to achieve the suggested minimum of 15 hours of oxygen usage per day. A recent guideline by the ATS for the use of home oxygen for patients with chronic lung disease has a conditional recommendation of using ambulatory oxygen in patients with COPD or ILD with severe exertional hypoxaemia with a saturation ≤ 88% in exercise but with low-quality evidence (Jacobs et al., 2020). A Cochrane Review showed that ambulatory oxygen can slightly reduce exertional dyspnoea during exercise tests, but there was no

evidence of decreased dyspnoea while performing activities of daily living (ADL) (Ekström et al., 2016a).

Finnish current care guidelines are based on the studies presented above. In addition, the criteria should be met repeatedly in a stable state at least 3 weeks apart, and the patient has to have quit smoking for at least 6 months prior. Furthermore, if a patient restarts smoking or uses LTOT less than the suggested 15 hours per day, LTOT should be discontinued (Current Care Guidelines in COPD, 2019).

In addition to COPD, LTOT is also used in patients with many other advanced diseases, such as interstitial lung diseases, cystic fibrosis, pulmonary hypertension and advanced cardiac failure, with the same criteria as in COPD, even though there is no clear evidence of a survival benefit or symptom alleviation in these other groups (Crockett et al., 2001; Hardinge et al., 2015; Raghu et al., 2011). However, LTOT should not be used without fulfilling the criteria (Hardinge et al., 2015). According to a review by Bell et al., there is no effect of supplementary oxygen on dyspnoea during exercise in patients with ILD, although supplementary oxygen increases exercise capacity (Bell et al., 2017). In pulmonary hypertension, LTOT is suggested for patients if the PaO_2 is consistently ≤ 8 kPa, even though there are no randomized studies on whether it is beneficial (Galiè et al., 2016; Hardinge et al., 2015). Patients with neuromuscular or chest wall disorders are recommended to use NIV as the first choice of treatment, but if hypoxemia still exists, LTOT can be used in addition to NIV, but with caution as the hypercapnia may worsen (Hardinge et al., 2015; Simonds, 2013).

Some patients with OHS need oxygen therapy in addition to CPAP to obtain normal saturation during sleep (Banerjee et al., 2007; Masa et al., 2016). Previous studies have shown that the level of carbon dioxide may rise when patients with stable OHS without NIV use supplemental oxygen rather than room air (Wijesinghe et al., 2011). Therefore, supplementary oxygen should be used only with NIV to avoid hypercapnia (Hardinge et al., 2015).

Although its benefit on symptoms remains to be shown, LTOT may be used as part of palliative treatment for patients with advanced disease due to lung cancer, ILD or cardiorespiratory disease if they suffer from breathlessness unresponsive to all other treatments and are also hypoxaemic (saturation ≤ 90%) (Bell et al., 2017; Hui et al., 2021). Opioids should be the first-line treatment for palliative treatment of breathlessness in patients with or without hypoxaemia (Hardinge et al., 2015). Supplementary oxygen has not been shown to relieve

breathlessness any better than room air in patients on palliative care with $PaO_2 \geq$ 7.3 kPa (Abernethy et al., 2010).

Noninvasive ventilation

Noninvasive ventilation (NIV) is a treatment for hypoventilation due to different underlying diseases in acute or chronic settings. NIV devices support ventilation through an interface without invasive procedures (Figure 2). NIV increases tidal volume by higher pressure in inspiration and lower pressure in expiration, leading to an increase in minute volume and thus reducing $PaCO_2$ (Windisch et al., 2006). The inspiratory and expiratory positive airway pressures (IPAP and EPAP, respectively) are adjusted for each patient individually based on the underlying disease and individual characteristics. With the help of NIV, breathing becomes easier. NIV improves gas exchange with better oxygenation and ventilation of the excess carbon dioxide, thus reducing the symptoms derived from hypercapnia, such as hypersomnolence and morning headache (Mehta & Hill, 2001; Robert & Argaud, 2007). The most commonly used interfaces are nasal and oro-nasal masks, which are fitted and adjusted based on personal characteristics.

Figure 2. Two examples of noninvasive ventilators used for home care in Tampere, Finland (Resmed Lumis 100® and Philips Dreamstation BiPAP S/T®) with their tubes and oro-nasal masks

NIV is recommended for use in acute hypercapnic respiratory insufficiency in patients with COPD, but its role in the treatment of chronic respiratory insufficiency in patients with COPD has been under debate (Davidson et al., 2016; Duiverman, 2018; Rochwerg et al., 2017; Wedzicha et al., 2017). Hypercapnia has been reported to predict mortality in patients with COPD needing LTOT (Ahmadi et al., 2014). The benefits of NIV in COPD have been studied with contradictory results over many decades (Casanova et al., 2000;

Duiverman, 2018; Lin, 1996; Struik et al., 2014; Strumpf et al., 1991). Several studies have shown that NIV with sufficient pressures targeted to normalise $PaCO_2$ improves survival and quality of life and reduces readmission and intubation rates after acute exacerbation in patients with stable hypercapnic COPD (Gantzhorn et al., 2019; Köhnlein et al., 2014; Murphy et al., 2017; Wilson et al., 2020; Windisch et al., 2002). However, the improvement in $PaCO_2$ alone might not be associated with improved survival (Raveling et al., 2018). Previous studies have shown the normalisation of $PaCO_2$ to be achieved in chronic hypoventilation by high-intensity pressures and the survival to be better in such patients than in patients using low-intensity ventilation (Blankenburg et al., 2017; Köhnlein et al., 2014; Schwarz et al., 2017). European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines suggest that NIV be used in patients with stable chronic hypercapnic COPD or in patients with COPD after a life-threatening acute episode of hypercapnic respiratory insufficiency needing NIV and with hypercapnia after the episode, targeting the normalisation of $PaCO_2$ levels (Ergan et al., 2019; Macrea et al., 2020).

According to a Consensus Conference Report, the criteria for the initiation of NIV in patients with stable COPD in a stable state with optimal medication are as follows: symptoms including fatigue, headache in the morning, and dyspnoea, with $PaCO_2 \geq 7.3$ kPa or $PaCO_2 \geq 6.7$-7.2 kPa in addition to nocturnal desaturation (saturation $\leq 88\%$ at least 5 minutes with oxygen therapy at least 2 l/min) or with at least 2 hospitalizations due to hypercapnic respiratory failure during the past year (Goldberg et al., 1999). However, a study concerning several European countries showed that NIV has been also used in patients with stable COPD if they have recurrent exacerbations or fail to be weaned off NIV after a hospital stay, even if they do not fulfil the criteria for NIV (Crimi et al., 2016).

The ATS guidelines for patients with OHS suggest interventions leading to a 25-30% weight reduction in actual body weight (Mokhlesi et al., 2019). The guidelines for OHS state that CPAP should be the first-line therapy for patients who have stable chronic respiratory insufficiency ($PaCO_2 < 7.0$ kPa) with concurrent severe obstructive sleep apnoea (AHI ≥ 30/h) (Masa et al., 2019a; Mokhlesi et al., 2019; Murphy et al., 2019). However, a previous review by Murphy et al. suggests that patients with $PaCO_2 > 7.0$ kPa or post-acute respiratory failure or concurrent COPD with $PaCO_2 > 6.0$ kPa should be considered for the initiation of NIV (Murphy et al., 2019). In the absence of severe obstructive sleep apnoea (AHI < 30/h), NIV should be the first-line therapy (Murphy et al., 2019). EPAP should be titrated, among other things,

aiming to achieve saturation > 90% and to reduce apnoeas and hypopnoeas (Böing & Randerath, 2015). The Pickwick Study showed that nocturnal saturation and quality of sleep were improved in both NIV and CPAP users, but $PaCO_2$ values improved more markedly with NIV (Masa et al., 2015).

A consensus for NIV in chronic respiratory failure and previous articles recommend NIV to be the first choice of treatment in symptomatic patients with chronic respiratory insufficiency due to neuromuscular diseases (Goldberg et al., 1999; Hill, 1994; Simonds, 2003).

In previous studies, survival has been shown to increase with NIV use in patients with Duchenne muscle dystrophy (DMD) (Eagle et al., 2002; Ishikawa et al., 2011; Simonds et al., 1998; Simonds, 2003; Vianello et al., 1994). The criteria for the initiation of NIV in DMD include any of the following: symptoms or signs of hypoventilation, oxygen saturation < 95% and/or $PaCO_2$ > 6.0 kPa while awake, AHI > 10/h or ≥ 4 episodes of SpO_2 < 92% or drops in SpO_2 at least 4%/h during sleep, and FVC < 50% of the predicted or maximum inspiratory pressure (MIP) < 60 cmH_2O (Birnkrant et al., 2018; Finder et al., 2004; Goldberg et al., 1999; Sheehan et al., 2018).

Additionally, in patients with ALS, previous studies have shown NIV use to increase survival compared with NIV non-use (Aboussouan et al., 1997; Bourke et al., 2006; Pinto et al., 1995). The criteria for the initiation of NIV are as follows: at least one symptom from chronic respiratory insufficiency or nocturnal sleep disturbance, especially orthopnoea or FVC < 80%, significant nocturnal desaturation or MIP max < 60 mmH_2O or $PaCO_2$ > 6.0 kPa (in the morning) or sniff nasal inspiratory pressure (SNIP) < 40 cmH_2O or MIP or SNIP decreasing > 10 cmH_2O/3 months (Andersen et al., 2012; Dorst & Ludolph, 2019; NICE, 2016).

NIV is also used in different restrictive disorders and has been shown to improve gas exchange and reduce the number of days spent in the hospital in patients with kyphoscoliosis and post-tuberculosis sequelae (Ellis et al., 1988; Leger et al., 1994; Mehta & Hill, 2001). The indications for the use of NIV in chronic respiratory insufficiency due to restrictive disorders such as poliomyelitis, chest wall deformities and kyphoscoliosis are symptoms of chronic respiratory insufficiency with $PaCO_2$ ≥ 6.0 kPa or nocturnal hypoxaemia ≤ 88% continuing for at least 5 minutes (Goldberg et al., 1999).

2.1.4 Prognosis of chronic respiratory insufficiency

Previous studies have shown that the survival of patients with chronic respiratory insufficiency differs widely according to the underlying disease, being worst in patients with ILD or ALS and best in patients with kyphoscoliosis or OHS (Chailleux et al., 1996; Laub & Midgren, 2007; Patout et al., 2020). In a recent study concerning patients on NIV, the overall median survival was 6.63 years, and the 5-year survival rate was 58.3% (Patout et al., 2020). According to the Swedish Swedevox register, the median overall survival time of all patients on LTOT is 1.4 years, with a 3-year survival of approximately 25%, an additional 25% of the patients live less than 6 months after the initiation of LTOT (Swedevox, 2020). The reported overall survival rates according to patients' underlying diseases causing chronic respiratory insufficiency are shown in Table 2.

Jensen et al. estimated the median life expectancy to be 67.2 years in patients with severe or very severe COPD (GOLD III-IV) (Jensen et al., 2013). Furthermore, in a study by Gainza-Miranda et al., the survival was only 8.3 months in patients with very severe COPD (GOLD IV) needing LTOT (32% with concomitant NIV) (Gainza-Miranda et al., 2019). In a study by Blankenburg et al. concerning patients with high-intensity NIV, the 1- and 3-year survival rates were 83% and 55% in patients with COPD and 85% and 68% in patients with OHS, respectively (Blankenburg et al., 2017).

Morbid obesity affects the survival worldwide, and overall survival has been estimated to be reduced by approximately 8-10 years in patients with BMI of 40-50 (Prospective Studies Collaboration, 2009). The 18-month survival rate of hospitalized patients is reported to be 91% and 77% in patients with only obesity (BMI $\geq$ 35) and patients meeting the criteria for OHS, respectively (Nowbar et al., 2004). The survival of patients with OHS on NIV therapy is reported to be 97% after a year and 70-77% after 5 years (Budweiser, et al., 2007a; Priou et al., 2010). These studies have also reported hypoxaemia or the need for LTOT to be associated with worse survival in patients with OHS (Budweiser, et al., 2007a; Priou et al., 2010).

Patients with interstitial lung diseases have one of the worst survival rates among patients with chronic respiratory insufficiency. The median survival of patients is 3-5 years after the diagnosis of IPF and is being better in patients with BMI $\geq$ 30 (Alakhras et al., 2007; Bjoraker et al., 1998; King et al., 2001). The overall survival of patients with IPF has increased since the development of

treatment options, as it has been estimated to be 10.3 years with antifibrotic drugs compared with 5.7 years without antifibrotic drugs (Guenther et al., 2018). However, in the Finnish IPF registry, the overall survival was 4.5 years, even though 26% of the patients were on antifibrotic treatment (Kaunisto et al., 2019). Furthermore, the survival has been reported to be only 8.4 months after the initiation of LTOT (Ahmadi et al., 2016b). The most common cause of death is an acute exacerbation, but comorbidities also affect the survival of patients with IPF (Daniels et al., 2008).

Table 2. Prognosis and survival according to the underlying disease causing chronic respiratory insufficiency

Primary diagnosis	Median/mean survival (years)	1-5 year survival rates	Studies, year
COPD			
• after the initiation of LTOT with or without NIV	2.7-3.9	71.8-73.0% (2-year) 55% (3-year)	(Blankenburg et al., 2017; Budweiser et al., 2007b; Chailleux et al., 1996; Patout et al., 2020)
OHS			
• after the initiation of NIV		68-88.3% (3-year) 70-77% (5-year)	(Blankenburg et al., 2017; Budweiser et al., 2007a; Priou et al., 2010)
IPF	4.5		(Kaunisto et al., 2019)
• after the initiation of LTOT	0.7	50% (1-year)	(Ahmadi et al., 2016b; Chailleux et al., 1996)
Duchenne muscle dystrophy	18.0-19.0		(Bushby et al., 2005; Ishikawa et al., 2011)
• after the initiation of NIV	25.5 (even 35.0-39.6)	82% (5-year)	(Eagle et al., 2002; Ishikawa et al., 2011; Kohler et al., 2009)
ALS	2.7-5.0		(Forsgren et al., 1983; Magnussen & Glass, 2017)
• after the initiation of ventilation	1.0	5% (5-year)*	(Laub & Midgren, 2007; Patout et al., 2020)
Kyphoscoliosis	8.0	75-79% (5-year)	(Chailleux et al., 1996; Laub & Midgren, 2007; Simonds & Elliott, 1995)
Poliomyelitis		100% (5-year)	(Simonds & Elliott, 1995)
Tuberculous sequelae		94% (5-year)	(Simonds & Elliott, 1995)
Pulmonary hypertension		75% (3-year) 65% (5-year)	(Escribano-Subias et al., 2012)

* On noninvasive ventilation (n = 161) or tracheostomized (n = 4)

COPD, Chronic Obstructive Pulmonary Disease; LTOT, Long-Term Oxygen Therapy; NIV, Noninvasive Ventilation; OHS, Obesity Hypoventilation Syndrome; IPF, Interstitial Pulmonary Fibrosis; ALS, Amyotrophic Lateral Sclerosis

In patients with Duchenne muscle dystrophy (DMD), the life expectancy has improved from a mean age of 18-19 years in 1970 without mechanical ventilation to a mean age of 25.5 years in 1990 (Bushby et al., 2005). At present, the mean survival has been shown to be up to 35.0-39.6 years with NIV (Calvert et al., 2006; Ishikawa et al., 2011; Kohler et al., 2009). The major causes of death are respiratory insufficiency and cardiomyopathy (Calvert et al., 2006; Kieny et al., 2013). At the time of vital capacity falling < 1.0 litres, the 5-year survival is reported to be only 8% (Phillips et al., 2002). However, the 5- and 10-year survival rates after the initiation of NIV have been reported to be 82% and 68%, respectively (Kohler et al., 2009).

The 5-year survival of patients with scoliosis, previous poliomyelitis and tuberculous sequelae is reported to be 79%, 100% and 94%, respectively (Simonds & Elliott, 1995). In patients with ALS, the median survival time after diagnosis is, on average, 3-5 years and after the initiation of NIV, the median survival time is only one year (Forsgren et al., 1983; Magnussen & Glass, 2017; Patout et al., 2020; Westeneng et al., 2018). Czaplinski et al. showed that FVC predicts the survival and the degree of progression in patients with ALS (Czaplinski et al., 2006). In their study, the survival was 2.9 and 4.1 years in patients with FVC < 75% and ≥ 75% at the time of diagnosis, respectively. In a study by Laub and Midgren, patients with ALS who were on NIV (98%) or were tracheotomised (2%, n = 4) had a 5-year survival rate of only 5%, whereas the 5-year survival rate was approximately 75% in patients with kyphoscoliosis, poliomyelitis or OHS (Laub & Midgren, 2007).a

2.2 Dyspnoea in advanced respiratory diseases

The definition of dyspnoea according to the ATS statement is "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses" (Meek et al., 1999). Dyspnoea can be acute, chronic or acute-on-chronic. The characteristics of dyspnoea can be paroxysmal, fluctuating or continuous; can be perceived only on exertion, in the supine position, or nocturnally; or can be a consequence of aggravating factors. The degree of dyspnoea may differ greatly among patients,

even with the same underlying disease. Dyspnoea can exist with or without respiratory insufficiency.

2.2.1 Prevalence of dyspnoea

The prevalence of persistent dyspnoea in the general population has been estimated to be 6.9% in women and 4.3% in men (Voll-Aanerud et al., 2007). In a study by Currow et al., approximately 1% of all contacts to general practitioners were due to dyspnoea, with the probability increasing at older age (Currow et al., 2013). The prevalence of different levels of dyspnoea severity according to modified Medical Research Council dyspnoea scale (mMRC) stages 1, 2, 3, and 4 is reported to be 6.2%, 1.1%, 1.0% and 0.3% in the general population, respectively (Currow et al., 2009). The prevalence of clinically significant dyspnoea in the older population is reported to be 25%, where it is associated with impaired well-being, the need for help in activities of daily living and greater use of health services (Smith et al., 2016). In a study by Johnson et al., 56.8% of the deceased elderly people had experienced dyspnoea during the last year of life, with increasing intensity towards death and an association with anxiety, depression and mobility problems (Johnson et al., 2016).

The prevalence of dyspnoea in patients with different diseases is shown in Table 3. The reasons for dyspnoea are most often COPD, asthma and chronic heart failure (Currow et al., 2013). In previous systematic reviews by Solano et al. and Moens et al., dyspnoea was reported to be present in 56-98% of patients with COPD (Moens et al., 2014; Solano et al., 2006). Most of the patients with moderate or severe COPD (72.5%) have been reported to suffer from dyspnoea with daily or weekly symptoms (Kessler et al., 2011). In a study by Mokhlesi et al., 69% of the patients with OHS suffered from moderate or severe dyspnoea (Mokhlesi et al., 2008). Furthermore, the prevalence of dyspnoea has been estimated to be 54-98% and 81-88% in patients with IPF and motor neuron disease, respectively (Carvajalino et al., 2018; Moens et al., 2014). In a study by Nicholson et al., 66% of the patients with ALS reported dyspnoea, and it was one of the most disturbing symptoms (Nicholson et al., 2018).

Altogether, 55% of the patients with chronic lung disease treated in palliative care were reported to suffer from dyspnoea (Wysham et al., 2015). In advanced disease, the severity of dyspnoea fluctuates in each patient and varies between individuals even if the disease progression is otherwise quite similar (Bausewein

et al., 2010; Ekström, et al., 2016). In a previous study by Rajala et al., the degree of dyspnoea was increased towards the end of life in patients with IPF (Rajala et al., 2018). In a study by Vender et al., only a few (2%) patients had dyspnoea at the onset of ALS symptoms, but most of the patients (81%) developed dyspnoea as the disease progressed (Vender et al., 2007).

Table 3. Prevalence of dyspnoea in the general population and according to the disease underlying respiratory insufficiency

Population	Prevalence of dyspnoea	Studies, year
General population	8.9%	(Currow et al., 2009)
- Women	6.9-11.3%	(Currow et al., 2009; Voll-Aanerud et al., 2007)
- Men	4.3-6.3%	(Voll-Aanerud et al., 2007)
- Elderly individuals (>70 years)	25%	(Smith et al., 2016)
COPD	72.5%	(Kessler et al., 2011)
IPF	52-98%	(Carvajalino et al., 2018; Guenther et al., 2018; Rajala et al., 2017)
Lung cancer	55-87%	(Bruera et al., 2000; Reuben & Mor, 1986; Smith et al., 2001; Tanaka et al., 2002)
Chronic heart failure	54-85.2%	(Barnes et al., 2006; Blinderman et al., 2009; Zambroski et al., 2005)
PAH	98%	(Matura et al., 2016)
ALS	66-88%	(Moens et al., 2014; Nicholson et al., 2018; Vender et al., 2007)
OHS	69%	(Mokhlesi et al., 2008)

COPD, Chronic Obstructive Pulmonary Disease; IPF, Interstitial Pulmonary Fibrosis; PAH, Pulmonary artery hypertension; ALS, Amyotrophic Lateral Sclerosis; OHS, Obesity Hypoventilation Syndrome

Over 90% of patients with hypercapnic respiratory failure needing NIV have been reported to experience dyspnoea along with other symptoms (Smith et al., 2019). Furthermore, the prevalence of dyspnoea is even more frequent in patients with oxygen-dependent COPD or ILD than in patients with advanced cancer (73% vs. 22% and 75% vs. 42%, respectively) (Ahmadi et al., 2015; Ahmadi et al., 2016b). In a study by Weingaertner et al., most (96%) of the patients with advanced COPD, of whom 54% were on LTOT, were reported to have dyspnoea (Weingaertner et al., 2014). In a study by Vender et al., the onset of dyspnoea, as well as the initiation of NIV, predicted survival of less than two years in patients with ALS (Vender et al., 2007).

The severity of dyspnoea has been reported to predict 5-year survival better than the disease severity staging based on the value of FEV_1 in patients with COPD (Nishimura et al., 2002). In a study by Gruenberger et al. concerning patients with COPD, patients with a higher degree of dyspnoea (mMRC stage ≥

2) had a lower quality of life, impaired physical activity and more emergency room visits (Gruenberger et al., 2017). A previous study concerning patients with IPF showed more intense dyspnoea to be associated with many symptoms, such as chest pain, dry mouth, tiredness and depression, and dyspnoea was also associated with impaired quality of life (Rajala et al., 2017). Furthermore, in a study by Ryerson et al., dyspnoea was associated with depressive symptoms and lower functional status in patients with ILD (Ryerson et al., 2011). Dyspnoea is reported to be intense and to persist even in light physical exertion between periods of NIV use in patients with ALS and chronic respiratory insufficiency (Morélot-Panzini et al., 2018).

2.2.2 Assessment of dyspnoea

Although dyspnoea is a common symptom in many advanced diseases, it is still poorly recognized. In a previous study on deceased patients, most of the patients had suffered from tachypnoea and had been on supplementary oxygen, but only half of the patients had dyspnoea recorded by the nursing staff (Morris & Galicia-Castillo, 2015). Dyspnoea is poorly recognized, especially in patients with advanced disease other than pulmonary disease, even with a high incidence of increased respiratory rate (Morris & Galicia-Castillo, 2015).

At least 33 different tools have been developed for evaluating dyspnoea (Bausewein et al., 2007). The ATS statement classifies the tests for the measurement of dyspnoea into three categories (Parshall et al., 2012). One of these categories is sensory-perceptual experience, i.e., how the patient is experiencing dyspnoea and its severity. This sensory-perceptual experience is commonly measured, for instance, with a numerical rating scale (NRS) (Gift & Narvasage, 1998), visual analogue scale (VAS) (Gift, 1989), Likert-type rating (Masters, 1974; Matell & Jacoby, 1971) or modified Borg scale (Borg, 1970; Burdon et al., 1982) (Parshall et al., 2012). An NRS is used for a single symptom, with responses ranging from 0 (no symptom) to 10 (symptom as bad as can be) (Gift & Narvasage, 1998). A VAS is a 10 cm visual scale with 0 cm corresponding to no symptoms and 10 cm corresponding to the worst imaginable symptoms. Likert-type ratings is based on different levels of agreement and disagreement options (Likert, 1932). The Borg scale is also used for a single question at a time, with responses ranging from 0 (no symptoms) to 10 (maximal symptoms) (Borg, 1970). The severity of distress or discomfort caused by dyspnoea may be

evaluated with single- or multiple-item scales (Parshall et al., 2012). Finally, the impact of dyspnoea on quality of life, i.e., how dyspnoea affects a patient's quality of life and ability to work or move, may be measured with the mMRC (Bestall et al., 1999; Fletcher et al., 1960; Mahler & Wells, 1988) and quality of life scales, such as the Severe Respiratory Insufficiency Questionnaire (SRI) and Maugeri Respiratory Failure Questionnaire (MRF-26) (Carone et al., 1999; Vidotto et al., 2007; Windisch et al., 2002) (Parshall et al., 2012). The severity of exertional dyspnoea can be measured with, for instance, the mMRC, a scale from 0 to 4, containing verbal descriptions of how dyspnoea affects the capability to move (Bestall et al., 1999). The SRI and MRF-26 are questionnaires that consist of specific items on various symptoms, such as dyspnoea, but the outcome reflects quality of life, and they are being developed for patients on home mechanical ventilation due to chronic respiratory insufficiency. The SRI and MRF-26 are comprehensive, with 49 and 26 items, respectively, measuring different aspects of life (Carone et al., 1999; Windisch et al., 2003).

The usability of the questionnaires depends on the physical condition of the target patient population. Longer and multidimensional questionnaires require good co-operation and cognition, which are frequently impaired in patients with advanced respiratory disease. Many of the questionnaires are quite long and difficult to complete; and therefore, some shorter questionnaires have been developed. Furthermore, the use of questionnaires differs between different centres.

Many of the dyspnoea measurement tools evaluate dyspnoea during exercise, while, for instance, patients with ALS suffer dyspnoea even in daily activities. Therefore, some disease-specific tests, such as the revised ALS Functional Rating Scale (ALSFRS-R), have been developed to measure the progression of respiratory defects. The ALSFRS-R is used in patients with ALS for the evaluation of dyspnoea, orthopnoea and the need for NIV, and the ALSFRS-R can be used to determine when to refer a patient to a pulmonologist (Cedarbaum et al., 1999). Additionally, some dyspnoea-specific tests have been developed for the measurement of dyspnoea in ALS, such as the Dyspnoea-ALS-Scale (DALS-15) and Motor Neuron Disease Dyspnoea Scale (MND-DS) (Helleman et al., 2020; Vogt et al., 2019).

While there is no single questionnaire that can be used to measure the sensation of dyspnoea or its effect on quality of life in all patients, a systematic review suggests using a combination of questionnaires; for example, a unidimensional test (e.g., a VAS, an NRS or the modified Borg Scale) with a

disease-specific (such as St. George's Respiratory Questionnaire, SGRQ (Jones et al., 1992)) or multidimensional scale in addition to other methods (Bausewein et al., 2007).

2.2.3 Management of dyspnoea

Dyspnoea has been shown to be less frequently completely relieved in oxygen-dependent patients with COPD or an ILD than in patients with cancer (22% vs. 37% and 17% vs. 33%, respectively) (Ahmadi et al., 2015; Ahmadi et al., 2016b). Integrated palliative care and respiratory management have been shown to relieve refractory dyspnoea and even to positively affect survival in patients with advanced COPD or ILD (Higginson et al., 2014).

The comprehensive management of dyspnoea includes the treatment of known underlying conditions and comorbidities, such as pleural effusion, chronic heart failure or airway obstruction (Hui et al., 2021).

In previous studies, opioids have been shown to reduce refractory dyspnoea in patients with advanced diseases and are considered standard care for refractory dyspnoea (Abernethy, 2003; Hui et al., 2021; Johnson et al., 2002; Mahler et al., 2010; Parshall et al., 2012). Opioids depress spontaneous respiratory drive and modulate cortical activity, thus reducing dyspnoea (Parshall et al., 2012). In a study by Ekström et al., opioids with careful dosing were not associated with an increased risk of hospitalization or death in patients with COPD needing LTOT (Ekstrom et al., 2014). A recent review concluded that the best evidence is for daily dosages of 10-30 mg oral morphine in opioid-naïve patients (Johnson & Currow, 2020). The review also showed that side effects such as constipation, nausea and vomiting resulting from the use of morphine are common; however, these side effects are usually mild and should be treated early and anticipated.

In previous studies, oxygen supplementation during exertion was reported to provide slight relief for dyspnoea during exercise in patients with COPD who do not fulfil the criteria for LTOT (Ekström et al., 2016a; Uronis et al., 2015). However, they also reported that supplementary oxygen did not affect dyspnoea in ADL or quality of life. In a previous study by Abernethy et al., continuous oxygen did not provide any additional benefit for relieving refractory dyspnoea compared with room air delivered by nasal cannula in patients with life-limiting illness without concurrent severe hypoxaemia (Abernethy et al., 2010). Airflow from the fan at rest improves dyspnoea and is therefore suggested to be a part of

comprehensive treatment of dyspnoea, although actual randomized controlled studies about the effect of fans do not exist (Swan et al., 2019).

2.3 Depression in advanced respiratory diseases

2.3.1 Prevalence of depression

Depression is common among patients with chronic respiratory disease, as 65% of these patients have been reported to have depression (Kunik et al., 2005). Almost three-quarters of patients with COPD have been reported to have depression, and half of them have moderate or severe depression (Miravitlles et al., 2014). Depression is reported to be common even in patients with mild COPD and is more prevalent in females (38.3%) than in males (12.9%) (Di Marco et al., 2006). The rate of depression in patients with COPD is approximately three times higher than that in a healthy population (Egede, 2007). Patients with IPF also experience depression, which affects 10-49% of these patients (Carvajalino et al., 2018; Ryerson et al., 2012). However, a study by Rajala et al., showed that up to 63% of the patients with IPF had depressive symptoms (Rajala et al., 2017). Altogether, 23% of the patients with motor neuron disease were reported to have depression, even though the duration of the disease varied among patients (Kristjanson et al., 2006).

A study by Kayhan et al. found that over half of the patients with severe COPD on LTOT suffered from depression, but only a few of them took an antidepressant medication (Kayhan et al., 2018; Lacasse et al., 2001). In a previous study by Martinez Rivera et al., patients with COPD and depression were more likely to be on LTOT (42.9%) than patients without depression (14.9%) (Martinez Rivera et al., 2016). However, some studies have shown that depression is prevalent regardless of the need for LTOT (Lewis et al., 2007). In a study by Borel et al., approximately one-third of the patients with OHS initiating NIV had depression (Borel et al., 2013).

In advanced disease, depression has been reported to be associated with higher overall symptom burden, such as more severe dyspnoea and pain, as well as impaired well-being (Delgado-Guay et al., 2009; Rajala et al., 2017; Ryerson et al., 2011, 2012). In a study by Martinez Rivera et al. on patients with severe COPD, patients with depression were also associated with a higher perception of

dyspnoea measured with the mMRC (mean stage 2.7) than patients without depression (mean 1.4) (Martinez Rivera et al., 2016). Apart from the severity of respiratory disease, Blakemore et al. showed in their study that depression is associated with an increased need for emergency care (Blakemore et al., 2019). In a small study (n = 40) on patients with obesity, OHS and obstructive sleep apnoea, all the patients with OHS had depressive symptoms that were significantly decreased upon initiation of NIV (Argun Baris et al., 2016). Perceived depressive symptoms have been reported to be increased towards the end of life in patients with IPF (Rajala et al., 2018).

2.3.2 Assessment of depression

Several questionnaires have been developed for screening depression in hospitals and primary care. In a literature synthesis by Williams et al., 16 different questionnaires were evaluated, showing that some of the questionnaires were shorter and some were longer and therefore more specific, with questions concerning the present state or previous condition during the last 1-4 weeks (Williams et al., 2002). The synthesis showed that the number of questions varied between 1 and 30, taking from less than 2 minutes up to 6 minutes to complete. Another systematic review showed that shorter tests serve as well as longer tests for screening depression, but shorter tests might lack some sections; therefore, detailed interviews are suggested for the diagnosis of depression (Akena et al., 2012). The Finnish Current Care Guideline for depression suggests the use of the Beck Depression Inventory (BDI) (Beck, 1961) and Finnish Depression Scale (DEPS) (Salokangas et al., 1995) for screening depression in the general population (Current Care Guidelines in Depression, 2021). The BDI has 21 questions, each scored from 0 to 3, and concerns the state experienced during the past week. The scoring varies from minimal (0-9) to severe (30-63) depression (Beck et al., 1988). The DEPS was developed for screening depression and includes 10 questions concerning the previous month, each scored from 0 to 3. In the DEPS, 9 and 12 points are the cut-off values for depressive symptoms and depression, respectively (Poutanen et al., 2010).

2.3.3 Management of depression

Anxiety and depression should be screened and treated with appropriate treatment, but in a study by Kunik et al., only 31% of patients with chronic respiratory disease received adequate treatment for depression (Kunik et al., 2005). However, in a recent study by Kerminen et al., only a few patients with chronic respiratory insufficiency and depressive symptoms agreed to be referred to a specialized unit for diagnosis and treatment (Kerminen et al., 2019). The management of depression consists of antidepressant drugs along with cognitive-behavioural therapy or interpersonal psychotherapy (Lin et al., 2019).

2.4 Other symptoms in advanced respiratory diseases

Several other symptoms are also prevalent in patients with advanced respiratory disease affecting the well-being of the patients. Some of the symptoms are derived from the underlying disease, some are directly associated with hypoxaemia or hypercapnia if inadequately treated, and some symptoms are derived from the medication used or other treatment.

2.4.1 Prevalence of other symptoms

The overall symptom burden has been reported to be more severe in patients with COPD than in those without COPD in a study concerning chronically ill patients confined to their homes (Wajnberg et al., 2013). In a study by Blinderman et al., over 50% of patients with very severe COPD suffered from fatigue, cough, anxiety and dry mouth in addition to dyspnoea (Blinderman et al., 2009). A lack of energy and dry mouth are reported to be more severe in patients with very severe COPD (GOLD IV) than in patients with moderate or severe COPD (GOLD II-III) (Christensen et al., 2016). Additionally, patients with IPF have been reported to have other symptoms beyond breathlessness and depression, such as cough (59-100%) and heartburn or chest pain (25-65%) (Carvajalino et al., 2018; Rajala et al., 2016, 2017). Patients with hypercapnic respiratory failure treated with NIV experience dry mouth, sputum production, sleep difficulties and a lack of energy in addition to dyspnoea (Smith et al., 2019).

Cough is one of the most prevalent symptoms in patients with advanced respiratory disease. In a previous study by Rajala et al. concerning patients with

IPF, during the last two years of life, cough was one of the most severe symptoms regardless of the disease phase (Rajala et al., 2018). In patients with IPF, an ILD other than IPF, and COPD, 74.7%, 50.4% and 78.2%, respectively, have been reported to suffer from cough (Behr et al., 2015; Guenther et al., 2018; Jones et al., 2012).

Pain is one of the most common symptoms suffered by patients with advanced disease as they approach death, and almost 40% of them report severe pain (Lynn, 1997). In a previous study by Rajala et al., 82% and 66% of the patients with IPF suffered from pain during movement and pain at rest, respectively (Rajala et al., 2017).

Anxiety is common in patients with advanced disease, but it remains underdiagnosed and undertreated (Cully et al., 2006). Anxiety was reported in 31-61% of the patients with IPF, with this percentage increasing in patients with more severe dyspnoea (Holland et al., 2014; Rajala et al., 2017). Altogether, 25-28% of the patients with COPD were reported to have anxiety, and anxiety was common even in mild disease (Di Marco et al., 2006; Lewis et al., 2007).

2.4.2 Assessment of other symptoms

Some questionnaires have been developed to measure the overall symptom burden in patients with advanced disease, such as the Edmonton Symptom Assessment System (ESAS) (Bruera et al., 1991; Chang et al., 2000; Hannon et al., 2015; Hui & Bruera, 2017). The ESAS is a questionnaire that measures some of the most important symptoms, such as pain, dyspnoea, depression, anxiety and nausea, with an NRS scale from 0 (no symptoms) to 10 (worst possible symptom). Some questionnaires evaluate various symptoms and their severities, even though their primary purpose is to measure the quality of life, such as the 15-Dimensional (15-D) instrument (Sintonen, 2001) and disease-specific questionnaires such as the Severe Respiratory Insufficiency Questionnaire (SRI) for patients with chronic respiratory insufficiency on noninvasive ventilation. The 15-D instrument is a generic, comprehensive and self-administered questionnaire that consists of 15 dimensions, such as mobility, vision, hearing, breathing, sleeping, and depression (Sintonen, 1981).

Disease-specific tests measure symptoms associated with the specific disease. The most often used tests in the COPD are COPD Assessment Test (CAT™) and St. George's Respiratory Questionnaire (SGRQ). The CAT has 8 questions,

each scored from 0 to 5, and the cut-off value for being symptomatic enough to trigger maintenance treatment has been considered to be 10 points or more ("GOLD," 2021; Jones et al., 2009; Jones et al., 2011). The SGRQ was developed for patients with chronic airflow limitations, and it contains 76 items with scoring varying between sections, such as 0-1 (false or true) or 1-5 (Jones et al., 1992). The cut-off score on the SGRQ for the initiation of treatment for COPD has been considered to be at least 25 ("GOLD," 2021; Jones et al., 1992; Nishimura et al., 2013). The SGRQ has also been used to measure the quality of life in patients with IPF, even though it was not developed for use in these patients (Richeldi et al., 2014).

2.4.3 Management of other symptoms

Comprehensive treatment of symptoms consists of several aspects that should be considered when treating patients with advanced disease. The treatment of end-stage respiratory disease consists of pharmacological (such as bronchodilators, inhaled and oral steroids, exertional or long-term oxygen therapy, oral opioids, mucolytics, antidepressants and anxiolytic drugs) and non-pharmacological therapies (such as a hand-held fan to blow air over the face, nutrition, physiotherapy for mucus clearance, psychosocial support and counselling, pulmonary rehabilitation, breathing techniques and NIV) (Leach, 2010).

Cough is difficult to treat, but opioids can be used at least in end-stage disease (Raghu et al., 2011). Cough can also be associated with respiratory secretions. Mucolytics can be used in patients with advanced COPD who suffer from moist cough (Maddocks et al., 2017). Towards the end of life, the amount of respiratory secretions may increase due to impaired swallowing and weakened cough reflexes, leading to difficulty in the removal of respiratory secretions, and these secretions should be treated individually with physiotherapy interventions, such as repositioning, or by oropharyngeal suction (Phillips & Agar, 2016). Anticholinergics should be used cautiously because they may cause side effects such as delirium or dry mouth. As a part of end-of-life (EOL) treatment, parenteral hydration should be avoided to prevent or reduce secretions (Phillips & Agar, 2016).

Pain should be routinely assessed with a screening tool such as an NRS and adequately treated with analgesics and non-pharmacological interventions (Phillips & Agar, 2016).

Anxiety can be a consequence of progressing disease, deriving from unrelieved pain, dyspnoea or other symptoms, but it can also be derived from a previous anxiety disorder or premorbid alcohol or drug usage (Phillips & Agar, 2016). Anxiety can be managed with antidepressants such as selective serotonin reuptake inhibitors (SSRIs), buspirone and low-dose benzodiazepines (Cully et al., 2006; Maurer et al., 2008). However, benzodiazepines may worsen hypercapnia in hypoventilation (Maurer et al., 2008). The anxiety of patients and their families can also be relieved by psychotherapy and good advance care planning (ACP) and by the provision of appropriate psychosocial support (Cully et al., 2006; "GOLD," 2021). Additionally, pulmonary rehabilitation can positively affect anxiety and therefore the quality of life in patients with milder disease (Yohannes et al., 2010).

2.5 Performance status in advanced respiratory diseases

Physical activity is reported to be markedly impaired in patients with COPD compared with healthy coeval subjects, and physical activity is reported to be even lower in patients with COPD than in those with other chronic diseases, such as heart and vascular diseases, arthritis or neuromuscular diseases (Pitta et al., 2005; Tudor-Locke et al., 2009). Patients with newly diagnosed COPD with mild or moderate disease already have reduced physical activity (Spruit et al., 2015). Furthermore, in a study by Vaes et al., the decline to low physical activity levels was associated with increased mortality in patients with or without COPD (Vaes et al., 2014). The six-minute walk test (6MWT) distance has been reported to be the strongest correlate of daily activity, and a markedly impaired 6MWT distance is associated with very low physical activity in daily life (Pitta et al., 2005). Physical activity has been reported to be associated with the severity of dyspnoea, being lower in those with severe dyspnoea (Katajisto et al., 2012).

Activities of daily living (ADL) consist of areas concerning functional performance in everyday life, such as bathing, dressing, going to the toilet, transferring, continence and feeding (Katz et al., 1963). In the general older population (≥ 70 years), the life expectancy has been reported to be markedly reduced according to the amount of help needed in ADL, with only 1.6 years of life expectancy in patients not capable of performing any ADL compared with 10.6 years in patients with no difficulty in performing ADL (Stineman et al., 2012). Furthermore, patients with dyspnoea have been reported to be more likely

to need help with ADL (17.2%) than patients without dyspnoea (7.9%) (Smith et al., 2016; Tanaka et al., 2002). Katz et al. developed a questionnaire to help measure independence in ADL in the 1950s, and this questionnaire is widely used even today (Katz, 1979).

Patients with COPD and those with more severe disease have also been reported to be more dependent on help with ADL than patients without COPD or those with less severe disease (Kanervisto et al., 2010; Liu et al., 2014). In a study by Okubadejo et al., patients on LTOT were associated with a greater need for help with ADL than those not on LTOT owing to more severe disease or the LTOT itself restricting daily activities (Okubadejo et al., 1997).

2.6 Advance care planning in advanced respiratory diseases

Advance care planning (ACP) was defined by a Delphi panel in 2017 to enable individuals to define goals and preferences for their future medical treatment and care, discuss these goals and preferences with their family and health-care providers, and record and review these preferences if appropriate (Rietjens et al., 2017; Singer et al., 1996). A consensus by the European Association for Palliative Care recommends that ACP can be engaged at any stage of an individual's life, but the content of ACP should be more targeted at later ages or when the condition of health worsens and should be updated regularly (Rietjens et al., 2017).

Detering et al. reported that ACP reduces symptoms of anxiety and depression as well as post-traumatic stress in family members (Detering et al., 2010). They also reported that patients and their families were satisfied with the quality of hospital care if ACP was integrated with usual care. In a study by Brinkman-Stoppelenburg et al., ACP was shown to positively impact the quality of end-of-life care (Brinkman-Stoppelenburg et al., 2014). They also reported that do not resuscitate (DNR) and do-not-hospitalize (DNH) orders reduced the number of hospitalizations and increased the use of hospice care. In a previous study by Edmonds et al., patients with lung cancer were more likely to have family members present at the time of death than patients with chronic lung disease (Edmonds et al., 2001); furthermore, the majority of the family members would have liked to have been present at the time of death.

The ATS and BTS guidelines, Finnish Current Care Guidelines, in addition to the GOLD guidelines for COPD, recommend ACP to be integrated in the

routine outpatient management of progressive or advanced respiratory disease (Current Care Guidelines in Palliative and Hospice Care, 2020; "GOLD," 2021; Davidson et al., 2016; Lanken et al., 2008). However, even though many patients with chronic respiratory disease and their health-care professionals are interested in ACP, only a few of them have had these conversations (Jabbarian et al., 2018). Some explanations for this have been suggested, such as the disease course often being complex and unpredictable; the uncertainty of the prognosis; the fear of health-care professionals of patients losing hope with the discussion of ACP; or some system-related causes such as a lack of time, education or continuity of care (Jabbarian et al., 2018; Meehan et al., 2020). Patients with lung cancer are 40% more likely to be offered palliative care than patients with COPD (Halpin, 2018). Furthermore, in a study by Edmonds et al., patients with lung cancer were more aware of approaching death, and they were told of it earlier prior to death than patients suffering chronic lung disease (Edmonds et al., 2001). In a study by Nava et al., only approximately one-fifth of the patients treated in European respiratory intermediate care units had end-of-life care decisions made, although the mortality rate was 68% during the study period of 6 months (Nava et al., 2007).

The timing of ACP conversations is difficult in advanced respiratory diseases, as the disease progress differs vastly among individuals. At the time of diagnosis, the disease stage can be from mild to very severe, and sudden exacerbations can further affect the progression of disease. A review by Patel et al. and the GOLD guidelines suggest discussing ACP with patients shortly after the diagnosis of COPD or after the first exacerbation or hospitalization ("GOLD," 2021; Patel et al., 2012). Furthermore, some trigger points may be used to initiate ACP conversations, even if they may be poorly recognized by clinicians and patients. These trigger points may be, e.g., FEV_1 under 30%, the need for LTOT or NIV, one or more hospitalized exacerbations during the previous year, weight loss or cachexia, age at least 70 years, decreased functional status, increased dependence on others, a lack of further treatment options or a request from the patient or family member (Jabbarian et al., 2018; Meehan et al., 2020; Patel et al., 2012).

The prognosis of patients with chronic respiratory insufficiency varies greatly as a result of different underlying diseases with varying disease progression. It is important to know different factors associated with prognosis in chronic respiratory insufficiency and thus to be able to recognize the trigger points for ACP conversations. Furthermore, sorting out the most typical and burdensome symptoms together with their relationship to other symptoms can provide the background for comprehensive therapy and the planning of palliative care.

3 AIMS OF THE STUDY

The study was conducted to assess symptoms and survival among patients with chronic respiratory insufficiency.

The specific aims of the study were as follows:

1. To describe the overall symptom burden and its relation to depression in patients with chronic respiratory insufficiency (Study I)
2. To evaluate the association between dyspnoea upon exercise and overall symptom burden in patients with chronic respiratory insufficiency due to COPD or ILDs (Study II)
3. To study the survival and factors associated with survival in patients with chronic respiratory insufficiency (Studies III and IV)
4. To study the end-of-life aspects in patients with chronic respiratory insufficiency (Studies III and IV)

4 MATERIALS AND METHODS

4.1 Data collection (Studies I-IV)

This was a retrospective study based on the evaluation of medical records. All patients were treated in the respiratory insufficiency clinic at Tampere University Hospital due to chronic respiratory insufficiency. Tampere University Hospital, as well as the respiratory insufficiency clinic, provides care for approximately 530 000 inhabitants of Pirkanmaa county. The initiation of LTOT or NIV takes place in the acute pulmonary ward or in the respiratory insufficiency clinic. After the first visit, patients visit the respiratory insufficiency clinic or the pulmonary ward after one to three months and 1-2 times a year thereafter, or in some cases, less frequently. The need for long-term NIV or LTOT was re-evaluated during the following visits, and only the patients who were eligible for long-term treatment were included in the studies. Chronic respiratory insufficiency was defined as the need for LTOT or NIV based on the international criteria (Andersen et al., 2012; Bushby et al., 2010; Current Care Guidelines, 2019; Goldberg et al., 1999; Hardinge et al., 2015; NICE, 2016; Windisch et al., 2010).

Collected data included sex; age; height and weight; smoking status; need for help with activities of daily living (ADL); diagnoses; comorbidities; the results of microspirometry or spirometry, and arterial or capillary blood gas analyses; and settings and usage data of LTOT or NIV. In addition, the date of death, decisions on not to resuscitate and decisions to start end-of-life care were recorded. The data of the death certificates were recorded for patients included in Studies III and IV. The need for help in ADL was defined as the need for assistance from a family member working as a caregiver, receiving home care services from society (e.g., dietary services, ablution, dressing or medication) or staying permanently in a nursing home or a community hospital.

In addition to patient characteristics, data from the questionnaires, including the ESAS, mMRC and DEPS, were recorded for the patients included in Studies I and II.

The oxygen flow and pressures of NIV were recorded when a patient was discharged at the time of the initiation of the treatment in Studies III and IV. The

median daily usage hours for NIV between the previous and current visits were recorded from the memory card of the device at each visit.

The disease causing chronic respiratory insufficiency and the need for long-term NIV or LTOT was defined as the primary diagnosis, while other diseases were considered comorbidities. The attending physician of the chronic respiratory insufficiency clinic or the acute pulmonary ward made the diagnosis of chronic respiratory insufficiency, as well as the underlying diseases, complying with the current guidelines and clinical practice. The Charlson comorbidity index (CCI) was calculated for each patient based on the number and severity of comorbidities (Charlson et al., 1987, 1994). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages for the severity of airflow limitation was defined for patients with COPD ("GOLD," 2021).

4.2 Patients (Studies I-IV)

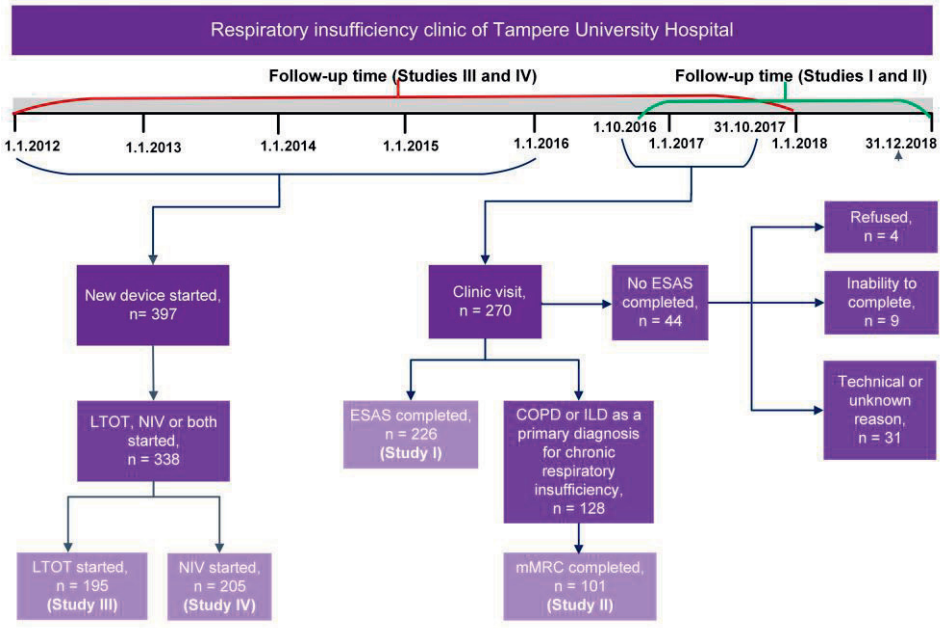


Figure 3. Selection of patients for enrolment in Studies I-IV

LTOT, Long-Term Oxygen Therapy; NIV, Noninvasive Ventilation; ESAS, Edmonton Symptom Assessment Scale; COPD, Chronic Obstructive Pulmonary Disease; ILD, Interstitial lung disease; mMRC, modified Medical Research Council dyspnoea scale

The key criteria for and timelines of patient selection for enrolment in the studies are shown in Figure 3.

4.2.1 Selection of patients (Studies I and II)

All the patients who visited the respiratory insufficiency clinic during the period from 1.10.2016 to 31.10.2017 were evaluated, and those included were followed up until 31.12.2018 or death. Patients who completed the ESAS questionnaire were included in Study I. Furthermore, patients who had COPD or an ILD as a primary diagnosis for chronic respiratory insufficiency and completed the mMRC were included in Study II.

4.2.2 Selection of patients (Studies III and IV)

Patients with chronic respiratory insufficiency who initiated LTOT (Study III) or NIV (Study IV) in the respiratory insufficiency clinic or pulmonary ward during the period from 1.1.2012 to 31.12.2015 were included in Studies III and IV. Only patients with no previous LTOT or NIV use were included. The patients were followed up until 31.12.2017 or death. During the study period, 397 patients were initiated with a new device. Of them 59 patients were initiated with only exertional oxygen. However, these patients were not included in this study because they did not fulfil the criteria for chronic respiratory insufficiency. Only 338 patients with LTOT (n = 133), NIV (n = 143) or both LTOT and NIV (n = 62) were included in Studies III and IV.

4.3 Questionnaires (Studies I and II)

The different symptoms affecting the everyday lives of patients with chronic respiratory insufficiency are evaluated routinely with different questionnaires in the respiratory insufficiency clinic. Patients complete the primary questionnaires (i.e., the ESAS and DEPS) and some other disease-specific secondary questionnaires (i.e., the mMRC, COPD Assessment Test, and Epworth Sleepiness Scale) to evaluate the treatment outcomes and well-being of the patients at each visit.

4.3.1 Edmonton Symptom Assessment System (ESAS)

The Edmonton Symptom Assessment System was originally developed to assess symptoms in patients with advanced cancer in palliative care (Bruera et al., 1991; Hui & Bruera, 2017) However, the ESAS has been widely used in many advanced diseases to assess the overall symptom burden (Hui & Bruera, 2017). The questionnaire assesses the severity of symptoms perceived on that day as self-rated on a numeric rating scale (NRS) from 0 (no symptoms) to 10 (worst possible symptoms) (Chang et al., 2000; Hannon et al., 2015). A modified version of the ESAS, first introduced in the Palliative Care Unit of Tampere University Hospital, was used in the respiratory insufficiency clinic during the study years. This modified version was also added with questions regarding pain in movement, dry mouth, insomnia and constipation compared with the widely used versions. In addition, drowsiness and tiredness were measured by only one question of tiredness/fatigue due to very similar expressions in the Finnish language. The modified version of the ESAS, with 12 questions, is shown in Table 4.

The cut-off value for moderate or severe symptoms was considered an ESAS score ≥ 4 points (Oldenmenger et al., 2013; Selby et al., 2010; Serlin et al., 1995).

Table 4. A modified version of the Edmonton Symptom Assessment System (ESAS) used in the respiratory insufficiency clinic of Tampere University Hospital

	No symptoms										Worst possible symptom
Pain at rest	0	1	2	3	4	5	6	7	8	9	10
Pain upon movement	0	1	2	3	4	5	6	7	8	9	10
Tiredness/Fatigue	0	1	2	3	4	5	6	7	8	9	10
Shortness of breath	0	1	2	3	4	5	6	7	8	9	10
Lack of appetite	0	1	2	3	4	5	6	7	8	9	10
Nausea	0	1	2	3	4	5	6	7	8	9	10
Dry mouth	0	1	2	3	4	5	6	7	8	9	10
Constipation	0	1	2	3	4	5	6	7	8	9	10
Depression	0	1	2	3	4	5	6	7	8	9	10
Anxiety	0	1	2	3	4	5	6	7	8	9	10
Insomnia	0	1	2	3	4	5	6	7	8	9	10
	Best										**Worst possible**
Well-being	0	1	2	3	4	5	6	7	8	9	10

4.3.2 Depression Scale (DEPS)

The Depression Scale questionnaire is a validated tool widely used in Finnish health care in which the patients self-rate their perceived mood and symptoms

during the last month (Salokangas et al., 1995). The DEPS was originally developed for screening for depression in primary health care, as shown in Table 5 (Salokangas et al., 1995). The questionnaire consists of 10 questions, each scored from zero to three points; thus, the total score varies from 0 to 30 points. The suggested cut-off scores are 9 points for depressive symptoms and 12 points for clinical depression (Kerminen et al., 2019; Poutanen et al., 2008, 2010;Sheehan & McGee, 2013). The cut-off score of 9 points has a high sensitivity for the identification of depressive symptoms and is therefore used as a threshold for further evaluation or diagnostic tests for depression (Kerminen et al., 2019; Poutanen et al., 2008, 2010).

Table 5. The Depression Scale (DEPS) questionnaire (Salokangas et al., 1995)

	Not at all	A little	Quite a lot	Extremely
I have suffered from insomnia	0	1	2	3
I have felt blue	0	1	2	3
I have felt everything was an effort	0	1	2	3
I have felt low energy or slowed down	0	1	2	3
I have felt lonely	0	1	2	3
I have felt hopeless about the future	0	1	2	3
I have not gotten any fun out of life	0	1	2	3
I have had feelings of worthlessness	0	1	2	3
I have felt all pleasure and joy has gone from life	0	1	2	3
I have felt that I cannot shake off the blues even with help from family and friends	0	1	2	3

4.3.3 Modified Medical Research Council dyspnoea scale (mMRC) questionnaire on dyspnoea

The modified Medical Research Council questionnaire on dyspnoea is a self-rated questionnaire on exertional dyspnoea (Bestall et al., 1999; Fletcher et al., 1960; Mahler & Wells, 1988). The scoring ranges from 0 to 4, as shown below in Table 6.

Table 6. Modified Medical Research Council dyspnoea scale (mMRC) (Mahler & Wells, 1988)

0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on the level or walking up a slight hill.
2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
3	I stop for breath after walking about 100 meters* or after a few minutes on the level.
4	I am too breathless to leave the house or I am breathless when dressing or undressing.

* Originally 100 yards, which accounts for 91.4 metres. The distance has been rounded to approximately 100 metres in SI units ("GOLD," 2021; Mahler & Wells, 1988).

4.4 Statistical analysis

Nonparametric tests were used because most of the distributions were non-normally distributed. The Mann-Whitney U or Kruskal-Wallis tests were used for comparisons of continuous variables, and Pearson's chi-square test or Fisher's exact test was used for comparisons of categorical variables for comparison between different groups. To calculate the survival estimates, the Kaplan-Meier method and Cox proportional hazard regression analysis were used. The statistical significance was set as $P < 0.05$.

In Study I, a receiver operating characteristic curve (ROC) analysis was used to evaluate the ability of the ESAS depression score to predict DEPS scores ≥ 9 points. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for ESAS depression scores of 0-10.

In Studies I and II, logistic regression multivariate analyses were conducted to assess the relationship between depression or dyspnoea upon exercise and other symptoms. In Study IV, Cox multivariate analysis was conducted in patients with COPD and OHS.

The data analyses were performed with IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY).

4.5 Ethical considerations

This was a retrospective study based on the evaluation of the medical records of patients treated in the respiratory insufficiency clinic of Tampere University Hospital. The Regional Ethics Committee of Tampere University Hospital, Finland, approved the study (approval code R15180/1.12.2015). The Research Director of Tampere University Hospital Research Centre approved access to medical records (10.12.2015).

5 SUMMARY OF RESULTS

5.1 Characteristics of the patients (Studies I-IV)

Overall, 270 patients visited the respiratory insufficiency clinic from 1.10.2016 to 31.10.2017. Of those, 226 patients who completed the ESAS questionnaire and 101 patients with COPD or an ILD and who completed the mMRC questionnaire were included in Studies I and II, respectively (Figure 3). For the patients included in Study I, the DEPS questionnaire was available for 208 patients. The ESAS and DEPS questionnaires were available in 98 and 91 patients in Study II, respectively.

Altogether, 338 patients initiated LTOT, NIV or both between 1.1.2012 and 31.12.2015. Of these patients, LTOT was initiated for 195 patients (Study III) and NIV was initiated for 205 patients (Study IV) (Figure 3). Both LTOT and NIV was initiated for 62 patients.

The patient characteristics are shown in Table 7. Most of the patients were men, and approximately two-thirds of the patients were ex-smokers or smokers in Studies III and IV. Patients on LTOT (Study III) were older (median age of 74 vs. 67 years, $P < 0.001$), had lower BMI (27.7 vs. 33.2, $P < 0.001$) and had more comorbidities (CCI 2.0 vs. 1.0, $P = 0.065$) than patients needing NIV (Study IV). The need for help with ADL was more common in patients on LTOT than in patients on NIV (46.2% vs. 34.6%, $P = 0.019$) (Studies III and IV). The most common diseases leading to chronic respiratory insufficiency were COPD and ILDs in patients on LTOT (Study III) and COPD and OHS in patients on NIV (Study IV). Of the patients with ILDs, 59.1% of them had IPF. Most of the patients with COPD had severe or very severe airflow limitation according to the GOLD classification, as 69.5% and 83.0% of the patients on LTOT or NIV belonged to GOLD III and IV, respectively (Studies III and IV) ("GOLD," 2021). Of the patients on LTOT or NIV, 17.0% and 27.2% belonged to GOLD II, respectively. Only three (3.3%) patients on LTOT had mild disease with severe emphysema.

Table 7. Patient characteristics (Studies I-IV)

	Study I	Study II	Study III	Study IV
Total, n	226	101	195	205
Sex, n (%)				
Male	130 (57.5)	65 (64.4)	121 (62.1)	120 (58.5)
Age, median (IQR)	72.0 (65.0–79.0)	75.0 (70.0–81.0)	74.0 (67.0–81.0)	67.0 (60.3–75.1)
BMI, kg/m^2, median (IQR)*	30.0 (23.8-38.5)‡	24.5 (21.1-29.3)	27.7 (23.1.-33.2)*	33.2 (25.5-43.3)†
Need for help in ADL, n (%)	78 (34.5)	38 (37.6)	90 (46.2)	71 (34.6)¥
Smoking status, n (%)				
Never-smoker	19 (8.4)	9 (8.9)	60 (30.8)	69 (33.7)
Ex-smoker	141 (62.4)	88 (87.1)	133 (68.2)	89 (43.4)
Smoker	65 (28.8)	4 (4.0)	1 (0.5)	46 (22.4)
Unknown	1 (0.4)	0 (0.0)	1 (0.5)	1 (0.5)
Primary disease causing the chronic respiratory insufficiency, n (%)				
COPD	104 (46.0)	89 (88.1)	92 (47.2)	53 (25.9)
Interstitial lung diseases	13 (5.8)	12 (11.9)	44 (22.6)	8 (3.9)
Heart diseases	12 (5.3)	0 (0.0)	15 (7.7)	0 (0.0)
Obesity hypoventilation syndrome	61 (27.0)	0 (0.0)	18 (9.2)	97 (47.3)
Amyotrophic lateral sclerosis	0 (0.0)	0 (0.0)	0 (0.0)	10 (4.9)
Other neurological diseases than Amyotrophic lateral sclerosis	14 (6.2)	0 (0.0)	3 (1.5)	17 (8.3)
Sleep apnoea	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Thoracic deformity	14 (6.2)	0 (0.0)	5 (2.6)	14 (6.8)
Other	6 (2.7)§	0 (0.0)	18 (9.2)Ÿ	6 (2.9)Ë
Comorbidities, n (%)				
Hypertension	151 (66.8)¥	65 (64.4)¥	120 (61.5)	127 (62.0)
Cardiovascular diseases	133 (58.8)¥	63 (63.4)¥	125 (64.1)	117 (57.1)
Diabetes	83 (36.7)¥	22 (21.8)¥	60 (30.8)	85 (41.5)
COPD	26 (11.5)¥	1 (1.0)¥	18 (9.2)	26 (12.7)
Asthma	55 (24.3)¥	21 (20.8)¥	27 (13.8)	48 (23.4)
Sleep apnoea	75 (33.2)¥	11 (10.9)¥	38 (19.5)	87 (42.4)
Neurological diseases	20 (8.8)¥	9 (8.9)¥	33 (16.9)	20 (9.8)
Renal diseases	25 (11.1)¥	8 (7.9)¥	18 (9.2)	19 (9.3)
Rheumatic diseases	16 (7.1)¥	7 (6.9)¥	18 (9.2)	15 (7.3)
Cancer	42 (18.6)¥	31 (30.7)¥	38 (19.5)	31 (15.1)
Others	70 (31.0)¥	22 (21.8)¥	49 (25.1)	99 (48.3)
No comorbidities			9 (4.6)	12 (5.9)
Charlson Comorbidity Index, median (IQR)	2.0 (1.0-3.0)	2.0 (0.0-2.0)	2.0 (1.0-3.0)	1.0 (1.0-2.0)

* Data missing in three patients due to being confined to bed, i.e., unable to perform measurements because of tetraplegia or muscle dystrophy

† Data missing in five patients due to being confined to bed, i.e., unable to perform measurements because of tetraplegia, multiple sclerosis, spinocerebellar ataxia or otherwise poor general condition (2)

‡ Data missing in one patient due to being confined to bed

§ Asthma with severe chronic obstruction (n = 4), bronchomalacia (n = 1), metastatic lung cancer (n = 1)

Ÿ Post pulmonary embolism (n = 9), postpneumonic state (n = 2), granulomatosis with polyangiitis (n = 1), asthma with severe chronic obstruction (n = 2), chronic multifocal Langerhans cell histiocytosis (n = 1), alcohol-related liver disease (n = 1), lung cancer (n = 1), malignant pleural mesothelioma (n = 1)

Ë Central hypoventilation due to opioids (n = 1), bronchiolitis obliterans (n = 1), severe asthma (n = 1), tracheobronchomalacia (n = 1), vocal cord dysfunction (n = 1), chronic pleuritis (n = 1)

¥ Unpublished data

IQR, Interquartile Range; BMI, Body Mass Index; ADL, Activities of Daily Living; COPD, Chronic Obstructive Pulmonary Disease

In Study I, 11 patients with heart disease had pulmonary hypertension and one patient had LTOT as a consequence of CHF being part of their palliative care. Patients with LTOT (Study III) and heart disease as the main cause of chronic respiratory insufficiency suffered from pulmonary hypertension (n = 11), very severe diastolic dysfunction (n = 2) and two patients with severe CHF received LTOT as part of their palliative treatment.

The most common comorbidities in all the studies were hypertension, cardiovascular diseases and diabetes (Table 7). Sleep apnoea was a comorbidity in 42.4% of the patients on NIV and in 33.2% of the patients included in Study I.

The results of spirometry and blood gas analyses, as well as the settings and usage data of the device used, are shown in Table 8. Spirometry results were available in all the studies, but the usage data and settings of devices and results of blood gas analyses were available only for the patients in Studies III and IV.

Table 8. Details of the spirometry and blood gas analyses and the settings and usage data of the device used (Studies I-IV)

	Study I	Study II	Study III	Study IV
Total, n (%)	226	101	195	205
FEV_1*				
litres, median (IQR)	1.16 (0.71-1.67)	0.90 (0.60-1.25)	1.30 (0.96-1.82)	1.23 (0.86-1.83)
% of predicted, median (IQR)	40.0 (27.0-57.0)	31.0 (23.0-48.5)	51.0 (36.5-64.5)	45.5 (33.0-59.0)
FVC*†				
litres, median (IQR)	2.46 (1.86-3.12)†	2.77 (2.20-3.37)†	2.49 (1.86-3.06)	2.30 (1.60-2.78)
% of predicted, median (IQR)	71.0 (54.0-83.0)†	77.0 (66.3-89.8)†	72.0 (57.0-84.0)	61.0 (49.0-71.5)
FEV_1/FVC, median (IQR)*†	0.62 (0.44-0.75)†	0.44 (0.31-0.62)†	0.63 (0.44-0.75)	0.67 (0.48-0.77)
PaO_2 with room air, (kPa), median (IQR)*			6.9 (6.3-7.4)	
PCO_2, (kPa), median (IQR)*				8.2 (7.1-9.6)
Used device, n (%)				
LTOT	85 (37.6)	64 (63.4)	133 (68.2)	0 (0.0)
NIV	92 (40.7)	10 (9.9)	0 (0.0)	143 (69.8)
LTOT and NIV	21 (9.3)	6 (5.9)	62 (31.8)	62 (30.2)
Portable oxygen only	22 (9.7)	17 (16.8)	0 (0.0)	0 (0.0)
CPAP	1 (0.4)	0 (0.0)	16 (8.2)	0 (0.0)
None	5 (2.2)	4 (5.9)	0 (0.0)	0 (0.0)
Oxygen flow, (l/min), median (IQR)*			1.5 (1.0-2.0)	
IPAP, cmH_2O, median (IQR)*				16.0 (14.0-18.0)
EPAP, cmH_2O, median (IQR)*				8.0 (6.0-10.0)
Average usage per day during the first year, hours, median (IQR)*			19.3 (10.0-24.0)†	5.9 (4.0-8.0)

* Number and reasons for missing values are described in detail in the original publications

† Unpublished data

FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; PaO2, Partial Pressure of Oxygen in arterial blood gas; PCO2, Partial Pressure of Carbon Dioxide in blood gases; LTOT, Long-Term Oxygen Therapy; NIV, Noninvasive Ventilation; CPAP, Continuous Positive Airway Pressure; IPAP, Inspiratory Positive Airway Pressure; EPAP, Expiratory Positive Airway Pressure

Concomitant LTOT and NIV were needed by 62 patients in Studies III (31.8%) and IV (30.2%), while only 9.3% and 5.9% of the patients in Studies I and II had concomitant needs for both LTOT and NIV, respectively. Five patients in Study I and four patients in Study II did not have either LTOT or NIV as they were unwilling to initiate LTOT or NIV, even they fulfilled the criteria for device initiation.

5.2 Overall symptom burden (Study I)

Measured with the ESAS questionnaire, the most severe symptoms in all the patients in Study I were shortness of breath (median 4.0, interquartile range (IQR) 2.0-7.0), pain upon movement (median, 3.0 IQR 0.0-6.0), tiredness (median 3.0, IQR 1.0-6.0) and dry mouth (median 3.0, IQR 1.0-7.0). Well-being was impaired as well (median 4.0, IQR 2.0-5.0). ESAS scores for pain at rest were missing in 9 patients and in other categories in 3-6 patients.

The threshold for moderate or severe symptom (NRS median score ≥ 4) was reached by 57.0% of the patients in shortness of breath, by 48.0% in dry mouth, by 44.1% in pain upon movement and by 41.8% in tiredness, as shown in Figure 4. The median scores and corresponding IQRs for each question in the ESAS questionnaire are shown in Figure 5.

The prevalence and severity of different symptoms according to the primary diagnosis are shown in Table 9. The most prevalent and severe symptoms in patients with COPD were shortness of breath and dry mouth. Pain upon movement was the most severe symptom in patients with OHS. Patients with ILDs had, on average, moderate or severe symptoms (NRS median score ≥ 4) in tiredness (median 5.0, IQR 1.5-8.0), shortness of breath (median 5.0, IQR 2.5-7.0) and dry mouth (median 7.0, IQR 4.5-9.0).

The median total score on the ESAS was 27.0 (IQR 14.5-43.0) for all patients. The total median scores for patients with COPD, OHS, ILDs and other diseases were 31.0 (IQR 20.0-45.0), 22.0 (9.5-39.5), 31.0 (20.0-52.0) and 22.5 (11.8-38.8), respectively.

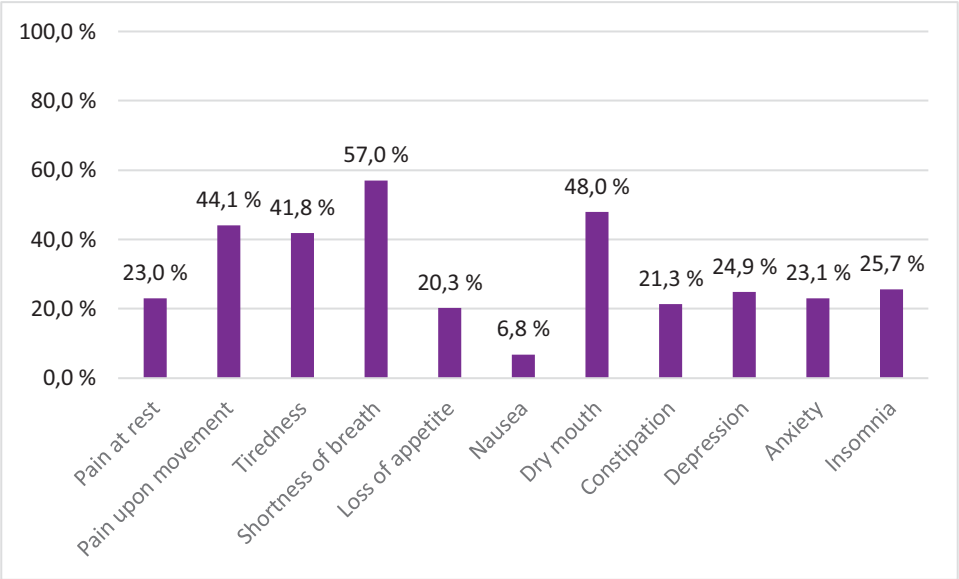


Figure 4. The proportion (%) of patients with at least moderate symptoms (≥ 4 points) on each question of the Edmonton Symptom Assessment System (ESAS) questionnaire (Study I)

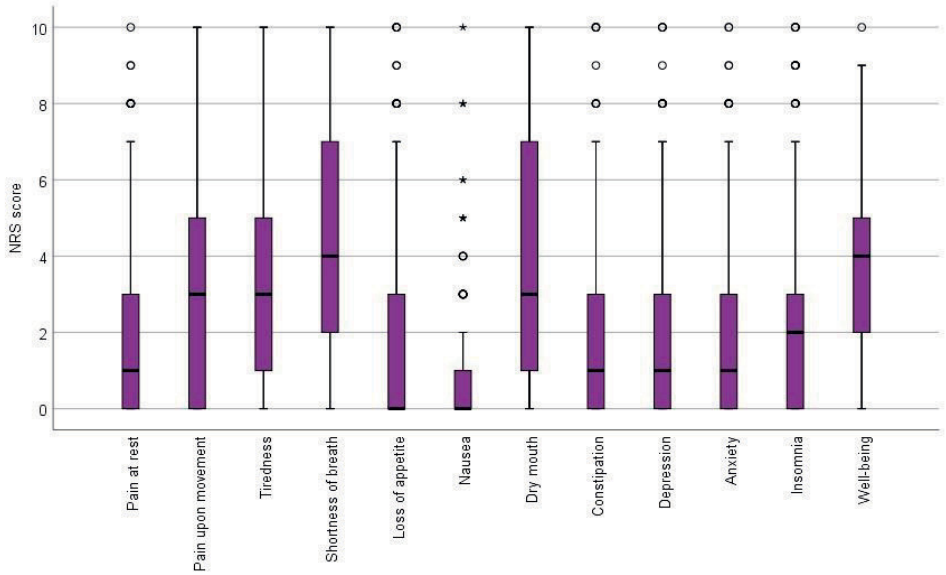


Figure 5. Median scores and interquartile ranges (IQRs) on the Edmonton Symptom Assessment System (ESAS) questionnaire in patients with chronic respiratory insufficiency (Study I)

NRS, Numeric Rating Scale

Table 9. Scores and prevalence of symptoms measured with the modified Edmonton Symptom Assessment Scale (ESAS) questionnaire according to the most prevalent disease responsible for respiratory insufficiency (Study I)

	COPD (n = 104)		OHS (n = 61)		Others† (n = 61)		P value
	Prevalence‡ (%)	Score, median (IQR)	Prevalence‡ (%)	Score, median (IQR)	Prevalence‡ (%)	Score, median (IQR)	
Symptoms							
Pain at rest	50.5	1.0 (0.0-3.0)	62.5	2.0 (0.0-4.0)	52.5	1.0 (0.0-2.0)	0.15
Pain upon movement	70.3	2.0 (0.0-5.5)	72.9	4.0 (0.0-7.0)	73.3	2.5 (0.0-4.0)	0.29
Tiredness	86.1	3.0 (2.0-6.0)	75.9	2.0 (0.8-6.0)	78.7	3.0 (1.0-5.0)	0.18
Shortness of breath	95.1	6.0 (3.0-8.0)	74.1	3.0 (0.0-5.0)	75.0	3.0 (0.3-5.0)	< 0.001
Lack of appetite	62.1	1.0 (0.0-4.0)	34.5	0.0 (0.0-2.0)	42.6	0.0 (0.0-2.0)	0.004
Nausea	33.0	0.0 (0.0-1.0)	24.6	0.0 (0.0-0.5)	28.3	0.0 (0.0-1.0)	0.60
Dry mouth	87.5	5.0 (2.0-7.0)	67.8	2.0 (0.0-6.0)	80.0	3.0 (1.0-7.0)	0.01
Constipation	53.4	1.0 (0.0-4.0)	47.4	0.0 (0.0-2.0)	50.0	1.0 (0.0-3.0)	0.47
Depression	56.9	1.0 (0.0-4.0)	51.7	1.0 (0.0-3.3)	54.1	1.0 (0.0-3.0)	0.91
Anxiety	55.9	1.0 (0.0-4.0)	46.6	0.0 (0.0-3.0)	52.5	1.0 (0.0-3.0)	0.50
Insomnia	70.6	2.0 (0.0-4.0)	54.2	1.0 (0.0-5.0)	62.3	1.0 (0.0-3.0)	0.40
Well-being		4.0 (2.5-5.0)		3.0 (1.8-5.3)		3.0 (2.0-5.0)	0.20

† Others consisted of neurological diseases (n = 14), thoracic deformity (n = 14), interstitial lung diseases (n = 13), heart diseases (n = 12), sleep apnoea (n = 2) and others (n = 6)

‡ Prevalence defined as the proportion of patients with ESAS score ≥ 1

COPD, Chronic Obstructive Pulmonary Disease; OHS, Obesity Hypoventilation Syndrome; IQR, Interquartile Range

5.3 Screening of depression and symptoms associated with depression (Studies I-II)

Although depression was not one of the most common symptoms reported in the ESAS questionnaire, one-fourth (24.9%) of the patients scored at least the threshold for moderate or severe symptoms (NRS median score ≥ 4) on the ESAS depression question (Study I). The median DEPS score was 6.5 (IQR 3.0-11.8) points for all patients. The threshold for depressive symptoms (DEPS score ≥ 9) and depression (DEPS score ≥ 12) was reached by 38.9% and 25.0% of the patients, respectively. The cut-off for depressive symptoms was reached by 41.7%, 38.2%, 53.8% and 36.4%, whereas the cut-off for depression was reached by 27.1%, 23.6%, 38.5% and 27.3% of the patients with COPD, OHS, ILDs and heart diseases, respectively. The median DEPS scores were 7.0 (IQR 3.0-12.0), 6.0 (IQR 2.0-11.0), 10.0 (IQR 5.5-15.0) and 8.0 (IQR 3.0-17.0) for patients with COPD, OHS, ILDs and heart diseases, respectively.

The capability of the ESAS depression score to predict DEPS scores ≥ 9 points was evaluated in Study I by an ROC curve (Figure 6) (Study I). The area under the curve was 0.840 ($P < 0.001$).

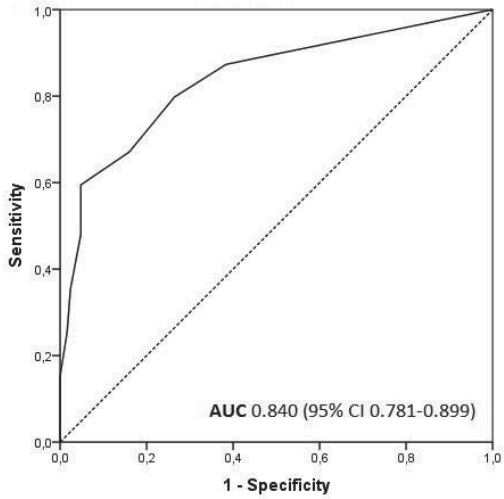


Figure 6. The receiver operating characteristic curve (ROC) for the Edmonton Symptom Assessment Scale (ESAS) depression score to predict a Depression Scale (DEPS) score of at least 9 points (Study I)

AUC, Area Under the Curve

The sensitivity, specificity, and positive and negative predictive values for ESAS scores to predict DEPS ≥ 9 points are shown in Table 10 (Study I). There was an 89% probability of a patient scoring under 9 points on the DEPS if he/she scored zero on the depression question of the ESAS. In addition, patients who scored at least four on the depression question of the ESAS had an 89% probability of scoring at least 9 points on the DEPS.

Table 10. Edmonton Symptom Assessment System (ESAS) depression scores' capability to predict Depression Scale (DEPS)* ≥ 9 points (Study I)

ESAS Depression score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
≥ 1	87	62	59	89	72
≥ 2	80	74	66	85	76
≥ 3	67	84	73	80	77
≥ 4	59	95	89	79	81
≥ 5	48	95	86	74	77
≥ 6	35	98	90	71	74
≥ 7	25	98	91	68	70
≥ 8	15	100	100	65	67
≥ 9	4	100	100	62	63
10	3	100	100	62	62

* DEPS was filled in 208 patients

PPV, Positive Predictive Value; NPV, Negative Predictive Value

The median scores and proportions of patients scoring at least four on each of the items of the ESAS questionnaire are shown according to DEPS category (< 9 or ≥ 9 points) in Table 11 (Study I). All the symptoms screened with the ESAS questionnaire were significantly more severe in patients scoring 9 points or more on the DEPS than in patients scoring < 9 points. Patients scoring at least 9 points on the DEPS had moderate or severe symptoms (NRS median score ≥ 4) in pain upon movement, tiredness, shortness of breath, dry mouth, depression and anxiety measured with the ESAS questionnaire. Overall well-being was better in patients scoring < 9 points on the DEPS than in patients scoring ≥ 9 points on the DEPS. The association of DEPS category with ESAS total score is shown in Figure 7.

Table 11. Median scores and proportions of patients with at least moderate symptoms (≥ 4 points) on the Edmonton Symptom Assessment System (ESAS) questionnaire according to Depression Scale (DEPS)† category (Study I)

	DEPS < 9 (n = 127)	DEPS ≥ 9 (n = 81)	P value*
ESAS scores			
Pain at rest			
median (IQR)	1.0 (0.0-3.0)	2.0 (0.0-4.5)	0.02
≥ 4, %	15.6	32.5	
Pain upon movement			
median (IQR)	2.0 (0.0-4.0)	4.5 (1.0-7.0)	0.001
≥ 4, %	36.3	57.7	
Tiredness			
median (IQR)	2.0 (0.0-4.0)	5.0 (3.0-7.0)	<0.001
≥ 4, %	29.0	63.3	
Shortness of breath			
median (IQR)	3.0 (1.0-5.0)	6.0 (3.0-8.0)	<0.001
≥ 4, %	48.8	69.2	
Lack of appetite			
median (IQR)	0.0 (0.0-2.0)	2.0 (0.0-5.0)	<0.001
≥ 4, %	10.4	38.0	
Nausea			
median (IQR)	0.0 (0.0-0.0)	1.0 (0.0-3.0)	<0.001
≥ 4, %	2.4	15.6	
Dry mouth			
median (IQR)	3.0 (1.0-5.0)	6.0 (3.0-8.0)	<0.001
≥ 4, %	36.2	67.9	
Constipation			
median (IQR)	0.0 (0.0-2.5)	2.0 (0.0-5.0)	<0.001
≥ 4, %	15.2	33.3	
Depression			
median (IQR)	0.0 (0.0-2.0)	4.0 (2.0-7.0)	<0.001
≥ 4, %	4.8	59.5	
Anxiety			
median (IQR)	0.0 (0.0-1.0)	4.0 (2.0-7.0)	<0.001
≥ 4, %	8.0	50.6	
Insomnia			
median (IQR)	1.0 (0.0-2.0)	3.0 (1.0-6.0)	<0.001
≥ 4, %	12.8	45.6	
Well-being			
median (IQR)	3.0 (1.0-5.0)	5.0 (4.0-6.0)	<0.001
Total score			
median (IQR)	21.0 (11.0-30.3)	43.0 (31.0-61.0)	

* Between patients with DEPS scores < 9 and those with DEPS scores ≥ 9 points

† DEPS score missing in 18 patients

IQR, Interquartile Range

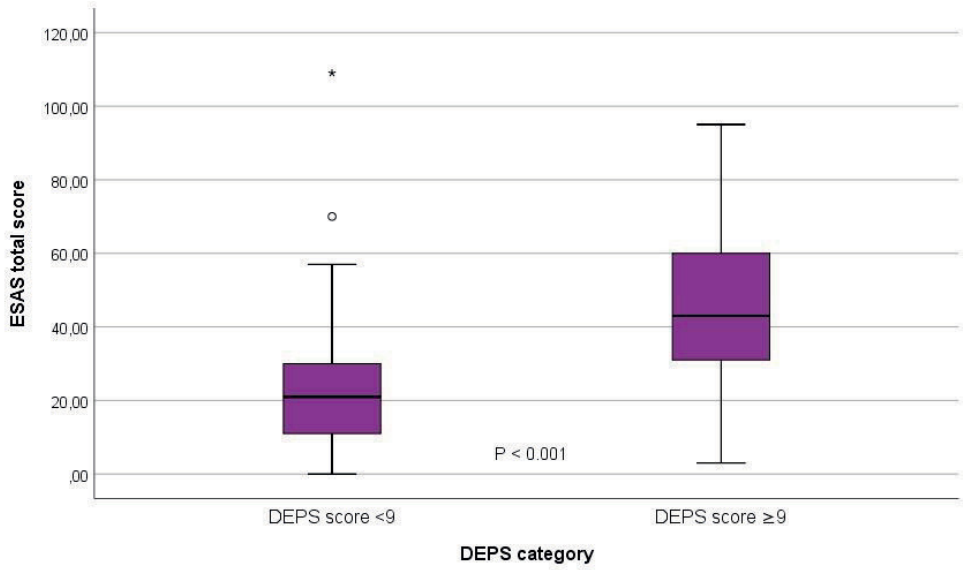


Figure 7. The total score on the Edmonton Symptom Assessment System (ESAS) according to the Depression Scale (DEPS) category in patients with chronic respiratory insufficiency (Study I)

Patients in categories mMRC 0-3 and mMRC 4 scored medians of 6.0 (2.5-10.5) and 9.5 (IQR 4.8-18.5) on the DEPS questionnaire, respectively (Study II). The cut-off threshold of 12 points on the DEPS, indicating depression, was reached by 20.8% and 42.1% of the patients in categories mMRC 0-3 and mMRC 4, respectively (P = 0.028) (Study II).

5.4 Symptoms and factors associated with exertional dyspnoea (Study II)

Patients with COPD and ILDs suffered from many symptoms, of which dyspnoea during exercise was the most common. Dyspnoea upon exercise was measured with the mMRC and ESAS questionnaires. The median dyspnoea scores on the mMRC and ESAS were 3.0 (IQR 3.0-4.0) and 6.0 (IQR 3.0-8.0), respectively. There was no difference in mMRC scores between patients with COPD (median 3.0, IQR 3.0-4.0) and those with ILDs (median 3.0, IQR 2.3-4.0) (P = 0.495). The median dyspnoea scores measured with the ESAS were 6.0 (IQR 3.5-8.0) for patients with COPD and 4.0 (IQR 2.3-6.8) for patients with ILDs (P = 0.175).

The symptom severities according to the mMRC category (mMRC 0-3 and mMRC 4) are shown in Table 12. Patients in category mMRC 4 had moderate or severe symptoms (NRS median score ≥ 4) measured with the ESAS questionnaire in pain upon movement, tiredness, shortness of breath and dry mouth. The total ESAS scores of the patients in mMRC categories 0-3 and 4 are shown in Figure 8.

Table 12. ESAS scores and prevalence of moderate and severe symptoms (NRS median score ≥ 4) according to mMRC* category in patients with chronic respiratory insufficiency due to COPD and ILDs (Study II)

	mMRC 0-3 (n = 55)	mMRC 4 (n = 43)	P value
ESAS scores			
Pain at rest			
median (IQR)	0.0 (0.0-3.0)	2.0 (0.0-4.0)	0.063
≥ 4, %	17.0	27.9	0.198
Pain upon movement			
median (IQR)	2.0 (0.0-4.0)	5.0 (0.0-6.0)	0.068
≥ 4, %	30.2	55.8	0.011
Tiredness			
median (IQR)	3.0 (1.0-5.0)	6.0 (3.0-7.0)	< 0.001
≥ 4, %	32.1	69.8	< 0.001
Shortness of breath			
median (IQR)	4.0 (2.0-6.0)	8.0 (6.0-9.0)	< 0.001
≥ 4, %	57.4	90.7	< 0.001
Lack of appetite			
median (IQR)	1.0 (0.0-3.0)	3.0 (0.0-6.0)	0.001
≥ 4, %	14.8	46.5	0.001
Nausea			
median (IQR)	0.0 (0.0-0.3)	0.0 (0.0-2.0)	0.027
≥ 4, %	3.7	9.3	0.255
Dry mouth			
median (IQR)	3.0 (1.0-6.0)	7.0 (4.0-8.0)	< 0.001
≥ 4, %	47.3	76.7	0.003
Constipation			
median (IQR)	1.0 (0.0-3.0)	2.0 (0.0-6.0)	0.072
≥ 4, %	18.5	41.9	0.012
Depression			
median (IQR)	1.0 (0.0-3.0)	2.0 (0.0-5.0)	0.120
≥ 4, %	22.2	40.5	0.053
Anxiety			
median (IQR)	1.0 (0.0-3.0)	3.0 (0.0-5.5)	0.007
≥ 4, %	22.2	45.2	0.017
Insomnia			
median (IQR)	2.0 (0.0-3.0)	3.0 (1.0-7.0)	0.027
≥ 4, %	18.9	39.5	0.025
Well-being			
median (IQR)	3.0 (2.0-5.0)	5.0 (4.0-6.0)	< 0.001
Total score			
median (IQR)	24.0 (15.8-34.8)	44.0 (34.0-63.0)	< 0.001

* Data missing in three patients: inability to fill in the questionnaire (2), unwillingness to answer the questionnaire (1).

ESAS, Edmonton Symptom Assessment System; NRS, Numeric Rating Scale; mMRC, modified Medical Research Council dyspnoea scale; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IQR, Interquartile range

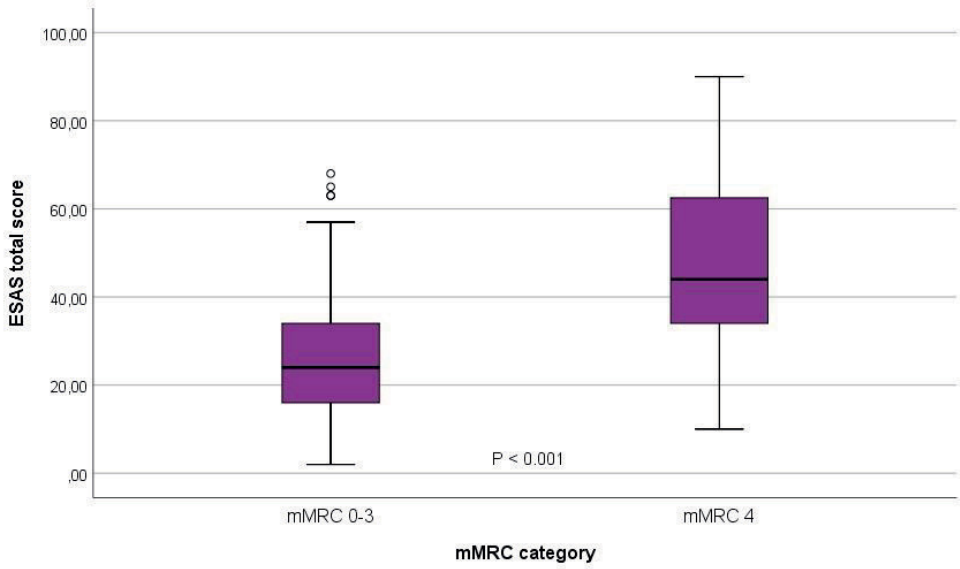


Figure 8. The total score on the Edmonton Symptom Assessment Scale (ESAS) according to the modified Medical Research Council dyspnoea scale (mMRC) category in patients with chronic respiratory insufficiency due to COPD and ILDs (Study II)

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IQR, Interquartile range

Patients with more severe dyspnoea (mMRC 4) were significantly more dependent on outside help in ADL (63.0%) than patients in dyspnoea categories mMRC 0-3 (16.4%, P <0.001).

5.5 Survival of the patients

5.5.1 Patients with chronic respiratory insufficiency and chronic respiratory insufficiency due to COPD or ILDs (Studies I and II)

Nearly one-third (31.4%, n = 71) of the patients included in Study I died during the follow-up time, and 59.2% of them died during the year following the visit to the respiratory insufficiency clinic (Study I, unpublished data). Of the patients included in Study II, 47.5% (n = 48) died during the follow-up time, and 60.4% of them died during the year following the visit to the clinic (Study II, unpublished data).

5.5.2 Patients on LTOT and NIV (Studies III and IV)

During the follow-up period, 133 (68.2%) and 90 (43.9%) of the patients on LTOT (Study III) and NIV (Study IV) died, respectively (Table 13). The overall survival of the patients using LTOT, NIV or both in Studies III and IV is shown in Figure 9.

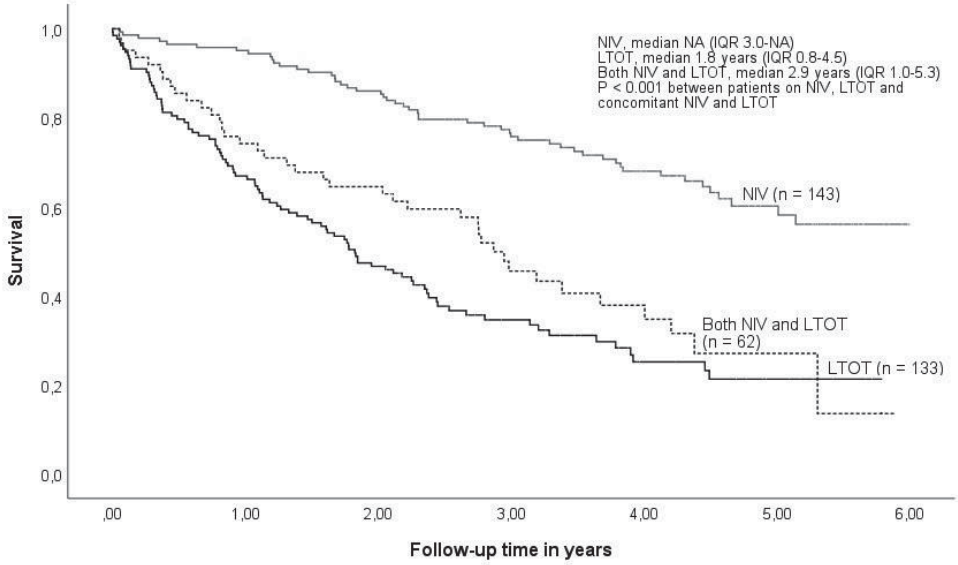


Figure 9. The overall survival of patients on NIV, LTOT and both NIV and LTOT (modified from Studies III and IV)

NIV, Noninvasive Ventilation; NA, Not Available; IQR, Interquartile Range; LTOT, Long-Term Oxygen Therapy

Patients needing only NIV had longer survival than patients needing only LTOT or patients needing both NIV and LTOT. The proportion of patients surviving over the first year after the initiation of LTOT, NIV or both was 66.9% (n = 89), 95.1% (n = 136) and 74.2% (n = 46), respectively (P < 0.001).

In patients on NIV (Study IV), the need for concomitant LTOT was associated with shorter survival than in no need for LTOT (hazard ratio, HR 2.8, 95% Confidence Interval, CI 1.9-4.3, P < 0.001). The median survival was 2.9 years (IQR 1.0-5.3) in patients with concomitant LTOT and the median was not reached in patients with only NIV (P < 0.001). Altogether, 69.6% (n = 16) of the patients who died during the first year after the initiation of NIV needed concomitant LTOT, whereas only 25.3% (n = 46) of the patients who survived

over the first year needed concomitant LTOT (P < 0.001) (Study IV, unpublished data).

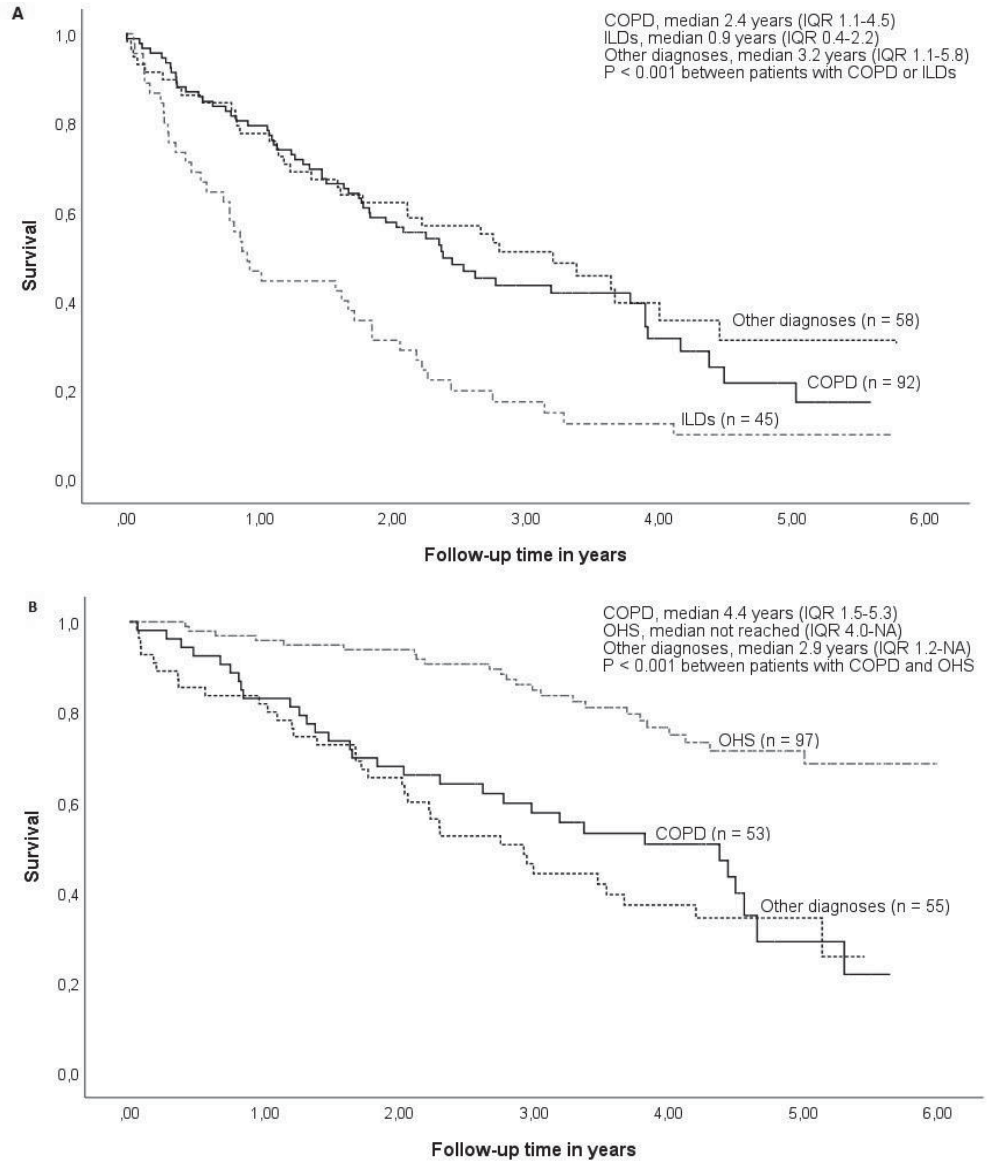


Figure 10. The survival of the patients according to the primary diagnosis causing the need for LTOT (Study III) (A) or NIV (Study IV) (B)

COPD, Chronic Obstructive Pulmonary Disease; IQR, Interquartile Range; ILDs, Interstitial Lung Diseases; OHS, Obesity Hypoventilation Syndrome

The survival of the patients varied according to the primary diagnosis (Figure 10). The median survival of the patients with COPD was 2.4 years and 4.4 years in Studies III and IV, respectively. The survival of the patients with ILDs was the worst, as 90.9% of the patients with ILDs needing LTOT and 100.0% (n = 8) of those needing NIV died during the follow-up period (Studies III and IV). There was no significant difference in survival between patients with IPF and those with other ILDs diagnoses, as the survival was 0.8 years (IQR 0.3-2.2) and 0.9 years (IQR 0.5-2.1) (P = 0.467) in patients with IPF and those with other diagnoses for ILDs, respectively (Study IV). Patients with COPD had longer survival than patients with ILDs (Study III). However, 63.0% and 58.5% of the patients with COPD on LTOT or NIV died during the follow-up, respectively (Studies III and IV). The detailed survival of patients on NIV due to other diagnoses shows that the median survival of patients with ALS, thoracic deformity or an ILD was 1.8, 3.7 and 0.2 years, respectively (Original publication IV, Supplementary Figure 1). The longest survival was in patients with OHS (Study IV).

Patients who were independent in ADL had longer survival than patients who needed help with ADL (Studies III and IV, Figure 11). The median survival of the patients needing help with ADL was 1.2 years (IQR 0.4-2.8, Study III) and 3.5 years (IQR 1.8-NA, Study IV) in patients with LTOT (with or without NIV) and NIV (with or without LTOT), respectively.

In multivariate analysis of patients on LTOT, the CCI and ILDs as the primary disease were independently associated with shorter survival (Table 3 in original publication of Study III). In patients on NIV, hypertension and older age were associated with shorter survival in multivariate analysis in patients with COPD, but none of the comorbidities were associated with shorter survival among patients with OHS (Supplementary Table 2 in original publication of Study IV).

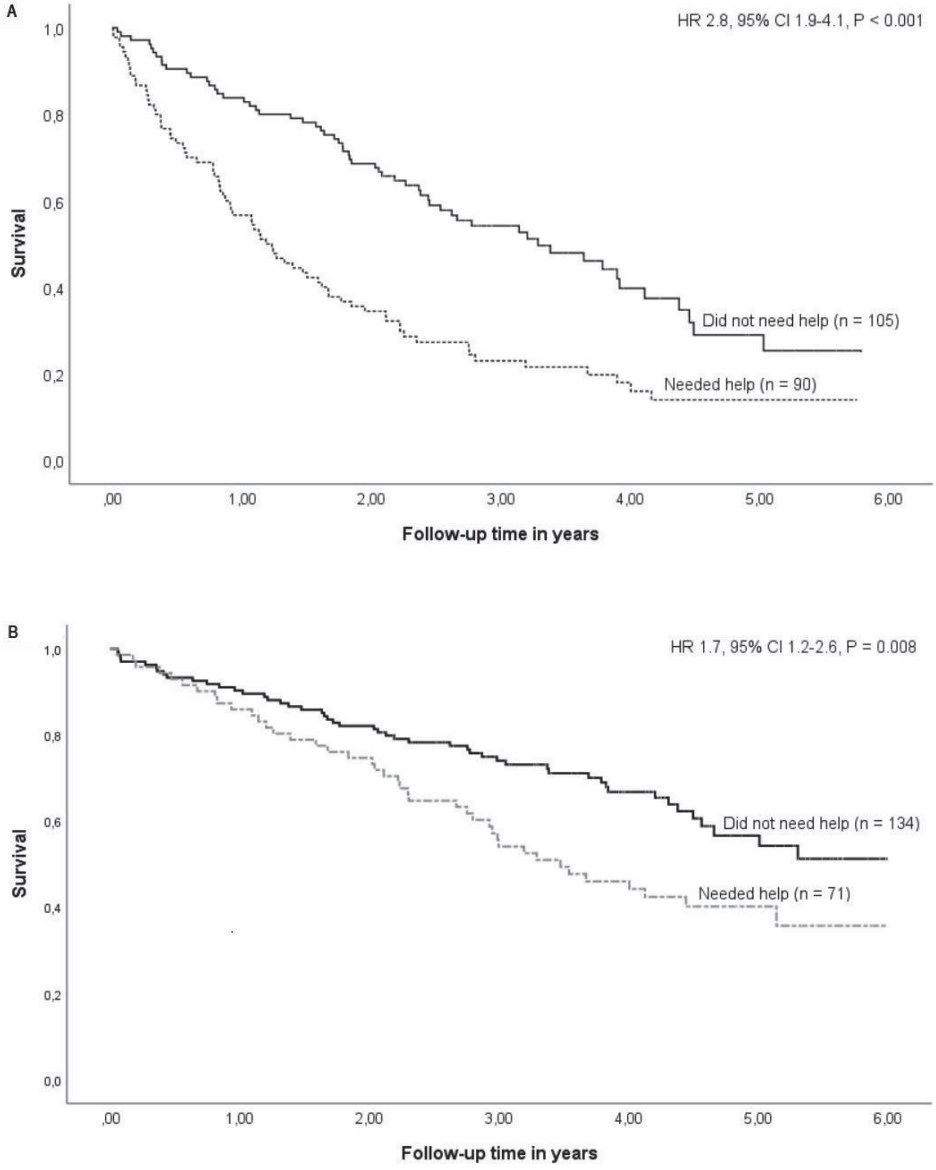


Figure 11. Survival of the patients according to the need for help in activities of daily living (ADL) in patients on long-term oxygen therapy (LTOT) (A) (Study III) and those on noninvasive ventilation (NIV) (B) (Study IV)

5.6 Aspects of end of life

Among patients with chronic respiratory insufficiency and treatment on LTOT or NIV, the reasons for death varied according to the underlying disease. In patients with COPD, the causes of death were COPD, heart diseases, cancer and chronic respiratory insufficiency in 59.2%, 22.5%, 15.5% and 2.8% of the patients, respectively. In patients with ILDs, the causes of death were ILD, heart diseases, cancer and other diseases in 62.5%, 10.0%, 15.0% and 12.5% of the patients, respectively. Finally, in patients with OHS, the causes of death were heart diseases, cancer, chronic respiratory insufficiency and other diseases in 36.0%, 12.0%, 16.0% and 36% of the patients, respectively. Overall, regardless of the device used, DNR and EOL decisions were made in 77.5% and 28.2% of the patients with COPD, respectively, and 40% of the patients with COPD and DNR decision arrived through the emergency department for the last hospitalization before death.

5.6.1 Patients on LTOT (Study III, unpublished data)

The end-of-life aspects in patients on LTOT are shown in Table 13 (Study III, unpublished data). Most of the patients had DNR decisions made previously or during the study period, and almost half of them had EOL decisions (consisting of decisions to withhold or withdraw life-prolonging treatments). The DNR decision was made for 70.7%, 80.0% and 80.0% of the deceased patients with COPD, ILDs and other diseases, respectively. The EOL decision was made for 29.3%, 27.5% and 51.4% of the patients with COPD, ILDs or other diseases, respectively. Altogether, 20 (76.9%) and 6 (23.1%) patients with IPF had DNR and EOL decisions made, respectively. The median time from DNR decision to death was 96 days (IQR 11-258) in all the patients on LTOT and 16 days (IQR 4-172) and 141 days (IQR 24-451) in patients with ILDs and COPD, respectively. Furthermore, 43.8% (n = 14) of the DNR decisions were made within 14 days prior to death in patients with ILDs.

Approximately half of the patients arrived through emergency care for the last hospitalization before death, and 60% of the deceased patients died in the hospital. Of the deceased patients, 51.7%, 70.0% and 62.9% of the patients with COPD, ILDs and other diseases died in the hospital, respectively. Altogether, 17 (66.7%) patients with IPF died in the hospital. Of the deceased patients with

COPD, 58.6% died due to COPD, and 60.0% of the patients with ILDs died due to ILD according to the death certificates.

Table 13. Characteristics related to the end of life among the deceased patients according to the device used (Studies III (unpublished data) and IV)

	LTOT	NIV
Total, *n*	195	205
Died before 31.12.2017, *n* (% of all)	133 (68.2)	90 (43.9)
Primary disease, n (%)		
COPD	58 (43.6)	31 (34.4)
OHS	7 (5.3)	24 (26.7)
ILDs	40 (30.1)	8 (8.9)
Cardiovascular disease	8 (6.0)	0 (0.0)
ALS	0 (0.0)	9 (10.0)
Neurological disease other than ALS	2 (1.5)	8 (8.9)
Others	18 (13.5)	10 (11.1)
DNR decision made before death, *n* (%)	101 (75.9)	79 (87.8)
End-of-life care decision made before death, *n* (%)	46 (34.6)	39 (43.3)
Place of death, *n* (%)		
Hospital	80 (60.2)	50 (55.6)
Home	22 (16.5)	18 (20.0)
Nursing home	11 (8.3)	7 (7.8)
Hospice	9 (6.8)	8 (8.9)
Emergency department	9 (6.8)	6 (6.7)
Not known	2 (1.5)	1 (1.1)
Cause of death, *n* (%)		
COPD	36 (27.1)	26 (28.9)
Heart disease	32 (24.1)	17 (18.9)
ILD	24 (18.0)	8 (8.9)
Cancer	21 (15.8)	10 (11.1)
Neurological disease	4 (3.0)	14 (15.6)
Chronic respiratory failure	3 (2.3)	5 (5.6)
Pneumonia or other infection	2 (1.5)	2 (2.2)
Other	11 (8.3)	8 (8.9)
Admission through the emergency department for the last hospitalization before death, *n* (%)	66 (49.6)	40 (44.4)

LTOT, Long-Term Oxygen Therapy; NIV, Noninvasive Ventilation; COPD, Chronic Obstructive Lung Disease; OHS, Obesity Hypoventilation Syndrome; ILD, Interstitial Lung Diseases; ALS, Amyotrophic Lateral Sclerosis; DNR, Do Not Resuscitate

5.6.2 Patients on NIV (Study IV)

The end-of-life characteristics of the deceased patients on NIV are shown in Table 13. The majority of the patients had DNR decisions made, and nearly half of them also had EOL decisions made. The DNR decision was made for 96.8%, 75.0% and 88.6% of the patients with COPD, OHS and other diseases, respectively. EOL decisions were made for 38.7%, 45.8% and 45.7% in patients with COPD, OHS and other diseases, respectively. The median time from DNR decision to death was 199 days (IQR 43-642) for all patients on NIV and 171 days (IQR 35-506) and 144 days (IQR 20-665) for patients with COPD and OHS, respectively. Of the patients with COPD, OHS and other diseases, 54.8%, 70.8%

and 45.7% died in the hospital, respectively. According to the death certificates, 74.2%, 12.9% and 12.9% of the patients with COPD died due to COPD, heart diseases and cancer, respectively, while the most common cause of death in patients with OHS was heart diseases (37.5%).

6 DISCUSSION

6.1 Patient populations

This thesis includes two retrospective samples of patients with chronic respiratory insufficiency who were treated in the respiratory insufficiency clinic of Tampere University Hospital. The first sample (Studies I and II) included patients visiting the clinic for about 12 months beginning in October 2016. These studies concentrated on the symptom burden in patients with chronic respiratory insufficiency and the association of dyspnoea or depression with other symptoms. Previous studies on overall symptom burden in patients with chronic respiratory insufficiency have been disease-specific, and patients in these studies often received LTOT with or without NIV. To our knowledge, there are no previous studies comparing the symptom burden between patients on LTOT and those on NIV due to COPD or other diseases. Gainza-Miranda et al. studied the symptom burden in patients with advanced COPD on LTOT, with one-third of them needing concomitant NIV (Gainza-Miranda et al., 2019). Other studies have focused on the symptom burden in specific diseases, in chronically ill patients or in association with specific symptoms, e.g., depression (Rajala et al., 2018; Wajnberg et al., 2013; Walke et al., 2006), but these have not reported the usage of LTOT or NIV. Some studies have reported the high prevalence of symptoms beyond respiratory symptoms in patients with acute exacerbations of COPD (Antoniu et al., 2019), but these patients are, of course, different from patients who have chronic respiratory insufficiency.

The second sample (Studies III and IV) included all patients who initiated LTOT or NIV between 2012 and 2015 due to chronic respiratory insufficiency. These patients were followed up until the end of 2017 or death, with follow-up times varying from 2 to 6 years, and information on survival and end-of-life aspects was obtained. Previous studies on undivided NIV users include the Eurovent study by Lloyd-Owen et al. in 2005 and a study by Cantero et al. in 2020, which focused mainly on the prevalence, aspects of initiation and settings used but not on end-of-life aspects or factors associated with survival. There are only a few studies on end-of-life aspects and survival in oxygen-dependent

patients with IPF and patients with OHS needing NIV, while the survival of patients with COPD is more widely studied (Ahmadi, et al., 2016b; Blankenburg et al., 2017; Budweiser, et al., 2007a).

6.2 Underlying diseases

In this thesis, the most common diseases leading to chronic respiratory insufficiency and the need for NIV were OHS and COPD, similar to the findings reported in a recent study by Cantero et al. (Cantero et al., 2020). However, in that cross-sectional study, COPD was by far the most common disease (38.9%), and only 26.0% of the patients had OHS, whereas in our study, 47.3% of the patients on newly initiated NIV had OHS. Furthermore, a smaller proportion of patients (27.0%) visiting the clinic during the year for routine check-ups had OHS because patients with OHS usually have less frequent follow-up check-ups if they have no problems with device usage. In contrast, patients with COPD had more frequent follow-ups due to more severe and advanced disease, as 46.0% of the patients visiting the clinic during the year had COPD. The most common diseases with indications for LTOT were COPD and ILDs, a finding that was also reported in a study by Ekström et al. (Ekström et al., 2017).

6.3 Symptom prevalence and degree of severity

In this study, patients with chronic respiratory insufficiency suffered from a variety of symptoms, which might be due to their primary disease or several comorbidities. The symptom burden in advanced cancer is far more studied than that in chronic respiratory insufficiency, and in fact, the ESAS was originally developed for screening symptoms in patients with advanced cancer (Hui & Bruera, 2017). In a previous study by Wajnberg et al., chronically ill patients were reported to have more severe symptoms if they had COPD (Wajnberg et al., 2013). In this thesis, the most severe symptoms in all the patients with chronic respiratory insufficiency were shortness of breath, dry mouth, pain upon movement and tiredness, as over 40% of the patients scored at least 4 in these categories. A previous study by Blinderman et al. reported that the most prevalent symptoms in patients with advanced COPD were dyspnoea, fatigue, dry mouth, cough and anxiety, as measured by another symptom questionnaire, the Memorial

Symptom Assessment Scale (MSAS) (Blinderman et al., 2009); however, in this study, the most prevalent symptoms in patients with advanced COPD were dyspnoea, tiredness, dry mouth, insomnia, pain upon movement and a lack of appetite.

Shortness of breath and dry mouth were found to be the most severe symptoms in patients with COPD and ILDs, which is understandable, as dyspnoea is one of the main symptoms in these diseases (Carvajalino et al., 2018; Moens et al., 2014). Furthermore, dyspnoea has also been reported to be the most bothersome symptom in COPD (Miravitlles et al., 2013). Dry mouth is less often recognized as an important symptom in COPD, although over half of the patients with at least moderate COPD suffer from it (Blinderman et al., 2009; Eckerblad et al., 2014), and dry mouth has been reported to increase before death in patients with IPF (Rajala et al., 2018). However, these earlier studies did not report the use of LTOT or NIV in the patients studied. In this thesis, the severity of dry mouth was more severe and prevalent in patients with chronic respiratory insufficiency due to COPD or ILDs compared with previous studies (Eckerblad et al., 2014; Lim et al., 2017; Rajala et al., 2018). This might be due to the more frequent use of NIV or LTOT, as all the patients in our study had either LTOT or NIV compared with these previous studies concerning the symptoms of patients with certain diseases needing or not needing LTOT or NIV. The use of NIV or LTOT might cause dry mouth through the stronger airflow. Additionally, other factors, such as medication (e.g., anticholinergics) and mouth breathing due to shortness of breath, may lead to dry mouth. We observed that patients with OHS also suffered from several symptoms, of which pain upon movement was the most severe. We suggest that this might be due to musculoskeletal symptoms as a result of overweight. To our knowledge, the symptom burden in patients with OHS has not been reported previously.

Altogether, 38.9% of the patients with chronic respiratory insufficiency suffered from depressive symptoms (scoring at least 9 points on the DEPS), as reported in a previous study by Kerminen et al. (34%) (Kerminen et al., 2019). Depression is often underdiagnosed in patients with COPD and has been reported to be common in those with severe COPD needing or not needing LTOT (Lewis et al., 2007). However, some previous studies have reported contradictory results that depression may be even more prevalent in patients needing LTOT than in those not needing LTOT (Kayhan et al., 2018; Lacasse et al., 2001; Matte et al., 2016). There are no specific studies on the prevalence of depression in the overall population of patients on NIV, as previous studies have

focused on some specific diseases. Few studies on patients with OHS have reported CPAP treatment to reduce depressive symptoms (Argun Baris et al., 2016; Bouloukaki et al., 2018). In our study, the median DEPS score was over 9 (threshold for depressive symptoms) in patients with ILDs and under 9 in patients with COPD, OHS or heart diseases. Previous studies have shown depression to be prevalent in patients with ILDs, especially IPF, even without oxygen therapy (Carvajalino et al., 2018; Lee et al., 2017).

Depression should be screened systematically in patients with chronic respiratory insufficiency, as depression has been reported to be associated with more exacerbations and a greater utilization of emergency care (Blakemore et al., 2019; Miravitlles et al., 2014). We observed that depressive symptoms (as determined by a score of at least 9 on the DEPS) were also associated with a higher overall symptom burden. In a previous study by Kerminen et al., depressive patients with chronic respiratory insufficiency were reported to have more severe dyspnoea than patients without depression (Kerminen et al., 2019). In this thesis, we observed that the threshold for depression in the DEPS was more commonly reached in patients with more severe dyspnoea and vice versa. Patients with depressive symptoms suffered from more severe dyspnoea, therefore suggesting that both were associated with each other. Additionally, previous studies have reported the association of dyspnoea and depression in patients with ILDs and COPD (Holland et al., 2014; Martinez Rivera et al., 2016; Rajala et al., 2017; Ryerson et al., 2011, 2012). Furthermore, pulmonary symptoms have been reported to be more severe in depressive patients with COPD (Doyle et al., 2013; Sundh & Ekström, 2016). However, to our knowledge, there are no previous studies concerning the association of other symptoms, apart from pulmonary symptoms, with depression in patients with chronic respiratory insufficiency.

In this study, we observed that the depression question on the ESAS was able to identify patients with depressive symptoms as measured with the DEPS questionnaire. Cut-point scores between 2 and 4 on the ESAS depression question have been suggested for patients with cancer or in palliative care as a trigger point for a more detailed depression evaluation (Boonyathee et al., 2018; Oldenmenger et al., 2013; Ripamonti et al., 2014; Vignaroli et al., 2006). Additionally, in this study, the probability of a patient scoring at least 9 on the DEPS was 89% if they scored at least 4 on the ESAS depression question. Therefore, a score of at least 4 on the ESAS depression question might also be

considered a trigger point for further diagnostic tests for depression in patients with chronic respiratory insufficiency.

Respiratory failure has been reported to be an independent factor associated with a higher perception of dyspnoea in general (Ekström et al., 2016b). We also observed that more severe dyspnoea was associated with a higher overall symptom burden, including depression, in patients with chronic respiratory insufficiency due to COPD or ILDs. In our study, patients with severe dyspnoea (mMRC 4) had moderate or severe symptoms of pain upon movement, tiredness, shortness of breath and dry mouth. They also had significantly higher total scores on the ESAS than patients scoring 0-3 on the mMRC. A previous study by Rajala et al. showed that a higher mMRC score was associated with a more severe overall symptom burden in patients with IPF, but they did not report whether this was associated with chronic respiratory insufficiency (Rajala et al., 2017). A previous study by Elbehairy et al. reported on the use of comprehensive, individualized treatment of dyspnoea to reduce perceived dyspnoea as well as emergency visits (Elbehairy et al., 2020).

More severe dyspnoea should be a trigger point for comprehensive symptom screening and the treatment of other possible symptoms. Depression should be screened for in every patient with chronic respiratory insufficiency, as it is common and might worsen the overall symptom burden and dyspnoea.

6.4 Survival and factors associated with survival

We observed that the survival was worse in patients on LTOT (68.2%) than in those needing NIV (43.9%). The median survival time was 1.8 years in patients on LTOT but slightly longer (2.9 years) in those needing concomitant NIV. In this study population, the median survival time was not reached in patients on NIV, as less than 50% of them died during the follow-up. However, a recent study by Patout et al. reported the median survival time to be 6.6 years in patients needing NIV due to various underlying diseases (Patout et al., 2020) The difference between survival in patients on LTOT and those on NIV is probably not due to the type of device used but the differences in the underlying diseases and the type of respiratory insufficiency concerned.

The survival of patients with chronic respiratory insufficiency was greatly associated with the underlying disease, as previously reported (Chailleux et al., 1996; Laub & Midgren, 2007; Patout et al., 2020). The survival was worst in

patients with ILDs, as 91% of these patients died during the follow-up time, and their median survival was only 0.9 years, which was approximately the same as that previously reported in a study by Ahmadi et al. on oxygen-dependent patients with ILDs (0.7 years) (Ahmadi et al., 2016b). However, a far earlier study reported a survival of 1.3 years in patients with pulmonary fibrosis on LTOT (Chailleux et al., 1996). In our study, IPF was the most common diagnosis in patients with ILDs. The disease course in IPF is often unpredictable, with varying disease progression, but its course is usually progressive and fatal, as the median survival time from diagnosis is only approximately 4.5 years (Kaunisto et al., 2019). As the disease progresses, impaired gas exchange leads to hypoxaemia; therefore, survival is even worse at the time of LTOT initiation. Only a small proportion of patients with ILDs needed both LTOT and NIV (8 patients), and their median survival was only 0.2 years.

In patients on LTOT, the survival of patients with ILDs was worse than that of patients with COPD (0.9 years vs. 2.4 years), which is in line with an earlier study by Crockett et al. (Crockett et al., 1991). The survival of patients with COPD on LTOT in our study was better than that in a study by Law et al. (1.5 years) (Law et al., 2014). The median survival of patients with COPD on NIV was slightly better (4.4 years) than that in a previous study by Blankenburg et al. (3.9 years) (Blankenburg et al., 2017). Survival has been reported to be poor despite the use of NIV in patients with COPD and LTOT (Murphy et al., 2017). The actual reason for this is probably not studied well enough; however, it might be due to the initiation of LTOT fairly late in the disease course, although according to the specific criteria defined by guidelines, or due to the worse survival in patients with an emphysematous phenotype causing hypoxaemia (Brat et al., 2021). Another COPD phenotype results in hypoventilation, in which goal-directed NIV has been reported to have an effect on mortality (Köhnlein et al., 2014) and thus probably better survival than patients on LTOT. A previous study by Gainza-Miranda et al. on patients with advanced COPD on LTOT, of whom one-third had concomitant NIV, reported the survival being only 8.3 months after these patients had been referred to palliative care (Gainza-Miranda et al., 2019) In our study, those patients on NIV, despite the underlying disease, who also needed LTOT had worse survival than those not on LTOT. Most of the previous studies have been conducted in patients with COPD receiving LTOT, and some of them have had concomitant NIV; thus, there are no specific studies on differences in survival between patients on NIV and patients on NIV and

concomitant LTOT concerning patients with chronic respiratory insufficiency due to heterogeneous underlying diseases.

Patients with OHS needing NIV had the best survival compared with patients with other diagnoses, even though approximately one-fourth of them died during the follow-up time; thus, the survival was approximately 75%, with varying median follow-up times of approximately 2-6 years. Previous studies have reported 5-year survival rates between 65.0 and 70.2% in patients with OHS needing NIV (Budweiser et al., 2007a; Masa et al., 2019b). Patients with OHS have hypoventilation due to obesity and not progressive or advanced respiratory disease, probably explaining their better survival than other patients on NIV (Patout et al., 2020). NIV may prolong survival but it does not affect the underlying disease progression in advanced respiratory diseases and ALS, whereas NIV may be regarded as a treatment modality for chronic and stable OHS. Even though the sample of patients with ALS was small, with only 10 patients, their median survival (1.8 years) was impaired compared with that in other patients. This median survival was slightly higher than that reported in previous studies by Kleopa et al. and Sancho et al., who reported a mean survival time of 1.2 years and a median survival time of 1.5 years, respectively (Kleopa et al., 1999; Sancho et al., 2018). A previous study by Laub et al. reported that the survival was only 20% 2 years after the initiation of NIV or invasive ventilation (2.4%) in patients with ALS (Laub & Midgren, 2007).

Being able to act independently in activities of daily living is an important factor affecting the survival of patients with chronic respiratory insufficiency. Even in the general population of elderly people, the increased need for help in ADL is associated with impaired survival in the short term (Stineman et al., 2012). In our study, in both patients on LTOT and those on NIV, needing help in ADL was associated with worse survival. In a previous study concerning ADL in people at least 70 years of age, patients with COPD were more likely to have difficulties in ADL and were less likely to be physically active than patients without COPD (Liu et al., 2014), and further, moderate and severe COPD was associated with increased difficulties in ADL (Kanervisto et al., 2010). Patients with COPD and on LTOT have been reported to be less likely to be independent in ADL than patients with COPD not needing LTOT, but several factors, such as depression, also affect the loss of independence in ADL (Okubadejo et al., 1997; Paneroni et al., 2019).

At the time a patient with ILD has an advanced disease leading to the initiation of LTOT, the end-of-life aspects should be taken into consideration with the

patient, as these patients are at risk of dying during the following year. Additionally, the initiation of LTOT for patients with COPD and the need for help with ADL should be trigger points for ACP conversations, as their survival is markedly impaired.

6.5 End-of-life aspects

Overall, most of the patients on LTOT and NIV had DNR decisions made, and these decisions were made approximately 3 and 6 months prior to death in patients on LTOT and NIV, respectively. Furthermore, far fewer patients had EOL decisions made before death, a finding that is in line with those of previous studies (Nava et al., 2007; Rajala et al., 2016; Tavares et al., 2017).

Of the patients with IPF and on LTOT, as many as 67% died in the hospital, which was considerably more than previously reported (46%) (Ahmadi et al., 2016b). Additionally, another previous study on patients with IPF that did not report the need for LTOT reported that 57% of the patients died in the hospital (Lindell et al., 2015). However, in a Finnish study on deceased patients with IPF, in 80% of the patients, the place of death was a hospital (Rajala et al., 2016). As the disease course is variable and unpredictable in IPF, it is difficult to make DNR decisions and have timely ACP conversations with well-planned and comprehensive treatment even in advanced disease, although this is strongly recommended (Jabbarian et al., 2018). In our study population, more patients with IPF on LTOT had DNR decisions made (83%) than in a previous study by Rajala et al. (57%), but fewer patients had EOL decisions made (25%) than in the studies by Rajala et al. (32%) and Ahmadi et al. (41%) (Ahmadi et al., 2016b; Rajala et al., 2016). In our patients with ILD, the median time from DNR decision to death was 16 days, and the DNR decision was made for 44% of the patients two weeks before death, whereas in the previously mentioned study by Rajala et al., as many as 42% of the DNR decisions were made 3 days prior to death. Taken together, these results show that DNR decisions are made very late in the course of disease, which therefore might explain, at least partly, the high proportion of hospital deaths. In the study by Lindell et al., only a few patients (13.7%) were referred to palliative care, which occurred close to death (Lindell et al., 2015). Patients with ILDs are even less likely to be referred to palliative care than patients with lung cancer, although they have been reported to suffer from more severe and often untreated dyspnoea (Ahmadi et al., 2016b).

The cause of death in patients with COPD was most commonly COPD (59%), and other causes were heart diseases, cancer and chronic respiratory insufficiency. A previous study by Soto-Campos et al. reported the causes of death to be malignancies, acute respiratory insufficiency and cardiovascular diseases in hospitalized patients with COPD (Soto-Campos et al., 2013). In this thesis, DNR decisions were made for approximately 78% of the patients with COPD on LTOT or NIV, which was slightly less than that in a previous study by Fu et al. (86%) (Fu et al., 2018). Fu et al. also reported that only 30% of the DNR decisions were made before the last admission prior to death. In this study, patients with COPD were less likely to die in the hospital than patients with ILDs, but 53% of patients with COPD died in the hospital. In a previous study by Gainza-Miranda et al., patients with advanced COPD treated by a palliative home care team reported that 55% had an ACP conversation before death, and only 9% of the patients died in the hospital (Gainza-Miranda et al., 2019). EOL decisions were made for 29% of the patients with COPD in our study population. Our number of patients with DNR decisions was far higher and our percentage of patients with EOL decisions was far lower than those in the study by Gainza-Miranda et al., but their study population concerned patients already in palliative care, which might partly explain the lower percentage of deaths in the hospital. However, the treatment of patients with advanced respiratory disease and chronic respiratory insufficiency should contain a more systematic evaluation of the state of disease and ACP conversations, as recommended in guidelines ("GOLD," 2021; Lanken et al., 2008).

Patients with OHS had better survival, with approximately 25% of them dying during the follow-up. The most common causes of death were heart diseases and other comorbidities. Previously hospitalized patients with OHS have been reported to have a survival of 81% at a mean follow-up time of 3.2 years, and 48% of them had been misdiagnosed as having COPD instead of OHS (Marik & Chen, 2016). Thus, OHS itself, if treated on NIV, might not affect survival as much as the prevalence and severity of other diseases associated with marked obesity, as these are more important predictors of survival (Borel et al., 2013), even though there are also controversial studies on the effect of comorbidities (Budweiser et al., 2007a).

DNR decisions were carried out well in patients with chronic respiratory insufficiency, but, especially in patients with ILDs, they were made too late in the course of disease. EOL decisions had been made for far fewer patients with chronic respiratory insufficiency, which might have affected the high proportion

of hospital deaths. Patients with COPD and ILDs died mainly of the disease concerned, but patients with OHS died of comorbidities, thus suggesting more comprehensive treatment of patients with OHS.

6.6 Strengths and limitations

This thesis, which was based on retrospective studies, provides a real-life undivided sample of patients visiting the respiratory insufficiency clinic and therefore also needing more health-care services. This study provides information on which aspects a clinician should pay attention to when treating a patient on LTOT or NIV. These studies have quite a long follow-up time, and the sample of patients is large. Additionally, comprehensive information on other diseases suffered by patients with chronic respiratory insufficiency is included. This thesis provides practical information for clinicians treating patients with chronic respiratory insufficiency, in particular, which patients needs closer follow-up and which factors may be trigger points for advance care planning.

In elderly multimorbid people it is sometimes difficult to state the main disease and primary cause of respiratory insufficiency and which diseases are comorbidities. Due to the retrospective nature of the study, there were missing values in questionnaires, arterial blood gas samples in room air and spirometry results as a result of poor condition or an unwillingness of patients or missing values for unknown reasons. Some of the arterial blood gas values were missing the information on whether they were taken with or without oxygen or NIV. The first study comprised patients who visited the clinic for one year. Therefore, the patients with more difficulties on LTOT or NIV might have had more visits to the clinic and therefore a greater tendency to be included in the study than the patients with fewer problems and longer periods between visits. Furthermore, some patients might have been more willing to answer the questionnaires than other patients with poorer clinical conditions and co-operation.

In Study IV, which dates back to 2012-2015, the pressures used in NIV were lower than suggested based on studies published after our study years (Duiverman, 2018). However, the target PCO_2 level was achieved in these patients as recommended (Ergan et al., 2019; Macrea et al., 2020), even though initiation in an acute setting might have affected the results. A previous study by Crimi et al. reported that although high-pressure settings have been recommended to normalise PCO_2 to obtain improved survival and quality of life,

the most common mode of NIV was still low-pressure settings (Crimi et al., 2016). Crimi et al. also reported that NIV was also initiated in some cases to relieve dyspnoea, reduce hospital admissions and improve quality of life in patients with COPD. However, based on the current recommendations, some of the patients might have needed higher pressures to obtain a faster and sufficient reduction in PCO_2 (Ergan et al., 2019).

6.7 Clinical implications and future considerations

Patients with chronic respiratory insufficiency suffer from a wide variety of symptoms that are often underdiagnosed and become more difficult and prevalent as the severity of dyspnoea increases. Depression is often underdiagnosed and undertreated in these patients, further increasing dyspnoea and overall symptom burden. Therefore, systematic overall symptom screening is suggested for all patients with chronic respiratory insufficiency. Furthermore, effective treatment of dyspnoea and depression is suggested, as it might positively affect the quality of life and use of health-care services in these patients. If a patient scores at least 4 points on the ESAS depression question, more accurate diagnostic tests of depression should be targeted for these patients, and, if needed, a referral to a psychiatric nurse or psychiatrist should be made. Overall, a score at least 4 on any of the ESAS questions should lead to a more precise evaluation and treatment of the symptoms.

Clinicians treating patients with chronic respiratory insufficiency should be aware of the factors associated with survival. Trigger points for ACP conversations might be the need to initiate LTOT, especially if the underlying disease is an ILD. However, the need for NIV in patients with OHS is not a sign of poor survival, but clinicians should pay attention to the comprehensive treatment of these patients, including comorbidities. In all the patients with chronic respiratory insufficiency, regardless of the underlying disease or the type of respiratory insufficiency, the need for help in ADL was associated with worse survival, and they were at a risk of dying during the following year or two after the initiation of LTOT and during the three years following the initiation of NIV. Therefore, the need for help in ADL should be screened at every follow-up visit, and when the time comes for the need for outside help, it might be considered a trigger point for ACP conversations.

The treatment of patients with chronic respiratory insufficiency should be even more comprehensive in the future, taking into account the symptoms deriving from the underlying disease and comorbidities. More research is needed to obtain long-term follow-up information on how the overall symptom burden evolves before death in patients with chronic respiratory insufficiency and how these symptoms respond to different treatments. Furthermore, more research is needed on how DNR decisions with ACP conversations affect health-care utilization in the last months of life in patients with chronic respiratory insufficiency. Additionally, education and guidelines for end-of-life planning are needed for the palliative care of patients with non-malignant diseases with chronic respiratory insufficiency, excluding OHS. There is some evidence that NIV and high-flow oxygen alleviate dyspnoea in patients with advanced cancer but more studies are needed (Hui et al., 2013). More studies are also needed to determine how patients on LTOT and NIV are cared for in different hospitals and for whom not to initiate LTOT or NIV. Furthermore, it is also important to develop national guidelines on how the processes of the initiation of LTOT and NIV are carried out, as well as how follow-ups are organized in the future to provide uniform treatment protocols for patients with chronic respiratory insufficiency, including symptom-centred and palliative care aspects.

7 SUMMARY AND CONCLUSION

This was a retrospective cross-sectional study concerning patients with chronic respiratory insufficiency visiting the respiratory insufficiency clinic of Tampere University Hospital. We studied the symptom burden among patients with chronic respiratory insufficiency (Studies I and II) and the survival and factors associated with survival in patients in whom long-term oxygen therapy or long-term noninvasive therapy was initiated (Studies III and IV).

The main findings are as follows:

1. Patients with chronic respiratory insufficiency suffered from a high symptom burden. The most severe symptoms were shortness of breath, dry mouth, tiredness and pain upon movement. The symptoms were more severe in patients with depressive symptoms, who scored at least 9 points on the Depression Scale questionnaire. The depression question on the ESAS seemed to be able to identify patients' depressive symptoms as measured by the DEPS questionnaire.
2. More severe dyspnoea upon exercise was associated with more severe symptoms and overall symptom burden in patients with chronic respiratory insufficiency due to COPD or ILDs, as tiredness, shortness of breath, a lack of appetite, nausea, dry mouth, anxiety and well-being measured with the ESAS were significantly more severe in patients with an mMRC score of 4 than in patients with mMRC score of 0-3. More severe dyspnoea upon exercise was also associated with an increased need for help in ADL.
3. The overall survival of patients with chronic respiratory insufficiency varied greatly depending on the underlying disease and type of chronic respiratory insufficiency. The need for help in activities of daily living was associated with shorter survival in all patients. Overall, patients on LTOT had shorter survival than patients on NIV, and of them, patients with ILDs were at a greater risk of dying in approximately one year. In addition, concomitant use of LTOT in patients on NIV was associated with poor survival.

4. Patients with chronic respiratory insufficiency mainly died in the hospital after they had been admitted through the emergency department. Most of the deceased patients had DNR decisions made, but less than half of them had EOL decisions made even though they had advanced disease with poor prognosis.

In conclusion, patients with chronic respiratory insufficiency suffer from a wide variety of symptoms, of which dyspnoea is the most common and severe, further aggravating other symptoms. Untreated depression further worsens dyspnoea and other symptoms. Therefore, comprehensive and systematic symptom screening and efficient symptom management are needed. As the survival of patients needing help with ADL and those on LTOT is poor, ACP conversations should be considered at the time of the initiation of LTOT or when a patient becomes more dependent on outside help in ADL. Since many of the deceased patients died in the hospital even though they had DNR decisions made, timely ACP conversations with context expanding over limits of care should be integrated for the treatment of patients with chronic respiratory insufficiency due to advanced respiratory disease to obtain a better quality of end of life.

8 REFERENCES

Abernethy, A. P. (2003). Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ*, *327*(7414), 523–528. https://doi.org/10.1136/bmj.327.7414.523

Abernethy, A. P., McDonald, C. F., Frith, P. A., Clark, K., Herndon, J. E., Marcello, J., Young, I. H., Bull, J., Wilcock, A., Booth, S., Wheeler, J. L., Tulsky, J. A., Crockett, A. J., & Currow, D. C. (2010). Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *The Lancet*, *376*(9743), 784–793. https://doi.org/10.1016/S0140-6736(10)61115-4

Aboussouan, L. S., Khan, S. U., Meeker, D. P., Kay, S., & Mitsumoto, H. (1997). Effect of Noninvasive Positive-Pressure Ventilation on Survival in Amyotrophic Lateral Sclerosis. *Annals of Internal Medicine*, *127*(6), 450. https://doi.org/10.7326/0003-4819-127-6-199709150-00006

Adeloye, D., Chua, S., Lee, C., Basquill, C., Papana, A., Theodoratou, E., Nair, H., Gasevic, D., Sridhar, D., Campbell, H., Chan, K. Y., Sheikh, A., & Rudan, I. (2015). Global and regional estimates of COPD prevalence: Systematic review and meta–analysis. *Journal of Global Health*, *5*(2). https://doi.org/10.7189/jogh.05.020415

Adler, D., & Janssens, J.-P. (2019). The Pathophysiology of Respiratory Failure: Control of Breathing, Respiratory Load, and Muscle Capacity. *Respiration*, *97*(2), 93–104. https://doi.org/10.1159/000494063

Ahmadi, Z., Bornefalk-Hermansson, A., Franklin, K. A., Midgren, B., & Ekström, M. P. (2014). Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study. *Respiratory Research*, *15*(1), 30. https://doi.org/10.1186/1465-9921-15-30

Ahmadi, Z., Lundström, S., Janson, C., Strang, P., Emtner, M., Currow, D. C., & Ekström, M. (2015). End-of-life care in oxygen-dependent COPD and cancer: a national population-based study. *European Respiratory Journal*, *46*(4), 1190–1193. https://doi.org/10.1183/09031936.00035915

Ahmadi, Z., Sundh, J., Bornefalk-Hermansson, A., & Ekström, M. (2016a). Long-Term Oxygen Therapy 24 vs 15 h/day and Mortality in Chronic Obstructive Pulmonary Disease. *PLOS ONE*, *11*(9), e0163293. https://doi.org/10.1371/journal.pone.0163293

Ahmadi, Z., Wysham, N. G., Lundström, S., Janson, C., Currow, D. C., & Ekström, M. (2016b). End-of-life care in oxygen-dependent ILD compared with lung cancer: a national population-based study. *Thorax*, *71*(6), 510–516. https://doi.org/10.1136/thoraxjnl-2015-207439

Akena, D., Joska, J., Obuku, E. A., Amos, T., Musisi, S., & Stein, D. J. (2012). Comparing the accuracy of brief versus long depression screening instruments which have been validated in low and middle income countries: a systematic review. *BMC Psychiatry*, *12*(1), 187. https://doi.org/10.1186/1471-244X-12-187

Alakhras, M., Decker, P. A., Nadrous, H. F., Collazo-Clavell, M., & Ryu, J. H. (2007). Body Mass Index and Mortality in Patients With Idiopathic Pulmonary Fibrosis. *Chest*, *131*(5), 1448–1453. https://doi.org/10.1378/chest.06-2784

Alison, J. A., McKeough, Z. J., Leung, R. W. M., Holland, A. E., Hill, K., Morris, N. R., Jenkins, S., Spencer, L. M., Hill, C. J., Lee, A. L., Seale, H., Cecins, N., & McDonald, C. F. (2019). Oxygen compared to air during exercise training in COPD with exercise-induced desaturation. *European Respiratory Journal*, *53*(5), 1802429. https://doi.org/10.1183/13993003.02429-2018

Andersen, P. M., Abrahams, S., Borasio, G. D., de Carvalho, M., Chio, A., Van Damme, P., Hardiman, O., Kollewe, K., Morrison, K. E., Petri, S., Pradat, P.-F., Silani, V., Tomik, B., Wasner, M., & Weber, M. (2012). EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) - revised report of an EFNS task force. *European Journal of Neurology*, *19*(3), 360–375. https://doi.org/10.1111/j.1468-1331.2011.03501.x

Antoniu, S. A., Apostol, A., & Boiculese, L. V. (2019). Extra-respiratory symptoms in patients hospitalized for a COPD exacerbation: Prevalence, clinical burden and their impact on functional status. *The Clinical Respiratory Journal*, *13*(12), 735–740. https://doi.org/10.1111/crj.13083

Argun Baris, S., Tuncel, D., Ozerdem, C., Kutlu, H., Onyilmaz, T., Basyigit, I., Boyaci, H., & Yildiz, F. (2016). The effect of positive airway pressure therapy on neurocognitive functions, depression and anxiety in obesity hypoventilation syndrome. *Multidisciplinary Respiratory Medicine*, *11*(1), 35. https://doi.org/10.1186/s40248-016-0071-2

Backman, H., Vanfleteren, L., Lindberg, A., Ekerljung, L., Stridsman, C., Axelsson, M., Nilsson, U., Nwaru, B. I., Sawalha, S., Eriksson, B., Hedman, L., Rådinger, M., Jansson, S. A., Ullman, A., Kankaanranta, H., Lötvall, J., Rönmark, E., & Lundbäck, B. (2020). Decreased COPD prevalence in Sweden after decades of decrease in smoking. *Respiratory Research*, *21*(1), 1–12. https://doi.org/10.1186/s12931-020-01536-4

Banerjee, D., Yee, B. J., Piper, A. J., Zwillich, C. W., & Grunstein, R. R. (2007). Obesity Hypoventilation Syndrome: Hypoxemia during continuous positive airway pressure. *Chest*, *131*(6), 1678–1684. https://doi.org/10.1378/chest.06-2447

Barnes, S., Gott, M., Payne, S., Parker, C., Seamark, D., Gariballa, S., & Small, N. (2006). Prevalence of Symptoms in a Community-Based Sample of Heart Failure Patients. *Journal of Pain and Symptom Management*, *32*(3), 208–216. https://doi.org/10.1016/j.jpainsymman.2006.04.005

Bausewein, C., Farquhar, M., Booth, S., Gysels, M., & Higginson, I. J. (2007). Measurement of breathlessness in advanced disease: A systematic review. *Respiratory Medicine*, *101*(3), 399–410. https://doi.org/10.1016/j.rmed.2006.07.003

Bausewein, Claudia, Booth, S., Gysels, M., Kühnbach, R., Haberland, B., & Higginson, I. J. (2010). Individual breathlessness trajectories do not match summary trajectories in advanced cancer and chronic obstructive pulmonary disease: results from a longitudinal study. *Palliative Medicine*, *24*(8), 777–786. https://doi.org/10.1177/0269216310378785

Beck, A. T. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry*, *4*(6), 561. https://doi.org/10.1001/archpsyc.1961.01710120031004

Beck, Aaron T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, *8*(1), 77–100. https://doi.org/10.1016/0272-7358(88)90050-5

Behr, J., Kreuter, M., Hoeper, M. M., Wirtz, H., Klotsche, J., Koschel, D., Andreas, S., Claussen, M., Grohé, C., Wilkens, H., Randerath, W., Skowasch, D., Meyer, F. J., Kirschner, J., Gläser, S., Herth, F. J. F., Welte, T., Huber, R. M., Neurohr, C., … Pittrow, D. (2015). Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. *European Respiratory Journal*, *46*(1), 186–196. https://doi.org/10.1183/09031936.00217614

Bell, E. C., Cox, N. S., Goh, N., Glaspole, I., Westall, G. P., Watson, A., & Holland, A. E. (2017). Oxygen therapy for interstitial lung disease: a systematic review. *European*

Respiratory Review, *26*(143), 160080. https://doi.org/10.1183/16000617.0080-2016

Bestall, J. C., Paul, E. A., Garrod, R., Garnham, R., Jones, P. W., & Wedzicha, J. A. (1999). Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*, *54*(7), 581–586. https://doi.org/10.1136/thx.54.7.581

Birnkrant, D. J., Bushby, K., Bann, C. M., Alman, B. A., Apkon, S. D., Blackwell, A., Case, L. E., Cripe, L., Hadjiyannakis, S., Olson, A. K., Sheehan, D. W., Bolen, J., Weber, D. R., & Ward, L. M. (2018). Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *The Lancet Neurology*, *17*(4), 347–361. https://doi.org/10.1016/S1474-4422(18)30025-5

Bjoraker, J. A., Ryu, J. H., Edwin, M. K., Myers, J. L., Tazelaar, H. D., Schroeder, D. R., & Offord, K. P. (1998). Prognostic Significance of Histopathologic Subsets in Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine*, *157*(1), 199–203. https://doi.org/10.1164/ajrccm.157.1.9704130

Blakemore, A., Dickens, C., Chew-Graham, C. A., Afzal, C. W., Tomenson, B., Coventry, P. A., & Guthrie, E. (2019). Depression predicts emergency care use in people with chronic obstructive pulmonary disease: a large cohort study in primary care. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 14*, 1343–1353. https://doi.org/10.2147/COPD.S179109

Blankenburg, T., Benthin, C., Pohl, S., Bramer, A., Kalbitz, F., Lautenschläger, C., & Schütte, W. (2017). Survival of Hypercapnic Patients with COPD and Obesity Hypoventilation Syndrome Treated with High Intensity Non Invasive Ventilation in the Daily Routine Care. *The Open Respiratory Medicine Journal*, *11*(1), 31–40. https://doi.org/10.2174/1874306401711010031

Blinderman, C. D., Homel, P., Andrew Billings, J., Tennstedt, S., & Portenoy, R. K. (2009). Symptom Distress and Quality of Life in Patients with Advanced Chronic Obstructive Pulmonary Disease. *Journal of Pain and Symptom Management*, *38*(1), 115–123. https://doi.org/10.1016/j.jpainsymman.2008.07.006

Böing, S., & Randerath, W. J. (2015). Chronic hypoventilation syndromes and sleep-related hypoventilation. *Journal of Thoracic Disease*, *7*(8), 1273–1285. https://doi.org/10.3978/j.issn.2072-1439.2015.06.10

Boonyathee, S., Nagaviroj, K., & Anothaisintawee, T. (2018). The Accuracy of the Edmonton Symptom Assessment System for the Assessment of Depression in Patients With Cancer: A Systematic Review and Meta-Analysis. *American Journal of Hospice and Palliative Medicine®*, *35*(4), 731–739. https://doi.org/10.1177/1049909117745292

Borel, J.-C., Burel, B., Tamisier, R., Dias-Domingos, S., Baguet, J.-P., Levy, P., & Pepin, J.-L. (2013). Comorbidities and Mortality in Hypercapnic Obese under Domiciliary Noninvasive Ventilation. *PLoS ONE*, *8*(1), e52006. https://doi.org/10.1371/journal.pone.0052006

Borg, G. (1970). Perceived exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitation Medicine*, *2*(2), 92–98.

Bouloukaki, I., Mermigkis, C., Michelakis, S., Moniaki, V., Mauroudi, E., Tzanakis, N., & Schiza, S. E. (2018). The Association Between Adherence to Positive Airway Pressure Therapy and Long-Term Outcomes in Patients With Obesity Hypoventilation Syndrome: A Prospective Observational Study. *Journal of Clinical Sleep Medicine*, *14*(09), 1539–1550. https://doi.org/10.5664/jcsm.7332

Bourke, S. C., Tomlinson, M., Williams, T. L., Bullock, R. E., Shaw, P. J., & Gibson, G. J. (2006). Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *The Lancet Neurology*, *5*(2), 140–147. https://doi.org/10.1016/S1474-4422(05)70326-4

Boyd, K., & Murray, S. A. (2010). Recognising and managing key transitions in end of life care. *BMJ*, *341*(sep16 2), c4863–c4863. https://doi.org/10.1136/bmj.c4863

Brat, K., Svoboda, M., Zatloukal, J., Plutinsky, M., Volakova, E., Popelkova, P., Novotna, B., Dvorak, T., & Koblizek, V. (2021). The Relation Between Clinical Phenotypes, GOLD Groups/Stages and Mortality in COPD Patients – A Prospective Multicenter Study. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 16*, 1171–1182. https://doi.org/10.2147/COPD.S297087

Brinkman-Stoppelenburg, A., Rietjens, J. A., & van der Heide, A. (2014). The effects of advance care planning on end-of-life care: A systematic review. *Palliative Medicine*, *28*(8), 1000–1025. https://doi.org/10.1177/0269216314526272

Bruera, E, Kuehn, N., Miller, M. J., Selmser, P., & Macmillan, K. (1991). The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *Journal of Palliative Care*, *7*(2), 6–9.

Bruera, Eduardo, Schmitz, B., Pither, J., Neumann, C. M., & Hanson, J. (2000). The Frequency and Correlates of Dyspnea in Patients with Advanced Cancer. *Journal of Pain and Symptom Management*, *19*(5), 357–362. https://doi.org/10.1016/S0885-3924(00)00126-3

Budweiser, S., Riedl, S. G., Jörres, R. A., Heinemann, F., & Pfeifer, M. (2007a). Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. *Journal of Internal Medicine*, *261*(4), 375–383. https://doi.org/10.1111/j.1365-2796.2007.01765.xBudweiser, S., Hitzl, A. P., Jörres, R. A., Heinemann, F., Arzt, M., Schroll, S., & Pfeifer, M. (2007b). Impact of noninvasive home ventilation on long-term survival in chronic hypercapnic COPD: a prospective observational study. *International Journal of Clinical Practice*, *61*(9), 1516–1522. https://doi.org/10.1111/j.1742-1241.2007.01427.x

Buist, A. S., McBurnie, M. A., Vollmer, W. M., Gillespie, S., Burney, P., Mannino, D. M., Menezes, A. M., Sullivan, S. D., Lee, T. A., Weiss, K. B., Jensen, R. L., Marks, G. B., Gulsvik, A., & Nizankowska-Mogilnicka, E. (2007). International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *The Lancet*, *370*(9589), 741–750. https://doi.org/10.1016/S0140-6736(07)61377-4

Burdon, J. G. W., Juniper, E. F., Killian, K. J., Hargreave, F. E., & Campbell, E. J. (1982). The perception of breathlessness in asthma. *American Review of Respiratory Disease*, *126*(5), 825–828. https://doi.org/10.1164/arrd.1982.126.5.825

Burwell, C. S., Robin, E. D., Whaley, R. D., & Bickelmann, A. G. (1956). Extreme obesity associated with alveolar hypoventilation—A pickwickian syndrome. *The American Journal of Medicine*, *21*(5), 811–818. https://doi.org/10.1016/0002-9343(56)90094-8

Bushby, K., Bourke, J., Bullock, R., Eagle, M., Gibson, M., & Quinby, J. (2005). The multidisciplinary management of Duchenne muscular dystrophy. *Current Paediatrics*, *15*(4), 292–300. https://doi.org/10.1016/j.cupe.2005.04.001

Bushby, Katharine, Finkel, R., Birnkrant, D. J., Case, L. E., Clemens, P. R., Cripe, L., Kaul, A., Kinnett, K., McDonald, C., Pandya, S., Poysky, J., Shapiro, F., Tomezsko, J., & Constantin, C. (2010). Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *The Lancet Neurology*, *9*(2), 177–189. https://doi.org/10.1016/S1474-4422(09)70272-8

Calvert, L. D., McKeever, T. M., Kinnear, W. J. M., & Britton, J. R. (2006). Trends in survival from muscular dystrophy in England and Wales and impact on respiratory services. *Respiratory Medicine*, *100*(6), 1058–1063. https://doi.org/10.1016/j.rmed.2005.09.030

Cantero, C., Adler, D., Pasquina, P., Uldry, C., Egger, B., Prella, M., Younossian, A. B., Soccal, P. M., Pépin, J.-L., & Janssens, J.-P. (2020). Long-Term Noninvasive Ventilation in the Geneva Lake Area. *Chest*, *158*(1), 279–291.

https://doi.org/10.1016/j.chest.2020.02.064

Carone, M., Bertolotti, G., Anchisi, F., Zotti, A. M., Donner, C. F., Jones, P. W., & on behalf of the "quality of Life in Chronic Respiratory Failure Group." (1999). Analysis of factors that characterize health impairment in patients with chronic respiratory failure. *European Respiratory Journal*, *13*(6), 1293. https://doi.org/10.1034/j.1399-3003.1999.13f13.x

Carvajalino, S., Reigada, C., Johnson, M. J., Dzingina, M., & Bajwah, S. (2018). Symptom prevalence of patients with fibrotic interstitial lung disease: a systematic literature review. *BMC Pulmonary Medicine*, *18*(1), 78. https://doi.org/10.1186/s12890-018-0651-3

Casanova, C., Celli, B. R., Tost, L., Soriano, E., Abreu, J., Velasco, V., & Santolaria, F. (2000). Long-term Controlled Trial of Nocturnal Nasal Positive Pressure Ventilation in Patients With Severe COPD. *Chest*, *118*(6), 1582–1590. https://doi.org/10.1378/chest.118.6.1582

Cedarbaum, J. M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., & Nakanishi, A. (1999). The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. *Journal of the Neurological Sciences*, *169*(1–2), 13–21. https://doi.org/10.1016/S0022-510X(99)00210-5

Chailleux, E., Fauroux, B., Binet, F., Dautzenberg, B., & Polu, J.-M. (1996). Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation: A 10-year analysis of ANTADIR observatory. *Chest*, *109*(3), 741–749. https://doi.org/10.1378/chest.109.3.741

Chang, V. T., Hwang, S. S., & Feuerman, M. (2000). Validation of the Edmonton Symptom Assessment Scale. *Cancer*, *88*(9), 2164–2171. https://doi.org/10.1002/(SICI)1097-0142(20000501)88:9<2164::AID-CNCR24>3.0.CO;2-5

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Charlson, M. E., Szatrowski, T. P., Peterson, J., & Gold, J. (1994). Validation of a combined comorbidity index. *Journal of Clinical Epidemiology*, *47*(11), 1245–1251. https://doi.org/10.1016/0895-4356(94)90129-5

Christensen, V. L., Holm, A. M., Cooper, B., Paul, S. M., Miaskowski, C., & Rustøen, T. (2016). Differences in Symptom Burden among Patients with Moderate, Severe, or Very Severe Chronic Obstructive Pulmonary Disease. *Journal of Pain and Symptom Management*, *51*(5), 849–859. https://doi.org/10.1016/j.jpainsymman.2015.12.324

COPD Working Group. (2012). Long-Term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis. In *Ontario Health Technology Assessment Series* (Vol. 12, Issue 7). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3384376/

Crimi, C., Noto, A., Princi, P., Cuvelier, A., Masa, J. F., Simonds, A., Elliott, M. W., Wijkstra, P., Windisch, W., & Nava, S. (2016). Domiciliary Non-invasive Ventilation in COPD: An International Survey of Indications and Practices. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *13*(4), 483–490. https://doi.org/10.3109/15412555.2015.1108960

Crockett, A. J., Alpers, J. H., & Moss, J. R. (1991). Home oxygen therapy: an audit of survival. *Australian and New Zealand Journal of Medicine*, *21*(2), 217–221. https://doi.org/10.1111/j.1445-5994.1991.tb00445.x

Crockett, A., Cranston, J. M., & Antic, N. (2001). Domiciliary oxygen for interstitial lung disease. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD002883

Cully, J. A., Graham, D. P., Stanley, M. A., Ferguson, C. J., Sharafkhaneh, A., Souchek, J., & Kunik, M. E. (2006). Quality of Life in Patients With Chronic Obstructive Pulmonary Disease and Comorbid Anxiety or Depression. *Psychosomatics*, *47*(4), 312–319. https://doi.org/10.1176/appi.psy.47.4.312

Current Care Guidelines in Chronic Obstructive Pulmonary Disease. Working Group Set up by the Finnish Medical Society Duodecim and the Finnish Respiratory Society. Helsinki: The Finnish Medical Society Duodecim, 2019. Date last assessed March 15th, 2021. Available from: www.kaypahoito.fi

Current Care Guidelines in Depression. Working Group Set up by the Finnish Medical Society Duodecim and the Finnish Psychiatric Association. Helsinki: The Finnish Medical Society Duodecim, 2021. Date last assessed May 5th, 2021. Available from: www.kaypahoito.fi

Current Care Guidelines in Palliative and Hospice care. Working Group Set up by the Finnish Medical Society Duodecim and the Finnish Palliative Medicine Society. Helsinki: The Finnish Medical Society Duodecim, 2020. Date last assessed October 28th, 2021. Available from: www.kaypahoito.fi

Currow, D. C., Plummer, J. L., Crockett, A., & Abernethy, A. P. (2009). A Community Population Survey of Prevalence and Severity of Dyspnea in Adults. *Journal of Pain and Symptom Management*, *38*(4), 533–545. https://doi.org/10.1016/j.jpainsymman.2009.01.006

Currow, D. C., Clark, K., Mitchell, G. K., Johnson, M. J., & Abernethy, A. P. (2013). Prospectively Collected Characteristics of Adult Patients, Their Consultations and Outcomes as They Report Breathlessness When Presenting to General Practice in Australia. *PLoS ONE*, *8*(9), e74814. https://doi.org/10.1371/journal.pone.0074814

Czaplinski, A., Yen, A. A., & Appel, S. H. (2006). Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population. *Journal of Neurology, Neurosurgery & Psychiatry*, *77*(3), 390–392. https://doi.org/10.1136/jnnp.2005.072660

Daniels, C. E., Yi, E. S., & Ryu, J. H. (2008). Autopsy findings in 42 consecutive patients with idiopathic pulmonary fibrosis. *European Respiratory Journal*, *32*(1), 170–174. https://doi.org/10.1183/09031936.00176307

Davidson, A. C., Banham, S., Elliott, M., Kennedy, D., Gelder, C., Glossop, A., Church, A. C., Creagh-Brown, B., Dodd, J. W., Felton, T., Foëx, B., Mansfield, L., McDonnell, L., Parker, R., Patterson, C. M., Sovani, M., & Thomas, L. (2016). BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. *Thorax*, *71*(Suppl 2), ii1–ii35. https://doi.org/10.1136/thoraxjnl-2015-208209

Delgado-Guay, M., Parsons, H. A., Li, Z., Palmer, J. L., & Bruera, E. (2009). Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. *Supportive Care in Cancer*, *17*(5), 573–579. https://doi.org/10.1007/s00520-008-0529-7

Detering, K. M., Hancock, A. D., Reade, M. C., & Silvester, W. (2010). The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. *BMJ*, *340*(mar23 1), c1345–c1345. https://doi.org/10.1136/bmj.c1345

Di Marco, F., Verga, M., Reggente, M., Maria Casanova, F., Santus, P., Blasi, F., Allegra, L., & Centanni, S. (2006). Anxiety and depression in COPD patients: The roles of gender and disease severity. *Respiratory Medicine*, *100*(10), 1767–1774. https://doi.org/10.1016/j.rmed.2006.01.026

Dorst, J., & Ludolph, A. C. (2019). Non-invasive ventilation in amyotrophic lateral sclerosis. *Therapeutic Advances in Neurological Disorders*, *12*(6), 175628641985704. https://doi.org/10.1177/1756286419857040

Doyle, T., Palmer, S., Johnson, J., Babyak, M. A., Smith, P., Mabe, S., Welty-Wolf, K., Martinu, T., & Blumenthal, J. A. (2013). Association of Anxiety and Depression with

Pulmonary-Specific Symptoms in Chronic Obstructive Pulmonary Disease. *The International Journal of Psychiatry in Medicine*, *45*(2), 189–202. https://doi.org/10.2190/PM.45.2.g

Dreher, M., Neuzeret, P.-C., Windisch, W., Martens, D., Hoheisel, G., Gröschel, A., Woehrle, H., Fetsch, T., Graml, A., & Köhnlein, T. (2019). Prevalence Of Chronic Hypercapnia In Severe Chronic Obstructive Pulmonary Disease: Data From The HOmeVent Registry. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 14*, 2377–2384. https://doi.org/10.2147/COPD.S222803

Duiverman, M. L. (2018). Noninvasive ventilation in stable hypercapnic COPD: what is the evidence? *ERJ Open Research*, *4*(2), 00012–02018. https://doi.org/10.1183/23120541.00012-2018

Eagle, M., Baudouin, S. V., Chandler, C., Giddings, D. R., Bullock, R., & Bushby, K. (2002). Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscular Disorders*, *12*(10), 926–929. https://doi.org/10.1016/S0960-8966(02)00140-2

Eckerblad, J., Tödt, K., Jakobsson, P., Unosson, M., Skargren, E., Kentsson, M., & Theander, K. (2014). Symptom burden in stable COPD patients with moderate or severe airflow limitation. *Heart & Lung*, *43*(4), 351–357. https://doi.org/10.1016/j.hrtlng.2014.04.004

Edmonds, P., Karlsen, S., Khan, S., & Addington-Hall, J. (2001). A comparison of the palliative care needs of patients dying from chronic respiratory diseases and lung cancer. *Palliative Medicine*, *15*(4), 287–295. https://doi.org/10.1191/026921601678320278

Egede, L. E. (2007). Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *General Hospital Psychiatry*, *29*(5), 409–416. https://doi.org/10.1016/j.genhosppsych.2007.06.002

Ekstrom, M. P., Bornefalk-Hermansson, A., Abernethy, A. P., & Currow, D. C. (2014). Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ*, *348*(jan30 2), g445–g445. https://doi.org/10.1136/bmj.g445

Ekström, M., Ahmadi, Z., Bornefalk-Hermansson, A., Abernethy, A., & Currow, D. (2016a). Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. *Cochrane Database of Systematic Reviews*, *11*, CD006429. https://doi.org/10.1002/14651858.CD006429.pub3

Ekström, M., Allingham, S. F., Eagar, K., Yates, P., Johnson, C., & Currow, D. C. (2016b). Breathlessness During the Last Week of Life in Palliative Care: An Australian Prospective, Longitudinal Study. *Journal of Pain and Symptom Management*, *51*(5), 816–823. https://doi.org/10.1016/j.jpainsymman.2015.12.311

Ekström, M., Ahmadi, Z., Larsson, H., Nilsson, T., Wahlberg, J., Ström, K. E., & Midgren, B. (2017). A nationwide structure for valid long-term oxygen therapy: 29-year prospective data in Sweden. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 12*, 3159–3169. https://doi.org/10.2147/COPD.S140264

Ekström, M., & Ringbaek, T. (2018). Which patients with moderate hypoxemia benefit from long-term oxygen therapy? Ways forward. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 13*, 231–235. https://doi.org/10.2147/COPD.S148673

Elbehairy, A. F., McIsaac, H., Hill, E., Norman, P. A., Day, A. G., Neder, J. A., O'Donnell, D. E., & Harle, I. A. (2020). Impact of a Specialized Ambulatory Clinic on Refractory Breathlessness in Subjects With Advanced COPD. *Respiratory Care*, *65*(4), 444–454. https://doi.org/10.4187/respcare.06950

Ellis, E. R., Grunstein, R. R., Chan, S., Bye, P. T. P., & Sullivan, C. E. (1988). Noninvasive Ventilatory Support during Sleep Improves Respiratory Failure in Kyphoscoliosis.

Chest, *94*(4), 811–815. https://doi.org/10.1378/chest.94.4.811

Ergan, B., Oczkowski, S., Rochwerg, B., Carlucci, A., Chatwin, M., Clini, E., Elliott, M., Gonzalez-Bermejo, J., Hart, N., Lujan, M., Nasilowski, J., Nava, S., Pepin, J. L., Pisani, L., Storre, J. H., Wijkstra, P., Tonia, T., Boyd, J., Scala, R., & Windisch, W. (2019). European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *European Respiratory Journal*, *54*(3), 1901003. https://doi.org/10.1183/13993003.01003-2019

Escribano-Subias, P., Blanco, I., López-Meseguer, M., Lopez-Guarch, C. J., Roman, A., Morales, P., Castillo-Palma, M. J., Segovia, J., Gómez-Sanchez, M. A., & Barberà, J. A. (2012). Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *European Respiratory Journal*, *40*(3), 596–603. https://doi.org/10.1183/09031936.00101211

Ferguson, G. T. (2006). Why Does the Lung Hyperinflate? *Proceedings of the American Thoracic Society*, *3*(2), 176–179. https://doi.org/10.1513/pats.200508-094DO

Fernandez, I. E., & Eickelberg, O. (2012). New cellular and molecular mechanisms of lung injury and fibrosis in idiopathic pulmonary fibrosis. *The Lancet*, *380*(9842), 680–688. https://doi.org/10.1016/S0140-6736(12)61144-1

Finder, J. D., Birnkrant, D., Carl, J., Farber, H. J., Gozal, D., Iannaccone, S. T., Kovesi, T., Kravitz, R. M., Panitch, H., Schramm, C., Schroth, M., Sharma, G., Sievers, L., Silvestri, J. M., & Sterni, L. (2004). Respiratory Care of the Patient with Duchenne Muscular Dystrophy. *American Journal of Respiratory and Critical Care Medicine*, *170*(4), 456–465. https://doi.org/10.1164/rccm.200307-885ST

Flemons, W. W., Buysse, D., Redline, S., Oack, A., Strohl, K., Wheatley, J., Young, T., Douglas, N., Levy, P., McNicolas, W., Fleetham, J., White, D., Schmidt-Nowarra, W., Carley, D., & Romaniuk, J. (1999). Sleep–Related Breathing Disorders in Adults: Recommendations for Syndrome Definition and Measurement Techniques in Clinical Research. *Sleep*, *22*(5), 667–689. https://doi.org/10.1093/sleep/22.5.667

Fletcher, C., Clifton, M., Fry, J., Gilson, J., Higgins, I., Mair, A., Pemberton, J., Rogan, J., Smith, D., & Wood, C. (1960). Standardized questionnaries on respiratory symptoms. *British Medical Journal*, 1665.

Forsgren, L., Almay, B. G. L., Holmgren, G., & Wall, S. (1983). Epidemiology of motor neuron disease in northern Sweden. *Acta Neurologica Scandinavica*, *68*, 20–29.

Fu, P. K., Tung, Y. C., Wang, C. Y., Hwang, S. F., Lin, S. P., Hsu, C. Y., & Chen, D. R. (2018). Early and late do-not-resuscitate (DNR) decisions in patients with terminal COPD: A retrospective study in the last year of life. *International Journal of COPD*, *13*, 2447–2454. https://doi.org/10.2147/COPD.S168049

Gainza-Miranda, D., Sanz-Peces, E. M., Alonso-Babarro, A., Varela-Cerdeira, M., Prados-Sánchez, C., Vega-Aleman, G., Rodriguez-Barrientos, R., & Polentinos-Castro, E. (2019). Breaking Barriers: Prospective Study of a Cohort of Advanced Chronic Obstructive Pulmonary Disease Patients To Describe Their Survival and End-of-Life Palliative Care Requirements. *Journal of Palliative Medicine*, *22*(3), 290–296. https://doi.org/10.1089/jpm.2018.0363

Galiè, N., Humbert, M., Vachiery, J.-L., Gibbs, S., Lang, I., Torbicki, A., Simonneau, G., Peacock, A., Vonk Noordegraaf, A., Beghetti, M., Ghofrani, A., Gomez Sanchez, M. A., Hansmann, G., Klepetko, W., Lancellotti, P., Matucci, M., McDonagh, T., Pierard, L. A., Trindade, P. T., Zompatori, M., & Hoeper, M. (2016). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal*, *37*(1), 67–119. https://doi.org/10.1093/eurheartj/ehv317

Gantzhorn, E. K., Prior, T. S., & Hilberg, O. (2019). Long-term non-invasive ventilation for stable chronic hypercapnic COPD. *European Clinical Respiratory Journal*, *6*(1), 1644893.

https://doi.org/10.1080/20018525.2019.1644893
Gift, A. G. (1989). Validation of a Vertical Visual Analogue Scale as a Measure of Clinical Dyspnea. *Rehabilitation Nursing*, *14*(6), 323–325. https://doi.org/10.1002/j.2048-7940.1989.tb01129.x
Gift, A. G., & Narvasage, G. (1998). Validity of the numeric rating scale as a measure of dyspnea. *American Journal of Critical Care*, *7*(3), 200–204. http://dx.doi.org/10.1016/j.jaci.2012.05.050
GOLD. (2021). In Global Initiative for Chronic Obstructive Lung Disease. Available from www.goldcopd.org, published in Fontana, WI, USA. Date last assessed May 25th, 2021.
Goldberg, A., Leger, P., Hill, N. S., & Criner, G. J. (1999). Clinical Indications for Noninvasive Positive Pressure Ventilation in Chronic Respiratory Failure Due to Restrictive Lung Disease, COPD, and Nocturnal Hypoventilation—A Consensus Conference Report. *Chest*, *116*(2), 521–534. https://doi.org/10.1378/chest.116.2.521
Gorecka, D., Gorzelak, K., Sliwinski, P., Tobiasz, M., & Zielinski, J. (1997). Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax*, *52*(8), 674–679. https://doi.org/10.1136/thx.52.8.674
Gruenberger, J., Vietri, J., Keininger, D., & Mahler, D. (2017). Greater dyspnea is associated with lower health-related quality of life among European patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 12*, 937–944. https://doi.org/10.2147/COPD.S123744
Guenther, A., Krauss, E., Tello, S., Wagner, J., Paul, B., Kuhn, S., Maurer, O., Heinemann, S., Costabel, U., Barbero, M. A. N., Müller, V., Bonniaud, P., Vancheri, C., Wells, A., Vasakova, M., Pesci, A., Sofia, M., Klepetko, W., Seeger, W., Drakopanagiotakis, F. & Crestani, B. (2018). The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. *Respiratory Research*, *19*(1), 141. https://doi.org/10.1186/s12931-018-0845-5
Gulbas, G., Gunen, H., In, E., & Kilic, T. (2012). Long-term follow-up of chronic obstructive pulmonary disease patients on long-term oxygen treatment. *International Journal of Clinical Practice*, *66*(2), 152–157. https://doi.org/10.1111/j.1742-1241.2011.02833.x
Halpin, D. M. G. (2018). Palliative care for people with COPD: effective but underused. *European Respiratory Journal*, *51*(2), 1702645. https://doi.org/10.1183/13993003.02645-2017
Hannon, B., Dyck, M., Pope, A., Swami, N., Banerjee, S., Mak, E., Bryson, J., Rodin, G., Ridley, J., Lo, C., Le, L. W., & Zimmermann, C. (2015). Modified Edmonton Symptom Assessment System Including Constipation and Sleep: Validation in Outpatients With Cancer. *Journal of Pain and Symptom Management*, *49*(5), 945–952. https://doi.org/10.1016/j.jpainsymman.2014.10.013
Hardinge, M., Annandale, J., Bourne, S., Cooper, B., Evans, A., Freeman, D., Green, A., Hippolyte, S., Knowles, V., MacNee, W., McDonnell, L., Pye, K., Suntharalingam, J., Vora, V., & Wilkinson, T. (2015). British Thoracic Society guidelines for home oxygen use in adults: accredited by NICE. *Thorax*, *70*(Suppl 1), i1–i43. https://doi.org/10.1136/thoraxjnl-2015-206865
Helleman, J., Kruitwagen-van Reenen, E. T., Bakers, J., Kruithof, W. J., van Groenestijn, A. C., Jaspers Focks, R. J. H., de Grund, A., van den Berg, L. H., Visser-Meily, J. M. A., & Beelen, A. (2020). Using patient-reported symptoms of dyspnea for screening reduced respiratory function in patients with motor neuron diseases. *Journal of Neurology*, *267*(11), 3310–3318. https://doi.org/10.1007/s00415-020-10003-5
Higginson, I. J., Bausewein, C., Reilly, C. C., Gao, W., Gysels, M., Dzingina, M., McCrone, P., Booth, S., Jolley, C. J., & Moxham, J. (2014). An integrated palliative and respiratory

care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *The Lancet Respiratory Medicine*, *2*(12), 979–987. https://doi.org/10.1016/S2213-2600(14)70226-7

Hill, N. S. (1994). Noninvasive Positive Pressure Ventilation in Neuromuscular Disease. *Chest*, *105*(2), 337–338. https://doi.org/10.1378/chest.105.2.337

Hodgson, U. (2002). Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: evidence of founder effect among multiplex families in Finland. *Thorax*, *57*(4), 338–342. https://doi.org/10.1136/thorax.57.4.338

Holland, A. E., Fiore, J. F., Bell, E. C., Goh, N., Westall, G., Symons, K., Dowman, L., & Glaspole, I. (2014). Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. *Respirology*, *19*(8), 1215–1221. https://doi.org/10.1111/resp.12360

Hui, D., Morgado, M., Chisholm, G., Withers, L., Nguyen, Q., Finch, C., Frisbee-Hume, S., & Bruera, E. (2013). High-Flow Oxygen and Bilevel Positive Airway Pressure for Persistent Dyspnea in Patients With Advanced Cancer: A Phase II Randomized Trial. *Journal of Pain and Symptom Management*, *46*(4), 463–473. https://doi.org/10.1016/j.jpainsymman.2012.10.284

Hui, D., & Bruera, E. (2017). The Edmonton Symptom Assessment System 25 Years Later: Past, Present, and Future Developments. *Journal of Pain and Symptom Management*, *53*(3), 630–643. https://doi.org/10.1016/j.jpainsymman.2016.10.370

Hui, D., Bohlke, K., Bao, T., Campbell, T. C., Coyne, P. J., Currow, D. C., Gupta, A., Leiser, A. L., Mori, M., Nava, S., Reinke, L. F., Roeland, E. J., Seigel, C., Walsh, D., & Campbell, M. L. (2021). Management of Dyspnea in Advanced Cancer: ASCO Guideline. *Journal of Clinical Oncology*, *39*(12), 1389–1411. https://doi.org/10.1200/JCO.20.03465

Ishikawa, Y., Miura, T., Ishikawa, Y., Aoyagi, T., Ogata, H., Hamada, S., & Minami, R. (2011). Duchenne muscular dystrophy: Survival by cardio-respiratory interventions. *Neuromuscular Disorders*, *21*(1), 47–51. https://doi.org/10.1016/j.nmd.2010.09.006

Jabbarian, L. J., Zwakman, M., van der Heide, A., Kars, M. C., Janssen, D. J. A., van Delden, J. J., Rietjens, J. A. C., & Korfage, I. J. (2018). Advance care planning for patients with chronic respiratory diseases: a systematic review of preferences and practices. *Thorax*, *73*(3), 222–230. https://doi.org/10.1136/thoraxjnl-2016-209806

Jacobs, S. S., Krishnan, J. A., Lederer, D. J., Ghazipura, M., Hossain, T., Tan, A.-Y. M., Carlin, B., Drummond, M. B., Ekström, M., Garvey, C., Graney, B. A., Jackson, B., Kallstrom, T., Knight, S. L., Lindell, K., Prieto-Centurion, V., Renzoni, E. A., Ryerson, C. J., Schneidman, A., … Holland, A. E. (2020). Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine*, *202*(10), e121–e141. https://doi.org/10.1164/rccm.202009-3608ST

Janssen, D. J. A., Spruit, M. A., Uszko-Lencer, N. H., Schols, J. M. G. A., & Wouters, E. F. M. (2011). Symptoms, Comorbidities, and Health Care in Advanced Chronic Obstructive Pulmonary Disease or Chronic Heart Failure. *Journal of Palliative Medicine*, *14*(6), 735–743. https://doi.org/10.1089/jpm.2010.0479

Janssens, J.-P., Derivaz, S., Breitenstein, E., de Muralt, B., Fitting, J.-W., Chevrolet, J.-C., & Rochat, T. (2003). Changing Patterns in Long-term Noninvasive Ventilation. *Chest*, *123*(1), 67–79. https://doi.org/10.1378/chest.123.1.67

Jensen, M. T., Marott, J. L., Lange, P., Vestbo, J., Schnohr, P., Nielsen, O. W., Jensen, J. S., & Jensen, G. B. (2013). Resting heart rate is a predictor of mortality in COPD. *European Respiratory Journal*, *42*(2), 341–349. https://doi.org/10.1183/09031936.00072212

Johnson, M. J., McDonagh, T. A., Harkness, A., McKay, S. E., & Dargie, H. J. (2002).

Morphine for the relief of breathlessness in patients with chronic heart failure - A pilot study. *European Journal of Heart Failure*, *4*(6), 753–756. https://doi.org/10.1016/S1388-9842(02)00158-7

Johnson, M. J., Bland, J. M., Gahbauer, E. A., Ekström, M., Sinnarajah, A., Gill, T. M., & Currow, D. C. (2016). Breathlessness in Elderly Adults During the Last Year of Life Sufficient to Restrict Activity: Prevalence, Pattern, and Associated Factors. *Journal of the American Geriatrics Society*, *64*(1), 73–80. https://doi.org/10.1111/jgs.13865

Johnson, M. J., & Currow, D. C. (2020). Opioids for breathlessness: A narrative review. *BMJ Supportive and Palliative Care*, *10*(3), 287–295. https://doi.org/10.1136/bmjspcare-2020-002314

Jones, P. W., Quirk, F. H., Baveystock, C. M., & Littlejohns, P. (1992). A Self-complete Measure of Health Status for Chronic Airflow Limitation: The St. George's Respiratory Questionnaire. *American Review of Respiratory Disease*, *145*(6), 1321–1327. https://doi.org/10.1164/ajrccm/145.6.1321

Jones, P. W., Harding, G., Berry, P., Wiklund, I., Chen, W.-H., & Kline Leidy, N. (2009). Development and first validation of the COPD Assessment Test. *European Respiratory Journal*, *34*(3), 648–654. https://doi.org/10.1183/09031936.00102509

Jones, P. W., Tabberer, M., & Chen, W.-H. (2011). Creating scenarios of the impact of copd and their relationship to copd assessment test (CAT™) scores. *BMC Pulmonary Medicine*, *11*(1), 42. https://doi.org/10.1186/1471-2466-11-42

Jones, P. W., Brusselle, G., Dal Negro, R. W., Ferrer, M., Kardos, P., Levy, M. L., Perez, T., Cataluña, J. J. S., van der Molen, T., Adamek, L., & Banik, N. (2012). Patient-centred assessment of COPD in primary care: experience from a cross-sectional study of health-related quality of life in Europe. *Primary Care Respiratory Journal*, *21*(3), 329–336. https://doi.org/10.4104/pcrj.2012.00065

Kainu, A., Rouhos, A., Sovijärvi, A., Lindqvist, A., Sarna, S., & Lundbäck, B. (2013). COPD in Helsinki, Finland: socioeconomic status based on occupation has an important impact on prevalence. *Scandinavian Journal of Public Health*, *41*(6), 570–578. https://doi.org/10.1177/1403494813484554

Kakazu, M. T., Soghier, I., Afshar, M., Brozek, J. L., Wilson, K. C., Masa, J. F., & Mokhlesi, B. (2020). Weight Loss Interventions as Treatment of Obesity Hypoventilation Syndrome. A Systematic Review. *Annals of the American Thoracic Society*, *17*(4), 492–502. https://doi.org/10.1513/AnnalsATS.201907-554OC

Kanervisto, M., Saarelainen, S., Vasankari, T., Jousilahti, P., Heistaro, S., Heliövaara, M., Luukkaala, T., & Paavilainen, E. (2010). COPD, chronic bronchitis and capacity for day-to-day activities: Negative impact of illness on the health-related quality of life. *Chronic Respiratory Disease*, *7*(4), 207–215. https://doi.org/10.1177/1479972310368691

Katajisto, M., Kupiainen, H., Rantanen, P., Kilpeläinen, M., Lindqvist, A., Tikkanen, H., & Laitinen, T. (2012). Physical inactivity in COPD and increased patient perception of dyspnea. *International Journal of Chronic Obstructive Pulmonary Disease*, *7*, 743. https://doi.org/10.2147/COPD.S35497

Katz, S. (1979). Assessing Self-maintenance: Activities of Daily Living, Mobility, and Instrumental Activities of Daily Living. *Journal of the American Geriatrics Society*, *31*(12), 721–727.

Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe, M. W. (1963). Studies of Illness in the Aged. The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. *JAMA*, *185*(12), 94–99. https://doi.org/10.1001/jama.1963.03060120024016

Kaunisto, J., Salomaa, E.-R., Hodgson, U., Kaarteenaho, R., & Myllärniemi, M. (2013). Idiopathic pulmonary fibrosis - a systematic review on methodology for the collection

of epidemiological data. *BMC Pulmonary Medicine*, *13*(1), 53. https://doi.org/10.1186/1471-2466-13-53

Kaunisto, J., Salomaa, E.-R., Hodgson, U., Kaarteenaho, R., Kankaanranta, H., Koli, K., Vahlberg, T., & Myllärniemi, M. (2019). Demographics and survival of patients with idiopathic pulmonary fibrosis in the FinnishIPF registry. *ERJ Open Research*, *5*(3), 00170–02018. https://doi.org/10.1183/23120541.00170-2018

Kayhan, F., Ilik, F., Karamanli, H., Cemal Pazarli, A., & Kayhan, A. (2018). Major Depression in Long-Term Oxygen Therapy Dependent Chronic Obstructive Pulmonary Disease. *Perspectives in Psychiatric Care*, *54*(1), 6–10. https://doi.org/10.1111/ppc.12169

Kerminen, H., Jämsen, E., Jäntti, P., Mattila, A. K., Leivo-Korpela, S., & Valvanne, J. (2019). Implementation of a depression screening protocol among respiratory insufficiency patients. *The Clinical Respiratory Journal*, *13*(1), 34–42. https://doi.org/10.1111/crj.12977

Kessler, R., Chaouat, A., Schinkewitch, P., Faller, M., Casel, S., Krieger, J., & Weitzenblum, E. (2001). The Obesity-Hypoventilation Syndrome Revisited. *Chest*, *120*(2), 369–376. https://doi.org/10.1378/chest.120.2.369

Kessler, R., Partridge, M. R., Miravitlles, M., Cazzola, M., Vogelmeier, C., Leynaud, D., & Ostinelli, J. (2011). Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *European Respiratory Journal*, *37*(2), 264–272. https://doi.org/10.1183/09031936.00051110

Kieny, P., Chollet, S., Delalande, P., Le Fort, M., Magot, A., Pereon, Y., & Perrouin Verbe, B. (2013). Evolution of life expectancy of patients with Duchenne muscular dystrophy at AFM Yolaine de Kepper centre between 1981 and 2011. *Annals of Physical and Rehabilitation Medicine*, *56*(6), 443–454. https://doi.org/10.1016/j.rehab.2013.06.002

Kim, H. J., Perlman, D., & Tomic, R. (2015). Natural history of idiopathic pulmonary fibrosis. *Respiratory Medicine*, *109*(6), 661–670. https://doi.org/10.1016/j.rmed.2015.02.002

King, C., & Nathan, S. D. (2013). Identification and treatment of comorbidities in idiopathic pulmonary fibrosis and other fibrotic lung diseases. *Current Opinion in Pulmonary Medicine*, *19*(5), 466–473. https://doi.org/10.1097/MCP.0b013e328363f460

King, T. E., Schwarz, M. I., Brown, K., Tooze, J. A., Colby, T. V., Waldron, J. A., Flint, A., Thurlbeck, W., & Cherniack, R. M. (2001). Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine*, *164*(6), 1025–1032. https://doi.org/10.1164/ajrccm.164.6.2001056

Kleopa, K. A., Sherman, M., Neal, B., Romano, G. J., & Heiman-Patterson, T. (1999). Bipap improves survival and rate of pulmonary function decline in patients with ALS. *Journal of the Neurological Sciences*, *164*(1), 82–88. https://doi.org/10.1016/S0022-510X(99)00045-3

Kohler, M., Clarenbach, C. F., Bahler, C., Brack, T., Russi, E. W., & Bloch, K. E. (2009). Disability and survival in Duchenne muscular dystrophy. *Journal of Neurology, Neurosurgery & Psychiatry*, *80*(3), 320–325. https://doi.org/10.1136/jnnp.2007.141721

Köhnlein, T., Windisch, W., Köhler, D., Drabik, A., Geiseler, J., Hartl, S., Karg, O., Laier-Groeneveld, G., Nava, S., Schönhofer, B., Schucher, B., Wegscheider, K., Criée, C. P., & Welte, T. (2014). Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *The Lancet Respiratory Medicine*, *2*(9), 698–705. https://doi.org/10.1016/S2213-2600(14)70153-5

Kotanen, P., Kreivi, H.-R., Kainu, A., & Brander, P. (2019). The prevalence of chronic respiratory failure treated with home mechanical ventilation in Helsinki, Finland. *European Respiratory Journal*, *54*(Suppl. 63), PA2311. https://doi.org/10.1183/13993003.congress-2019.PA2311

Kristjanson, L. J., Aoun, S. M., & Oldham, L. (2006). Palliative care and support for people

with neurodegenerative conditions and their carers. *International Journal of Palliative Nursing*, *12*(8), 368–377. https://doi.org/10.12968/ijpn.2006.12.8.368

Kunik, M. E., Roundy, K., Veazey, C., Souchek, J., Richardson, P., Wray, N. P., & Stanley, M. A. (2005). Surprisingly High Prevalence of Anxiety and Depression in Chronic Breathing Disorders. *Chest*, *127*(4), 1205–1211. https://doi.org/10.1016/S0012-3692(15)34468-8

Lacasse, Y., Rousseau, L., & Maltais, F. (2001). Prevalence of Depressive Symptoms and Depression in Patients With Severe Oxygen-Dependent Chronic Obstructive Pulmonary Disease. *Journal of Cardiopulmonary Rehabilitation*, *21*(2), 80–86. https://doi.org/10.1097/00008483-200103000-00004

Lanken, P. N., Terry, P. B., DeLisser, H. M., Fahy, B. F., Hansen-Flaschen, J., Heffner, J. E., Levy, M., Mularski, R. A., Osborne, M. L., Prendergast, T. J., Rocker, G., Sibbald, W. J., Wilfond, B., & Yankaskas, J. R. (2008). An Official American Thoracic Society Clinical Policy Statement: Palliative Care for Patients with Respiratory Diseases and Critical Illnesses. *American Journal of Respiratory and Critical Care Medicine*, *177*(8), 912–927. https://doi.org/10.1164/rccm.200605-587ST

Laub, M., & Midgren, B. (2007). Survival of patients on home mechanical ventilation: A nationwide prospective study. *Respiratory Medicine*, *101*(6), 1074–1078. https://doi.org/10.1016/j.rmed.2006.10.007

Law, S., Boyd, S., MacDonald, J., Raeside, D., & Anderson, D. (2014). Predictors of survival in patients with chronic obstructive pulmonary disease receiving long-term oxygen therapy. *BMJ Supportive & Palliative Care*, *4*(2), 140–145. https://doi.org/10.1136/bmjspcare-2012-000432

Leach, R. M. (2010). Palliative Care in non-malignant, end-stage respiratory disease. In G. Hanks, N. I. Cherny, N. A. Christakis, M. Fallon, S. Kaasa, & R. K. Portenoy (Eds.), *Oxford Textbook of Palliative Medicine* (4., pp. 1241–1245). Oxford University Press.

Lederer, D. J., & Martinez, F. J. (2018). Idiopathic Pulmonary Fibrosis. *New England Journal of Medicine*, *378*(19), 1811–1823. https://doi.org/10.1056/NEJMra1705751

Lee, Y. J., Choi, S. M., Lee, Y. J., Cho, Y.-J., Yoon, H. Il, Lee, J.-H., Lee, C.-T., & Park, J. S. (2017). Clinical impact of depression and anxiety in patients with idiopathic pulmonary fibrosis. *PLOS ONE*, *12*(9), e0184300. https://doi.org/10.1371/journal.pone.0184300

Leger, P., Bedicam, J. M., Cornette, A., Reybet-Degat, O., Langevin, B., Polu, J. M., Jeannin, L., & Robert, D. (1994). Nasal intermittent positive pressure ventilation: Long-term follow-up in patients with severe chronic respiratory insufficiency. *Chest*, *105*(1), 100–105. https://doi.org/10.1378/chest.105.1.100

Lewis, K. E., Annandale, J. A., Sykes, R. N., Hurlin, C., Owen, C., & Harrison, N. K. (2007). Prevalence of Anxiety and Depression in Patients with Severe COPD: Similar High Levels with and without LTOT. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *4*(4), 305–312. https://doi.org/10.1080/15412550701595716

Likert, R. (1932). A Technique for the Measurement of Attitudes. In *Archives of Psychology* (Vol. 22, Issue 140, pp. 1–55). SAGE Publications, Inc. https://doi.org/10.4135/9781412961288.n454

Lim, K. E., Kim, S. R., Kim, H. K., & Kim, S. R. (2017). Symptom Clusters and Quality of Life in Subjects With COPD. *Respiratory Care*, *62*(9), 1203–1211. https://doi.org/10.4187/respcare.05374

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., AlMazroa, M. A., Amann, M., Anderson, H. R., Andrews, K. G., Aryee, M., Atkinson, C., Bacchus, L. J., Bahalim, A. N., Balakrishnan, K., Balmes, J., Barker-Collo, S., Baxter, A., Bell, M. L., … Ezzati, M. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a

systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, *380*(9859), 2224–2260. https://doi.org/10.1016/S0140-6736(12)61766-8

Lin, C. C. (1996). Comparison between nocturnal nasal positive pressure ventilation combined with oxygen therapy and oxygen monotherapy in patients with severe COPD. *American Journal of Respiratory and Critical Care Medicine*, *154*(2), 353–358. https://doi.org/10.1164/ajrccm.154.2.8756806

Lin, E. H., Jacques, P., Breland-noble, A. M., Cuijpers, P., Sciences, M., Amsterdam, V. U., Greenberg, L. S., Jones, V. Y., Mufson, L. H., Nezu, A. M., Reynolds, C. F., Scogin, F., Directorate, P., Psychological, A., Halfond, R. W., Directorate, P., Kurtzman, H. S., Directorate, S., & Psychological, A. (2019). Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts. *American Psychological Association*, 1–213. https://www.apa.org/depression-guideline/guideline.pdf

Lindell, K. O., Liang, Z., Hoffman, L. A., Rosenzweig, M. Q., Saul, M. I., Pilewski, J. M., Gibson, K. F., & Kaminski, N. (2015). Palliative Care and Location of Death in Decedents With Idiopathic Pulmonary Fibrosis. *Chest*, *147*(2), 423–429. https://doi.org/10.1378/chest.14-1127

Littleton, S. W., & Mokhlesi, B. (2009). The Pickwickian Syndrome—Obesity Hypoventilation Syndrome. *Clinics in Chest Medicine*, *30*(3), 467–478. https://doi.org/10.1016/j.ccm.2009.05.004

Liu, Y., Croft, J., Anderson, L., Wheaton, A., Presley-Cantrell, L., & Ford, E. (2014). The association of chronic obstructive pulmonary disease, disability, engagement in social activities, and mortality among US adults aged 70 years or older, 1994–2006. *International Journal of Chronic Obstructive Pulmonary Disease*, *9*, 75. https://doi.org/10.2147/COPD.S53676

Lloyd-Owen, S. J., Donaldson, G. C., Ambrosino, N., Escarabill, J., Farre, R., Fauroux, B., Robert, D., Schoenhofer, B., Simonds, A. K., & Wedzicha, J. A. (2005). Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *European Respiratory Journal*, *25*(6), 1025–1031. https://doi.org/10.1183/09031936.05.00066704

Long-Term Oxygen Treatment Trial Research Group, Albert, R. K., Au, D. H., Blackford, A. L., Casaburi, R., Jr, J. A. C., Criner, G. J., Diaz, P., Fuhlbrigge, A. L., Gay, S. E., Kanner, R. E., MacIntyre, N., Martinez, F. J., Panos, R. J., Piantadosi, S., Sciurba, F., Shade, D., Stibolt, T., Stoller, J. K., … Bailey, W. (2016). A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation. *New England Journal of Medicine*, *375*(17), 1617–1627. https://doi.org/10.1056/NEJMoa1604344

Lynn, J. (1997). Perceptions by Family Members of the Dying Experience of Older and Seriously Ill Patients. *Annals of Internal Medicine*, *126*(2), 97. https://doi.org/10.7326/0003-4819-126-2-199701150-00001

MacNee, W. (2012). Chronic Obstructive Pulmonary Disease: Epidemiology, Pathophysiology and Clinical Evaluation. In S. G. Spiro, G. A. Silvestri, & A. Agustí (Eds.), *Clinical Respiratory Medicine* (4th ed., pp. 542–544). Elsevier Saunders.

Macrea, M., Oczkowski, S., Rochwerg, B., Branson, R. D., Celli, B., Coleman, J. M., Hess, D. R., Knight, S. L., Ohar, J. A., Orr, J. E., Piper, A. J., Punjabi, N. M., Rahangdale, S., Wijkstra, P. J., Yim-Yeh, S., Drummond, M. B., & Owens, R. L. (2020). Long-Term Noninvasive Ventilation in Chronic Stable Hypercapnic Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine*, *202*(4), e74–e87. https://doi.org/10.1164/rccm.202006-2382ST

Maddocks, M., Lovell, N., Booth, S., Man, W. D., & Higginson, I. J. (2017). Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *The Lancet*, *390*(10098), 988–1002. https://doi.org/10.1016/S0140-

6736(17)32127-X
Magnussen, M. J., & Glass, J. D. (2017). Natural History of Amyotrophic Lateral Sclerosis. In *Molecular and Cellular Therapies for Motor Neuron Diseases* (Vol. 43, pp. 25–41). Elsevier. https://doi.org/10.1016/B978-0-12-802257-3.00002-X
Mahler, D. A., & Wells, C. K. (1988). Evaluation of Clinical Methods for Rating Dyspnea. *Chest*, *93*(3), 580–586. https://doi.org/10.1378/chest.93.3.580
Mahler, D. A., Selecky, P. A., Harrod, C. G., Benditt, J. O., Carrieri-Kohlman, V., Curtis, J. R., Manning, H. L., Mularski, R. A., Varkey, B., Campbell, M., Carter, E. R., Chiong, J. R., Ely, E. W., Hansen-Flaschen, J., O'Donnell, D. E., & Waller, A. (2010). American College of Chest Physicians Consensus Statement on the Management of Dyspnea in Patients With Advanced Lung or Heart Disease. *Chest*, *137*(3), 674–691. https://doi.org/10.1378/chest.09-1543
Marik, P. E., & Chen, C. (2016). The clinical characteristics and hospital and post-hospital survival of patients with the obesity hypoventilation syndrome: analysis of a large cohort. *Obesity Science & Practice*, *2*(1), 40–47. https://doi.org/10.1002/osp4.27
Martinez Rivera, C., Costan Galicia, J., Alcázar Navarrete, B., Garcia-Polo, C., Ruiz Iturriaga, L. A., Herrejón, A., Ros Lucas, J. A., García-Sidro, P., Tirado-Conde, G., López-Campos, J. L., Mayoralas Alises, S., de Miguel-Díez, J., Esquinas, C., & Miravitlles, M. (2016). Factors Associated with Depression in COPD: A Multicenter Study. *Lung*, *194*(3), 335–343. https://doi.org/10.1007/s00408-016-9862-7
Masa, J. F., Celli, B. R., Riesco, J. A., Hernaéndez, M., Saénchez de Cos, J., & Disdier, C. (2001). The Obesity Hypoventilation Syndrome Can Be Treated With Noninvasive Mechanical Ventilation. *Chest*, *119*(4), 1102–1107. https://doi.org/10.1378/chest.119.4.1102
Masa, J. F., Corral, J., Alonso, M. L., Ordax, E., Troncoso, M. F., Gonzalez, M., Lopez-Martínez, S., Marin, J. M., Marti, S., Díaz-Cambriles, T., Chiner, E., Aizpuru, F., & Egea, C. (2015). Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome. Pickwick Study. *American Journal of Respiratory and Critical Care Medicine*, *192*(1), 86–95. https://doi.org/10.1164/rccm.201410-1900OC
Masa, J. F., Corral, J., Romero, A., Caballero, C., Terán-Santos, J., Alonso-Álvarez, M. L., Gomez-Garcia, T., González, M., López-Martínez, S., De Lucas, P., Marin, J. M., Marti, S., Díaz-Cambriles, T., Chiner, E., Merchan, M., Egea, C., Obeso, A., & Mokhlesi, B. (2016). The Effect of Supplemental Oxygen in Obesity Hypoventilation Syndrome. *Journal of Clinical Sleep Medicine*, *12*(10), 1379–1388. https://doi.org/10.5664/jcsm.6194
Masa, J. F., Pépin, J.-L., Borel, J.-C., Mokhlesi, B., Murphy, P. B., & Sánchez-Quiroga, M. Á. (2019a). Obesity hypoventilation syndrome. *European Respiratory Review*, *28*(151), 180097. https://doi.org/10.1183/16000617.0097-2018
Masa, J. F., Mokhlesi, B., Benítez, I., Gomez de Terreros, F. J., Sánchez-Quiroga, M. Á., Romero, A., Caballero-Eraso, C., Terán-Santos, J., Alonso-Álvarez, M. L., Troncoso, M. F., González, M., López-Martín, S., Marin, J. M., Martí, S., Díaz-Cambriles, T., Chiner, E., Egea, C., Barca, J., Vázquez-Polo, F.-J., … Bengoa, M. (2019b). Long-term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomised controlled trial. *The Lancet*, *393*(10182), 1721–1732. https://doi.org/10.1016/S0140-6736(18)32978-7
Masters, J. R. (1974). The Relationship Between Number Of Response Categories And Reliability Of Likert-Type Questionnaires. *Journal of Educational Measurement*, *11*(1), 49–53. https://doi.org/10.1111/j.1745-3984.1974.tb00970.x
Matell, M. S., & Jacoby, J. (1971). Is There an Optimal Number of Alternatives for Likert Scale Items? Study I: Reliability and Validity. *Educational and Psychological Measurement*,

31(3), 657–674. https://doi.org/10.1177/001316447103100307
Matte, D. L., Pizzichini, M. M. M., Hoepers, A. T. C., Diaz, A. P., Karloh, M., Dias, M., & Pizzichini, E. (2016). Prevalence of depression in COPD: A systematic review and meta-analysis of controlled studies. *Respiratory Medicine*, *117*, 154–161. https://doi.org/10.1016/j.rmed.2016.06.006
Matura, L. A., McDonough, A., & Carroll, D. L. (2016). Symptom Prevalence, Symptom Severity, and Health-Related Quality of Life Among Young, Middle, and Older Adults With Pulmonary Arterial Hypertension. *American Journal of Hospice and Palliative Medicine®*, *33*(3), 214–221. https://doi.org/10.1177/1049909114554079
Maurer, J., Rebbapragada, V., Borson, S., Goldstein, R., Kunik, M. E., Yohannes, A. M., & Hanania, N. A. (2008). Anxiety and Depression in COPD. *Chest*, *134*(4), 43S-56S. https://doi.org/10.1378/chest.08-0342
Medical Research Council Working Party, R. (1981). Long Term Domiciliary Oxygen Therapy in Chronic Hypoxic Cor Pulmonale Complicating Chronic Bronchitis and Emphysema. In *The Lancet* (Vol. 317, Issue 8222). https://doi.org/10.1016/S0140-6736(81)91970-X
Meehan, E., Foley, T., Kelly, C., Burgess Kelleher, A., Sweeney, C., Hally, R. M., Detering, K., & Cornally, N. (2020). Advance Care Planning for Individuals With Chronic Obstructive Pulmonary Disease: A Scoping Review of the Literature. *Journal of Pain and Symptom Management*, *59*(6), 1344–1361. https://doi.org/10.1016/j.jpainsymman.2019.12.010
Meek, P. M., Schwartzstein, R. M., Adams, L., Altose, M. D., Breslin, E. H., Carrieri-Kohlman, V. L., Gift, A. G., Hanley, M. V, Harver, A., Jones, P. W., Killian, K., Knebel, A., Lareau, S. C., Mahler, D. A., O'Donnell, D., Steele, B., Stuhlbarg, M., & Titler, M. (1999). Dyspnea. *American Journal of Respiratory and Critical Care Medicine*, *159*(1), 321–340. https://doi.org/10.1164/ajrccm.159.1.ats898
Mehta, S., & Hill, N. S. (2001). State of the Art Noninvasive Ventilation. *American Journal of Respiratory and Critical Care Medicine*, *163*(2), 540–577.
Miravitlles, M., Ferrer, J., Baró, E., Lleonart, M., & Galera, J. (2013). Differences between physician and patient in the perception of symptoms and their severity in COPD. *Respiratory Medicine*, *107*(12), 1977–1985. https://doi.org/10.1016/j.rmed.2013.06.019
Miravitlles, M., Molina, J., Quintano, J. A., Campuzano, A., Pérez, J., & Roncero, C. (2014). Factors associated with depression and severe depression in patients with COPD. *Respiratory Medicine*, *108*(11), 1615–1625. https://doi.org/10.1016/j.rmed.2014.08.010
Miravitlles, M., & Ribera, A. (2017). Understanding the impact of symptoms on the burden of COPD. *Respiratory Research*, *18*(1), 67. https://doi.org/10.1186/s12931-017-0548-3
Moens, K., Higginson, I. J., Harding, R., Brearley, S., Caraceni, A., Cohen, J., Costantini, M., Deliens, L., Francke, A. L., Kaasa, S., Linden, K., Meeussen, K., Miccinesi, G., Onwuteaka-Philipsen, B., Pardon, K., Pasman, R., Pautex, S., Payne, S., & Van den Block, L. (2014). Are There Differences in the Prevalence of Palliative Care-Related Problems in People Living With Advanced Cancer and Eight Non-Cancer Conditions? A Systematic Review. *Journal of Pain and Symptom Management*, *48*(4), 660–677. https://doi.org/10.1016/j.jpainsymman.2013.11.009
Mokhlesi, B., Kryger, M. H., & Grunstein, R. R. (2008). Assessment and Management of Patients with Obesity Hypoventilation Syndrome. *Proceedings of the American Thoracic Society*, *5*(2), 218–225. https://doi.org/10.1513/pats.200708-122MG
Mokhlesi, B. (2010). Obesity hypoventilation syndrome: a state-of-the-art review. *Respiratory Care*, *55*(10), 134–135.
Mokhlesi, B., Masa, J. F., Brozek, J. L., Gurubhagavatula, I., Murphy, P. B., Piper, A. J., Tulaimat, A., Afshar, M., Balachandran, J. S., Dweik, R. A., Grunstein, R. R., Hart, N., Kaw, R., Lorenzi-Filho, G., Pamidi, S., Patel, B. K., Patil, S. P., Pépin, J. L., Soghier, I.,

Tamae Kakazu, M., & Teodorescu, M. (2019). Evaluation and Management of Obesity Hypoventilation Syndrome. An Official American Thoracic Society Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine*, *200*(3), e6–e24. https://doi.org/10.1164/rccm.201905-1071ST

Morélot-Panzini, C., Perez, T., Sedkaoui, K., de Bock, E., Aguilaniu, B., Devillier, P., Pignier, C., Arnould, B., Bruneteau, G., & Similowski, T. (2018). The multidimensional nature of dyspnoea in amyotrophic lateral sclerosis patients with chronic respiratory failure: Air hunger, anxiety and fear. *Respiratory Medicine*, *145*(October), 1–7. https://doi.org/10.1016/j.rmed.2018.10.010

Morris, D., & Galicia-Castillo, M. (2015). Dying With Dyspnea in the Hospital. *The American Journal of Hospice & Palliative Care*, *34*(2), 132–134. https://doi.org/1049909115604140 [pii]

Murphy, P. B., Rehal, S., Arbane, G., Bourke, S., Calverley, P. M. A., Crook, A. M., Dowson, L., Duffy, N., Gibson, G. J., Hughes, P. D., Hurst, J. R., Lewis, K. E., Mukherjee, R., Nickol, A., Oscroft, N., Patout, M., Pepperell, J., Smith, I., Stradling, J. R., Wedzicha, J. A., Polkey, M. I., Elliot, M. W. & Hart, N. (2017). Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation. *JAMA*, *317*(21), 2177. https://doi.org/10.1001/jama.2017.4451

Murphy, P. B., Suh, E., & Hart, N. (2019). Non-invasive ventilation for obese patients with chronic respiratory failure: Are two pressures always better than one? *Respirology*, *24*(10), 952–961. https://doi.org/10.1111/resp.13588

Nava, S., Sturani, C., Hartl, S., Magni, G., Ciontu, M., Corrado, A., & Simonds, A. (2007). End-of-life decision-making in respiratory intermediate care units: a European survey. *European Respiratory Journal*, *30*(1), 156–164. https://doi.org/10.1183/09031936.00128306

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., Mullany, E. C., Biryukov, S., Abbafati, C., Abera, S. F., Abraham, J. P., Abu-Rmeileh, N. M. E., Achoki, T., AlBuhairan, F. S., Alemu, Z. A., Alfonso, R., Ali, M. K., Ali, R., Guzman, N. A., … Gakidou, E. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*, *384*(9945), 766–781. https://doi.org/10.1016/S0140-6736(14)60460-8

NICE. (2016). Motor Neurone Disease: Assessment and Management. In *NICE guideline NG42 Methods, evidence and recommendations* (Issue February). https://www.ncbi.nlm.nih.gov/books/NBK349620/pdf/Bookshelf_NBK349620.pdf

Nicholson, K., Murphy, A., McDonnell, E., Shapiro, J., Simpson, E., Glass, J., Mitsumoto, H., Forshew, D., Miller, R., & Atassi, N. (2018). Improving symptom management for people with amyotrophic lateral sclerosis. *Muscle & Nerve*, *57*(1), 20–24. https://doi.org/10.1002/mus.25712

Nishimura, K., Izumi, T., Tsukino, M., & Oga, T. (2002). Dyspnea Is a Better Predictor of 5-Year Survival Than Airway Obstruction in Patients With COPD. *Chest*, *121*(5), 1434–1440. https://doi.org/10.1378/chest.121.5.1434

Nishimura, K., Mitsuma, S., Kobayashi, A., Yanagida, M., Nakayasu, K., Hasegawa, Y., & Jones, P. W. (2013). COPD and disease-specific health status in a working population. *Respiratory Research*, *14*(1), 61. https://doi.org/10.1186/1465-9921-14-61

Nocturnal Oxygen Therapy Trial Group. (1980). Continuous or Nocturnal Oxygen Therapy in Hypoxemic Chronic Obstructive Lung Disease. *Annals of Internal Medicine*, *93*(3), 391. https://doi.org/10.7326/0003-4819-93-3-391

Nowbar, S., Burkart, K. M., Gonzales, R., Fedorowicz, A., Gozansky, W. S., Gaudio, J. C., Taylor, M. R. ., & Zwillich, C. W. (2004). Obesity-Associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *The American Journal of Medicine*, *116*(1), 1–7. https://doi.org/10.1016/j.amjmed.2003.08.022

Okubadejo, A. A., O'Shea, L., Jones, P. W., & Wedzicha, J. A. (1997). Home assessment of activities of daily living in patients with severe chronic obstructive pulmonary disease on long-term oxygen therapy. *European Respiratory Journal*, *10*(7), 1572–1575. https://doi.org/10.1183/09031936.97.10071572

Oldenmenger, W. H., de Raaf, P. J., de Klerk, C., & van der Rijt, C. C. D. (2013). Cut Points on 0–10 Numeric Rating Scales for Symptoms Included in the Edmonton Symptom Assessment Scale in Cancer Patients: A Systematic Review. *Journal of Pain and Symptom Management*, *45*(6), 1083–1093. https://doi.org/10.1016/j.jpainsymman.2012.06.007

Orphanet Report Series. (2020). Prevalence and incidence of rare diseases: Bibliographic data. Prevalence, incidence or number of published cases listed by diseases (in alphabetical order). *Orphanet Report Series Rare Diseases Collection*, *1*(1), 1–94. Available from: http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_diseases.pdf. Date last assessed: April 6th, 2021.

Ottenheijm, C. A. C., Heunks, L. M. A., & Dekhuijzen, P. N. R. (2007). Diaphragm Muscle Fiber Dysfunction in Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, *175*(12), 1233–1240. https://doi.org/10.1164/rccm.200701-020PP

Paneroni, M., Ambrosino, N., Simonelli, C., Bertacchini, L., Venturelli, M., & Vitacca, M. (2019). Physical Activity in Patients with Chronic Obstructive Pulmonary Disease on Long-Term Oxygen Therapy: A Cross-Sectional Study. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 14*, 2815–2823. https://doi.org/10.2147/COPD.S228465

Parshall, M. B., Schwartzstein, R. M., Adams, L., Banzett, R. B., Manning, H. L., Bourbeau, J., Calverley, P. M., Gift, A. G., Harver, A., Lareau, S. C., Mahler, D. A., Meek, P. M., & O'Donnell, D. E. (2012). An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea. *American Journal of Respiratory and Critical Care Medicine*, *185*(4), 435–452. https://doi.org/10.1164/rccm.201111-2042ST

Patel, K., Janssen, D. J. A., & Curtis, R. J. (2012). Advance care planning in COPD. *Respirology*, *17*(1), 72–78. https://doi.org/10.1111/j.1440-1843.2011.02087.x

Patout, M., Lhuillier, E., Kaltsakas, G., Benattia, A., Dupuis, J., Arbane, G., Declercq, P.-L., Ramsay, M., Marino, P., Molano, L.-C., Artaud-Macari, E., Viacroze, C., Steier, J., Douiri, A., Muir, J.-F., Cuvelier, A., Murphy, P. B., & Hart, N. (2020). Long-term survival following initiation of home non-invasive ventilation: a European study. *Thorax*, *75*(11), 965–973. https://doi.org/10.1136/thoraxjnl-2019-214204

Phillips, J. L., & Agar, M. R. (2016). Symptom management at the end of life. In Claudia Bausewein, D. C. Currow, & M. J. Johnson (Eds.), *ERS Monograph Palliative Care in Respiratory Disease* (pp. 221–232). European Respiratory Society. https://doi.org/10.1183/2312508X.10014216

Phillips, M. F., Smith, P. E. M., Carroll, N., Edwards, R. H. T., & Calverley, P. M. A. (1999). Nocturnal Oxygenation and Prognosis in Duchenne Muscular Dystrophy. *American Journal of Respiratory and Critical Care Medicine*, *160*(1), 198–202. https://doi.org/10.1164/ajrccm.160.1.9805055

Phillips, M. F., Quinlivan, R. C. M., Edwards, R. H. T., & Calverley, P. M. A. (2002). Changes in Spirometry Over Time as a Prognostic Marker in Patients with Duchenne Muscular Dystrophy. *American Journal of Respiratory and Critical Care Medicine*, *164*(12), 2191–2194.

https://doi.org/10.1164/ajrccm.164.12.2103052
Pinto, A. C., Evangelista, T., Carvalho, M., Alves, M. A., & Sales Luís, M. L. (1995). Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: Survival rates in a controlled trial. *Journal of the Neurological Sciences*, *129*(SUPPL.), 19–26. https://doi.org/10.1016/0022-510X(95)00052-4
Piper, A. J., & Grunstein, R. R. (2010). Big breathing: the complex interaction of obesity, hypoventilation, weight loss, and respiratory function. *Journal of Applied Physiology*, *108*(1), 199–205. https://doi.org/10.1152/japplphysiol.00713.2009
Pitta, F., Troosters, T., Spruit, M. A., Probst, V. S., Decramer, M., & Gosselink, R. (2005). Characteristics of Physical Activities in Daily Life in Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, *171*(9), 972–977. https://doi.org/10.1164/rccm.200407-855OC
Poutanen, O., Koivisto, A.-M., & Salokangas, R. K. R. (2008). The Depression Scale (DEPS) as a case finder for depression in various subgroups of primary care patients. *European Psychiatry*, *23*(8), 580–586. https://doi.org/10.1016/j.eurpsy.2008.06.007
Poutanen, O., Koivisto, A.-M., Kaaria, S., & Salokangas, R. K. R. (2010). The validity of the Depression Scale (DEPS) to assess the severity of depression in primary care patients. *Family Practice*, *27*(5), 527–534. https://doi.org/10.1093/fampra/cmq040
Priou, P., Hamel, J.-F., Person, C., Meslier, N., Racineux, J.-L., Urban, T., & Gagnadoux, F. (2010). Long-Term Outcome of Noninvasive Positive Pressure Ventilation for Obesity Hypoventilation Syndrome. *Chest*, *138*(1), 84–90. https://doi.org/10.1378/chest.09-2472
Prospective Studies Collaboration. (2009). Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *The Lancet*, *373*(9669), 1083–1096. https://doi.org/10.1016/S0140-6736(09)60318-4
Raghu, G., Weycker, D., Edelsberg, J., Bradford, W. Z., & Oster, G. (2006). Incidence and Prevalence of Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine*, *174*(7), 810–816. https://doi.org/10.1164/rccm.200602-163OC
Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K., Colby, T. V, Cordier, J.-F., Flaherty, K. R., Lasky, J. A., Lynch, D. A., Ryu, J. H., Swigris, J. J., Wells, A. U., Ancochea, J., Bouros, D., Carvalho, C., Costabel, U., Ebina, M., … Schünemann, H. J. (2011). An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *American Journal of Respiratory and Critical Care Medicine*, *183*(6), 788–824. https://doi.org/10.1164/rccm.2009-040GL
Raghu, G., Rochwerg, B., Zhang, Y., Garcia, C. A. C., Azuma, A., Behr, J., Brozek, J. L., Collard, H. R., Cunningham, W., Homma, S., Johkoh, T., Martinez, F. J., Myers, J., Protzko, S. L., Richeldi, L., Rind, D., Selman, M., Theodore, A., Wells, A. U., Hoogsteden, H., & Schünemann, H. J. (2015). An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine*, *192*(2), e3–e19. https://doi.org/10.1164/rccm.201506-1063ST
Raghu, G., & Richeldi, L. (2017). Current approaches to the management of idiopathic pulmonary fibrosis. *Respiratory Medicine*, *129*, 24–30. https://doi.org/10.1016/j.rmed.2017.05.017
Raghu, G., Remy-Jardin, M., Myers, J. L., Richeldi, L., Ryerson, C. J., Lederer, D. J., Behr, J., Cottin, V., Danoff, S. K., Morell, F., Flaherty, K. R., Wells, A., Martinez, F. J., Azuma, A., Bice, T. J., Bouros, D., Brown, K. K., Collard, H. R., Duggal, A., … Wilson, K. C. (2018). Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American Journal of Respiratory and*

Critical Care Medicine, *198*(5), e44–e68. https://doi.org/10.1164/rccm.201807-1255ST

Rajala, K., Lehto, J. T., Saarinen, M., Sutinen, E., Saarto, T., & Myllärniemi, M. (2016). End-of-life care of patients with idiopathic pulmonary fibrosis. *BMC Palliative Care*, *15*(1), 85. https://doi.org/10.1186/s12904-016-0158-8

Rajala, K., Lehto, J. T., Sutinen, E., Kautiainen, H., Myllärniemi, M., & Saarto, T. (2017). mMRC dyspnoea scale indicates impaired quality of life and increased pain in patients with idiopathic pulmonary fibrosis. *ERJ Open Research*, *3*(4), 00084–02017. https://doi.org/10.1183/23120541.00084-2017

Rajala, K., Lehto, J. T., Sutinen, E., Kautiainen, H., Myllärniemi, M., & Saarto, T. (2018). Marked deterioration in the quality of life of patients with idiopathic pulmonary fibrosis during the last two years of life. *BMC Pulmonary Medicine*, *18*(1), 172. https://doi.org/10.1186/s12890-018-0738-x

Raveling, T., Bladder, G., Vonk, J., Nieuwenhuis, J., Verdonk-Struik, F., Wijkstra, P., & Duiverman, M. (2018). Improvement in hypercapnia does not predict survival in COPD patients on chronic noninvasive ventilation. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 13*, 3625–3634. https://doi.org/10.2147/COPD.S169951

Reuben, D. B., & Mor, V. (1986). Dyspnea in Terminally Ill Cancer Patients. *Chest*, *89*(2), 234–236. https://doi.org/10.1378/chest.89.2.234

Richeldi, L., du Bois, R. M., Raghu, G., Azuma, A., Brown, K. K., Costabel, U., Cottin, V., Flaherty, K. R., Hansell, D. M., Inoue, Y., Kim, D. S., Kolb, M., Nicholson, A. G., Noble, P. W., Selman, M., Taniguchi, H., Brun, M., Le Maulf, F., Girard, M., Stowasser, S., Schlenker-Herceg, R., Disse, B., & Collard, H. R. (2014). Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. *New England Journal of Medicine*, *370*(22), 2071–2082. https://doi.org/10.1056/NEJMoa1402584

Rideau, Y., Gatin, G., Bach, J., & Gines, G. (1983). Prolongation of life in Duchenne's muscular dystrophy. *Acta Neurologica*, *5*, 118–124.

Rietjens, J. A. C., Sudore, R. L., Connolly, M., van Delden, J. J., Drickamer, M. A., Droger, M., van der Heide, A., Heyland, D. K., Houttekier, D., Janssen, D. J. A., Orsi, L., Payne, S., Seymour, J., Jox, R. J., & Korfage, I. J. (2017). Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. *The Lancet Oncology*, *18*(9), e543–e551. https://doi.org/10.1016/S1470-2045(17)30582-X

Ripamonti, C. I., Bandieri, E., Pessi, M. A., Maruelli, A., Buonaccorso, L., & Miccinesi, G. (2014). The Edmonton Symptom Assessment System (ESAS) as a screening tool for depression and anxiety in non-advanced patients with solid or haematological malignancies on cure or follow-up. *Supportive Care in Cancer*, *22*(3), 783–793. https://doi.org/10.1007/s00520-013-2034-x

Robert, D., & Argaud, L. (2007). Non-invasive positive ventilation in the treatment of sleep-related breathing disorders. *Sleep Medicine*, *8*(4), 441–452. https://doi.org/10.1016/j.sleep.2007.03.009

Rochwerg, B., Brochard, L., Elliott, M. W., Hess, D., Hill, N. S., Nava, S., Navalesi, P., Antonelli, M., Brozek, J., Conti, G., Ferrer, M., Guntupalli, K., Jaber, S., Keenan, S., Mancebo, J., Mehta, S., & Raoof, S. (2017). Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *European Respiratory Journal*, *50*(2), 1602426. https://doi.org/10.1183/13993003.02426-2016

Rockey, D. C., Bell, P. D., & Hill, J. A. (2015). Fibrosis — A Common Pathway to Organ Injury and Failure. *New England Journal of Medicine*, *372*(12), 1138–1149. https://doi.org/10.1056/NEJMra1300575

Roussos, C., & Koutsoukou, A. (2003). Respiratory failure. *European Respiratory Journal*,

22(Supplement 47), 3s-14s. https://doi.org/10.1183/09031936.03.00038503

Ruparel, M., Quaife, S. L., Dickson, J. L., Horst, C., Tisi, S., Hall, H., Taylor, M. N., Ahmed, A., Shaw, P. J., Burke, S., Soo, M.-J., Nair, A., Devaraj, A., Sennett, K., Hurst, J. R., Duffy, S. W., Navani, N., Bhowmik, A., Baldwin, D. R., & Janes, S. M. (2020). Prevalence, Symptom Burden, and Underdiagnosis of Chronic Obstructive Pulmonary Disease in a Lung Cancer Screening Cohort. *Annals of the American Thoracic Society*, *17*(7), 869–878. https://doi.org/10.1513/AnnalsATS.201911-857OC

Ryerson, C. J., Berkeley, J., Carrieri-Kohlman, V. L., Pantilat, S. Z., Landefeld, C. S., & Collard, H. R. (2011). Depression and Functional Status Are Strongly Associated With Dyspnea in Interstitial Lung Disease. *Chest*, *139*(3), 609–616. https://doi.org/10.1378/chest.10-0608

Ryerson, C. J., Arean, P. A., Berkeley, J., Carrieri-Kohlman, V. L., Pantilat, S. Z., Landefeld, C. S., & Collard, H. R. (2012). Depression is a common and chronic comorbidity in patients with interstitial lung disease. *Respirology*, *17*(3), 525–532. https://doi.org/10.1111/j.1440-1843.2011.02122.x

Salokangas, R. K. R., Poutanen, O., & Stengård, E. (1995). Screening for depression in primary care Development and validation of the Depression Scale, a screening instrument for depression. *Acta Psychiatrica Scandinavica*, *92*(1), 10–16. https://doi.org/10.1111/j.1600-0447.1995.tb09536.x

Sancho, J., Martínez, D., Bures, E., Díaz, J. L., Ponz, A., & Servera, E. (2018). Bulbar impairment score and survival of stable amyotrophic lateral sclerosis patients after noninvasive ventilation initiation. *ERJ Open Research*, *4*(2), 00159–02017. https://doi.org/10.1183/23120541.00159-2017

Schwarz, S. B., Magnet, F. S., & Windisch, W. (2017). Why High-Intensity NPPV is Favourable to Low-Intensity NPPV: Clinical and Physiological Reasons. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *14*(4), 389–395. https://doi.org/10.1080/15412555.2017.1318843

Selby, D., Cascella, A., Gardiner, K., Do, R., Moravan, V., Myers, J., & Chow, E. (2010). A Single Set of Numerical Cutpoints to Define Moderate and Severe Symptoms for the Edmonton Symptom Assessment System. *Journal of Pain and Symptom Management*, *39*(2), 241–249. https://doi.org/10.1016/j.jpainsymman.2009.06.010

Serlin, R. C., Mendoza, T. R., Nakamura, Y., Edwards, K. R., & Cleeland, C. S. (1995). When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain*, *61*(2), 277–284. https://doi.org/10.1016/0304-3959(94)00178-H

Sheehan, A. M., & McGee, H. (2013). Screening for depression in medical research: ethical challenges and recommendations. *BMC Medical Ethics*, *14*(1), 4. https://doi.org/10.1186/1472-6939-14-4

Sheehan, D. W., Birnkrant, D. J., Benditt, J. O., Eagle, M., Finder, J. D., Kissel, J., Kravitz, R. M., Sawnani, H., Shell, R., Sussman, M. D., & Wolfe, L. F. (2018). Respiratory Management of the Patient With Duchenne Muscular Dystrophy. *Pediatrics*, *142*(Supplement 2), S62–S71. https://doi.org/10.1542/peds.2018-0333H

Simonds, A. K., & Elliott, M. W. (1995). Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. *Thorax*, *50*(6), 604–609. https://doi.org/10.1136/thx.50.6.604

Simonds, A. K., Muntoni, F., Heather, S., & Fielding, S. (1998). Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax*, *53*(11), 949–952. https://doi.org/10.1136/thx.53.11.949

Simonds, A. K. (2003). Home ventilation. *European Respiratory Journal*, *22*(Supplement 47), 38s-46s. https://doi.org/10.1183/09031936.03.00029803

Simonds, A. K. (2006). Recent Advances in Respiratory Care for Neuromuscular Disease.

Chest, *130*(6), 1879–1886. https://doi.org/10.1378/chest.130.6.1879

Simonds, A. K. (2013). Chronic hypoventilation and its management. *European Respiratory Review*, *22*(129), 325–332. https://doi.org/10.1183/09059180.00003113

Singer, P. A., Robertson, G., & Roy, D. J. (1996). Bioethics for clinicians: 6. Advance care planning. *Canadian Medical Association*, *155*(12), 1689–1692.

Sintonen, H. (1981). An approach to measuring and valuing health states. *Social Science & Medicine. Part C: Medical Economics*, *15*(2), 55–65. https://doi.org/10.1016/0160-7995(81)90019-8

Sintonen, H. (2001). The 15D instrument of health-related quality of life: properties and applications. *Annals of Medicine*, *33*(5), 328–336. https://doi.org/10.3109/07853890109002086

Smith, A. K., Currow, D. C., Abernethy, A. P., Johnson, M. J., Miao, Y., Boscardin, W. J., & Ritchie, C. S. (2016). Prevalence and Outcomes of Breathlessness in Older Adults: A National Population Study. *Journal of the American Geriatrics Society*, *64*(10), 2035–2041. https://doi.org/10.1111/jgs.14313

Smith, E. L., Hann, D. M., Ahles, T. A., Furstenberg, C. T., Mitchell, T. A., Meyer, L., Maurer, L. H., Rigas, J., & Hammond, S. (2001). Dyspnea, Anxiety, Body Consciousness, and Quality of Life in Patients with Lung Cancer. *Journal of Pain and Symptom Management*, *21*(4), 323–329. https://doi.org/10.1016/S0885-3924(01)00255-X

Smith, M., & Wrobel, J. (2014). Epidemiology and clinical impact of major comorbidities in patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, *9*, 871. https://doi.org/10.2147/COPD.S49621

Smith, T. A., Ingham, J. M., & Jenkins, C. R. (2019). Respiratory Failure, Noninvasive Ventilation, and Symptom Burden: An Observational Study. *Journal of Pain and Symptom Management*, *57*(2), 282-289.e1. https://doi.org/10.1016/j.jpainsymman.2018.10.505

Solano, J. P., Gomes, B., & Higginson, I. J. (2006). A Comparison of Symptom Prevalence in Far Advanced Cancer, AIDS, Heart Disease, Chronic Obstructive Pulmonary Disease and Renal Disease. *Journal of Pain and Symptom Management*, *31*(1), 58–69. https://doi.org/10.1016/j.jpainsymman.2005.06.007

Soriano, J. B., Abajobir, A. A., Abate, K. H., Abera, S. F., Agrawal, A., Ahmed, M. B., Aichour, A. N., Aichour, I., Aichour, M. T. E., Alam, K., Alam, N., Alkaabi, J. M., Al-Maskari, F., Alvis-Guzman, N., Amberbir, A., Amoako, Y. A., Ansha, M. G., Antó, J. M., Asayesh, H., … Vos, T. (2017). Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet Respiratory Medicine*, *5*(9), 691–706. https://doi.org/10.1016/S2213-2600(17)30293-X

Soto-Campos, J. G., Plaza, V., Soriano, J. B., Cabrera-López, C., Almonacid-Sánchez, C., Vazquez-Oliva, R., Serrano, J., Ballaz-Quincoces, A., Padilla-Galo, A., & Santos, V. (2013). "Causes of death in asthma, COPD and non-respiratory hospitalized patients: a multicentric study." *BMC Pulmonary Medicine*, *13*(1), 73. https://doi.org/10.1186/1471-2466-13-73

Spruit, M. A., Pitta, F., McAuley, E., ZuWallack, R. L., & Nici, L. (2015). Pulmonary Rehabilitation and Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, *192*(8), 924–933. https://doi.org/10.1164/rccm.201505-0929CI

Stineman, M. G., Xie, D., Pan, Q., Kurichi, J. E., Zhang, Z., Saliba, D., Henry-Sánchez, J. T., & Streim, J. (2012). All-Cause 1-, 5-, and 10-Year Mortality in Elderly People According to Activities of Daily Living Stage. *Journal of the American Geriatrics Society*, *60*(3), 485–492. https://doi.org/10.1111/j.1532-5415.2011.03867.x

Struik, F. M., Sprooten, R. T. M., Kerstjens, H. A. M., Bladder, G., Zijnen, M., Asin, J., Cobben, N. A. M., Vonk, J. M., & Wijkstra, P. J. (2014). Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax*, *69*(9), 826–834. https://doi.org/10.1136/thoraxjnl-2014-205126

Strumpf, D. A., Millman, R. P., Carlisle, C. C., Grattan, L. M., Ryan, S. M., Erickson, A. D., & Hill, N. S. (1991). Nocturnal Positive-Pressure Ventilation via Nasal Mask in Patients with Severe Chronic Obstructive Pulmonary Disease. *American Review of Respiratory Disease*, *144*(6), 1234–1239. https://doi.org/10.1164/ajrccm/144.6.1234

Sturm, R. (2007). Increases in morbid obesity in the USA: 2000–2005. *Public Health*, *121*(7), 492–496. https://doi.org/10.1016/j.puhe.2007.01.006

Sundh, J., & Ekström, M. (2016). Persistent disabling breathlessness in chronic obstructive pulmonary disease. *International Journal of COPD*, *11*(1), 2805–2812. https://doi.org/10.2147/COPD.S119992

Sundh, J., & Ekström, M. (2017). Risk factors for developing hypoxic respiratory failure in COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 12*, 2095–2100. https://doi.org/10.2147/COPD.S140299

Swan, F., Newey, A., Bland, M., Allgar, V., Booth, S., Bausewein, C., Yorke, J., & Johnson, M. (2019). Airflow relieves chronic breathlessness in people with advanced disease: An exploratory systematic review and meta-analyses. *Palliative Medicine*, *33*(6), 618–633. https://doi.org/10.1177/0269216319835393

Swedevox. (2020). Swedish National Register for Respiratory Failure (Swedevox). Annual report. 2019. Date last assessed: January 15th, 2021. Available from: www.ucr.uu.se/swedevox.

Tanaka, K., Akechi, T., Okuyama, T., Nishiwaki, Y., & Uchitomi, Y. (2002). Prevalence and Screening of Dyspnea Interfering with Daily Life Activities in Ambulatory Patients with Advanced Lung Cancer. *Journal of Pain and Symptom Management*, *23*(6), 484–489. https://doi.org/10.1016/S0885-3924(02)00394-9

Tavares, N., Jarrett, N., Hunt, K., & Wilkinson, T. (2017). Palliative and end-of-life care conversations in COPD: a systematic literature review. *ERJ Open Research*, *3*(2), 00068–02016. https://doi.org/10.1183/23120541.00068-2016

Temel, J. S., Greer, J. A., Muzikansky, A., Gallagher, E. R., Admane, S., Jackson, V. A., Dahlin, C. M., Blinderman, C. D., Jacobsen, J., Pirl, W. F., Billings, J. A., & Lynch, T. J. (2010). Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, *363*(8), 733–742. https://doi.org/10.1056/NEJMoa1000678

Travis, W. D., & King, T. E. (2002). American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *American Journal of Respiratory and Critical Care Medicine*, *165*(2), 277–304. https://doi.org/10.1164/ajrccm.165.2.ats01

Tudor-Locke, C., Washington, T. L., & Hart, T. L. (2009). Expected values for steps/day in special populations. *Preventive Medicine*, *49*(1), 3–11. https://doi.org/10.1016/j.ypmed.2009.04.012

Uronis, H. E., Ekström, M. P., Currow, D. C., McCrory, D. C., Samsa, G. P., & Abernethy, A. P. (2015). Oxygen for relief of dyspnoea in people with chronic obstructive pulmonary disease who would not qualify for home oxygen: a systematic review and meta-analysis: Figure 1. *Thorax*, *70*(5), 492–494. https://doi.org/10.1136/thoraxjnl-2014-205720

Vaes, A. W., Garcia-Aymerich, J., Marott, J. L., Benet, M., Groenen, M. T. J., Schnohr, P., Franssen, F. M. E., Vestbo, J., Wouters, E. F. M., Lange, P., & Spruit, M. A. (2014). Changes in physical activity and all-cause mortality in COPD. *European Respiratory*

Journal, *44*(5), 1199–1209. https://doi.org/10.1183/09031936.00023214

Vanfleteren, L. E. G. W., Spruit, M. A., Wouters, E. F. M., & Franssen, F. M. E. (2016). Management of chronic obstructive pulmonary disease beyond the lungs. *The Lancet Respiratory Medicine*, *4*(11), 911–924. https://doi.org/10.1016/S2213-2600(16)00097-7

Vasankari, T. M., Impivaara, O., Heliovaara, M., Heistaro, S., Liippo, K., Puukka, P., Saarelainen, S., Kanervisto, M., & Jousilahti, P. (2010). No increase in the prevalence of COPD in two decades. *European Respiratory Journal*, *36*(4), 766–773. https://doi.org/10.1183/09031936.00178109

Vender, R. L., Mauger, D., Walsh, S., Alam, S., & Simmons, Z. (2007). Respiratory systems abnormalities and clinical milestones for patients with amyotrophic lateral sclerosis with emphasis upon survival. *Amyotrophic Lateral Sclerosis*, *8*(1), 36–41. https://doi.org/10.1080/17482960600863951

Vianello, A., Bevilacqua, M., Salvador, V., Cardaioli, C., & Vincenti, E. (1994). Long-term Nasal Intermittent Positive Pressure Ventilation in Advanced Duchenne's Muscular Dystrophy. *Chest*, *105*(2), 445–448. https://doi.org/10.1378/chest.105.2.445

Vidotto, G., Carone, M., Jones, P. W., Salini, S., Bertolotti, G., & On behalf of the Quess Group. (2007). Maugeri Respiratory Failure questionnaire reduced form: A method for improving the questionnaire using the Rasch model. *Disability and Rehabilitation*, *29*(13), 991–998. https://doi.org/10.1080/09638280600926678

Vignaroli, E., Pace, E. A., Willey, J., Palmer, J. L., Zhang, T., & Bruera, E. (2006). The Edmonton Symptom Assessment System as a Screening Tool for Depression and Anxiety. *Journal of Palliative Medicine*, *9*(2), 296–303. https://doi.org/10.1089/jpm.2006.9.296

Vitacca, M., Grassi, M., Barbano, L., Galavotti, G., Sturani, C., Vianello, A., Zanotti, E., Ballerin, L., Potena, A., Scala, R., Peratoner, A., Ceriana, P., Di Buono, L., Clini, E., Ambrosino, N., Hill, N., & Nava, S. (2010). Last 3 months of life in home-ventilated patients: the family perception. *European Respiratory Journal*, *35*(5), 1064–1071. https://doi.org/10.1183/09031936.00061009

Vogt, S., Schreiber, S., Kollewe, K., Körner, S., Heinze, H.-J., Dengler, R., Petri, S., & Vielhaber, S. (2019). Dyspnea in amyotrophic lateral sclerosis: The Dyspnea-ALS-Scale (DALS-15) essentially contributes to the diagnosis of respiratory impairment. *Respiratory Medicine*, *154*(April), 116–121. https://doi.org/10.1016/j.rmed.2019.06.014

Voll-Aanerud, M., Eagan, T. M. L., Wentzel-Larsen, T., Gulsvik, A., & Bakke, P. S. (2007). Changes in Respiratory Symptoms and Health-Related Quality of Life. *Chest*, *131*(6), 1890–1897. https://doi.org/10.1378/chest.06-2629

Vos, T., Lim, S. S., Abbafati, C., Abbas, K. M., Abbasi, M., Abbasifard, M., Abbasi-Kangevari, M., Abbastabar, H., Abd-Allah, F., Abdelalim, A., Abdollahi, M., Abdollahpour, I., Abolhassani, H., Aboyans, V., Abrams, E. M., Abreu, L. G., Abrigo, M. R. M., Abu-Raddad, L. J., Abushouk, A. I., … Murray, C. J. L. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9

Wagner, P. D. (2012). Gas Exchange. In S. G. Spiro, G. A. Silvestri, & A. G. Agusti (Eds.), *Clinical Respiratory Medicine* (4th ed., p. 43). Elsevier Saunders.

Wajnberg, A., Ornstein, K., Zhang, M., Smith, K. L., & Soriano, T. (2013). Symptom Burden in Chronically Ill Homebound Individuals. *Journal of the American Geriatrics Society*, *61*(1), 126–131. https://doi.org/10.1111/jgs.12038

Walke, L. M., Byers, A. L., McCorkle, R., & Fried, T. R. (2006). Symptom Assessment in Community-Dwelling Older Adults with Advanced Chronic Disease. *Journal of Pain and Symptom Management*, *31*(1), 31–37.

https://doi.org/10.1016/j.jpainsymman.2005.05.014
Wedzicha, J. A., Miravitlles, M., Hurst, J. R., Calverley, P. M. A., Albert, R. K., Anzueto, A., Criner, G. J., Papi, A., Rabe, K. F., Rigau, D., Sliwinski, P., Tonia, T., Vestbo, J., Wilson, K. C., & Krishnan, J. A. (2017). Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *European Respiratory Journal*, *49*(3), 1600791. https://doi.org/10.1183/13993003.00791-2016
Weingaertner, V., Scheve, C., Gerdes, V., Schwarz-Eywill, M., Prenzel, R., Bausewein, C., Higginson, I. J., Voltz, R., Herich, L., & Simon, S. T. (2014). Breathlessness, Functional Status, Distress, and Palliative Care Needs Over Time in Patients With Advanced Chronic Obstructive Pulmonary Disease or Lung Cancer: A Cohort Study. *Journal of Pain and Symptom Management*, *48*(4), 569-581.e1. https://doi.org/10.1016/j.jpainsymman.2013.11.011
Wells, J. M., Estepar, R. S. J., McDonald, M.-L. N., Bhatt, S. P., Diaz, A. A., Bailey, W. C., Jacobson, F. L., Dransfield, M. T., Washko, G. R., Make, B. J., Casaburi, R., van Beek, E. J. R., Hoffman, E. A., Sciurba, F. C., Crapo, J. D., Silverman, E. K., & Hersh, C. P. (2016). Clinical, physiologic, and radiographic factors contributing to development of hypoxemia in moderate to severe COPD: a cohort study. *BMC Pulmonary Medicine*, *16*(1), 169. https://doi.org/10.1186/s12890-016-0331-0
Westeneng, H.-J., Debray, T. P. A., Visser, A. E., van Eijk, R. P. A., Rooney, J. P. K., Calvo, A., Martin, S., McDermott, C. J., Thompson, A. G., Pinto, S., Kobeleva, X., Rosenbohm, A., Stubendorff, B., Sommer, H., Middelkoop, B. M., Dekker, A. M., van Vugt, J. J. F. A., van Rheenen, W., Vajda, A., … van den Berg, L. H. (2018). Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. *The Lancet Neurology*, *17*(5), 423–433. https://doi.org/10.1016/S1474-4422(18)30089-9
WHO, & WHPCA. (2020). *Global Atlas of Palliative Care 2nd Edition* (Issue January). Date last assessed March 15th, 2021. Available from: http://www.who.int/cancer/publications/palliative-care-atlas/en/
Wijesinghe, M., Williams, M., Perrin, K., Weatherall, M., & Beasley, R. (2011). The Effect of Supplemental Oxygen on Hypercapnia in Subjects With Obesity-Associated Hypoventilation. *Chest*, *139*(5), 1018–1024. https://doi.org/10.1378/chest.10-1280
Williams, J. W., Pignone, M., Ramirez, G., & Perez Stellato, C. (2002). Identifying depression in primary care: a literature synthesis of case-finding instruments. *General Hospital Psychiatry*, *24*(4), 225–237. https://doi.org/10.1016/S0163-8343(02)00195-0
Wilson, M. E., Dobler, C. C., Morrow, A. S., Beuschel, B., Alsawas, M., Benkhadra, R., Seisa, M., Mittal, A., Sanchez, M., Daraz, L., Holets, S., Murad, M. H., & Wang, Z. (2020). Association of Home Noninvasive Positive Pressure Ventilation With Clinical Outcomes in Chronic Obstructive Pulmonary Disease. *JAMA*, *323*(5), 455. https://doi.org/10.1001/jama.2019.22343
Windisch, W., Vogel, M., Sorichter, S., Hennings, E., Bremer, H., Hamm, H., Matthys, H., & Virchow, J. C. (2002). Normocapnia during nIPPV in chronic hypercapnic COPD reduces subsequent spontaneous PaCO2. *Respiratory Medicine*, *96*(8), 572–579. https://doi.org/10.1053/rmed.2002.1326
Windisch, Wolfram, Freidel, K., Schucher, B., Baumann, H., Wiebel, M., Matthys, H., & Petermann, F. (2003). The Severe Respiratory Insufficiency (SRI) Questionnaire A specific measure of health-related quality of life in patients receiving home mechanical ventilation. *Journal of Clinical Epidemiology*, *56*(8), 752–759. https://doi.org/10.1016/S0895-4356(03)00088-X
Windisch, Wolfram, Dreher, M., Storre, J. H., & Sorichter, S. (2006). Nocturnal non-invasive positive pressure ventilation: Physiological effects on spontaneous breathing. *Respiratory*

Physiology & Neurobiology, *150*(2–3), 251–260. https://doi.org/10.1016/j.resp.2005.05.017

Windisch, W., Walterspacher, S., Siemon, K., Geiseler, J., & Sitter, H. (2010). Guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. *Pneumologie*, *64*(10), 640–652. https://doi.org/10.1055/s-0030-1255558

Wysham, N. G., Cox, C. E., Wolf, S. P., & Kamal, A. H. (2015). Symptom Burden of Chronic Lung Disease Compared with Lung Cancer at Time of Referral for Palliative Care Consultation. *Annals of the American Thoracic Society*, *12*(9), 1294–1301. https://doi.org/10.1513/AnnalsATS.201503-180OC

Yohannes, A. M., Willgoss, T. G., Baldwin, R. C., & Connolly, M. J. (2010). Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *International Journal of Geriatric Psychiatry*, *25*(12), 1209–1221. https://doi.org/10.1002/gps.2463

Zambroski, C. H., Moser, D. K., Bhat, G., & Ziegler, C. (2005). Impact of Symptom Prevalence and Symptom Burden on Quality of Life in Patients with Heart Failure. *European Journal of Cardiovascular Nursing*, *4*(3), 198–206. https://doi.org/10.1016/j.ejcnurse.2005.03.010

9 APPENDIX

Edmonton Symptom Assessment System (ESAS) Questionnaire

Nimi _____

TAYS
OIREKYSELYKAAVAKE
ESAS (mukaeltu versio)

Henkilötunnus _____

Pvm _____ Osasto_____

Kuinka voitte <u>tänään?</u>

Ympyröikää sopivin vaihtoehto numeroista ajatellen vointianne nykyisellä lääkityksellä ja hoidolla.Lopuksi alleviivatkaa häiritsevin oire.

Kipu- levossa

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Kipu-liikkuessa

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Väsymys/uupumus

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Hengenahdistus

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Ruokahaluttomuus

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Pahoinvointi

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Suun kuivuminen

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Ummetus

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Masennus

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Ahdistuneisuus

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Unettomuus

Ei lainkaan 0 1 2 3 4 5 6 7 8 9 10 Pahin mahdollinen

Millaisena koette vointinne kokonaisuudessaan tänään ?

Paras mahdollinen 0 1 2 3 4 5 6 7 8 9 10 Huonoin mahdollinen

Depression Scale (DEPS)

DEPS-testi

Alla olevassa luettelossa esitetään Sinua itseäsi koskevia väitteitä. Valitse jokaisen väitteen kohdista se vaihtoehto, joka parhaiten vastaa mielentilaasi viimeksi kuluneen kuukauden aikana.

Viimeksi kuluneen kuukauden aikana	En lainkaan (0 p)	Jonkin verran (1 p)	Melko paljon (2 p)	Erittäin paljon (3 p)
Kärsin unettomuudesta.	☐	☐	☐	☐
Tunsin itseni surumieliseksi.	☐	☐	☐	☐
Minusta tuntui, että kaikki vaati ponnistusta.	☐	☐	☐	☐
Tunsin itseni tarmottomaksi.	☐	☐	☐	☐
Tunsin itseni yksinäiseksi.	☐	☐	☐	☐
Tulevaisuus näytti toivottomalta.	☐	☐	☐	☐
En nauttinut elämästäni.	☐	☐	☐	☐
Tunsin itseni arvottomaksi.	☐	☐	☐	☐
Tunsin, että kaikki ilo on hävinnyt elämästäni.	☐	☐	☐	☐
Minusta tuntui, ettei alakuloisuuteni hellittänyt edes perheeni tai ystävieni avulla.	☐	☐	☐	☐

Pisteet yhteensä: _____

DEPS-seulassa 9 pistettä tai enemmän saaneista noin kolmasosalla ja 12 pistettä tai enemmän saaneista lähes puolella on depressio.

Medical Research Council Dyspnoea Scale (mMRC)

Medical Research Councilin hengenahdistusasteikko

Nimi ja sotu: _____
Pvm:

Laittakaa rasti sen tason kohdalle, joka kuvastaa hengenahdistustanne parhaiten.

Hengästyn vain rasittavasta liikunnasta	taso 0
Hengästyn, jos liikun kiireisesti tasamaalla tai kävelen loivaa ylämäkeä	taso 1
Kävelen hengenahdistuksen takia samanikäisiä ihmisiä hitaammin tasamaalla tai minun täytyy pysähtyä hengittämään, kun kävelen tasamaalla omaan tahtiini	taso 2
Pysähdyn hengittämään käveltyäni noin 100 metriä tai muutaman minuutin tasamaalla	taso 3
Olen niin hengästynyt, etten voi lähteä kotoa tai hengästyn, kun pukeudun tai riisuudun	taso 4

10 PUBLICATIONS

PUBLICATION I

Assessing symptom burden and depression in subjects with chronic respiratory insufficiency.

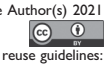
Rantala Heidi A, Leivo-Korpela Sirpa, Lehtimäki Lauri, Lehto Juho T

Journal of Palliative Care [Internet]. November 2021
doi:10.1177/08258597211049592

Publication reprinted with the permission of the copyright holders.

Check for updates

Original Article

Journal of Palliative Care
8
© The Author(s) 2021

Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/08258597211049592
journals.sagepub.com/home/pal

Assessing Symptom Burden and Depression in Subjects With Chronic Respiratory Insufficiency

Heidi A. Rantala, MD[1,2], Sirpa Leivo-Korpela, MD, PhD[1,2], Lauri Lehtimäki, MD, PhD[2,3], and Juho T. Lehto, MD, PhD[2,4]

Abstract

Objectives: Patients with chronic respiratory insufficiency suffer from advanced disease, but their overall symptom burden is poorly described. We evaluated the symptoms and screening of depression in subjects with chronic respiratory insufficiency by using the Edmonton symptom assessment system (ESAS). **Methods:** In this retrospective study, 226 subjects with chronic respiratory insufficiency answered the ESAS questionnaire measuring symptoms on a scale from 0 (no symptoms) to 10 (worst possible symptom), and the depression scale (DEPS) questionnaire, in which the cut-off point for depressive symptoms is 9. **Results:** The most severe symptoms measured with ESAS (median [interquartile range]) were shortness of breath 4.0 (1.0-7.0), dry mouth 3.0 (1.0-7.0), tiredness 3.0 (1.0-6.0), and pain on movement 3.0 (0.0-6.0). Subjects with a chronic obstructive pulmonary disease as a cause for chronic respiratory insufficiency had significantly higher scores for shortness of breath, dry mouth, and loss of appetite compared to others. Subjects with DEPS $\geq$9 reported significantly higher symptom scores in all ESAS categories than subjects with DEPS <9. The area under the receiver operating characteristic curve for ESAS depression score predicting DEPS $\geq$9 was 0.840 ($P < .001$). If the ESAS depression score was 0, there was an 89% probability of the DEPS being <9, and if the ESAS depression score was $\geq$4, there was an 89% probability of the DEPS being $\geq$9. The relation between ESAS depression score and DEPS was independent of subjects' characteristics and other ESAS items. **Conclusions:** Subjects with chronic respiratory insufficiency suffer from a high symptom burden due to their advanced disease. The severity of symptoms increases with depression and 4 or more points in the depression question of ESAS should lead to a closer diagnostic evaluation of depression. Symptom-centered palliative care including psychosocial aspects should be early integrated into the treatment of respiratory insufficiency.

Keywords

chronic respiratory insufficiency, Edmonton symptom assessment system, depression, symptoms, chronic obstructive pulmonary disease

Introduction

Chronic respiratory insufficiency and the need for noninvasive ventilation (NIV) or long-term oxygen therapy (LTOT) are often signs of advanced disease and poor prognosis. Patients with advanced respiratory disease typically have severe breathlessness, but some other symptoms are reported as well.[1–5] Patients may suffer from pain, loss of energy, dry mouth, cough, depression, and anxiety in addition to dyspnea.[6–9] Comorbidities further enhance the symptom burden in advanced respiratory diseases and significantly affect patients' quality of life and survival.[10,11] Guidelines and previous studies have recommended to systematically screen symptoms other than dyspnea in patients with advanced respiratory disease.[1,12,13]

Depression is common in diseases causing chronic respiratory insufficiency, such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease.[3,9,14] Depressive symptoms increase perceived symptom burden and impair quality of life.[3,4,15,16] They have also been associated with a risk of hospitalization, emergency care use, and impaired prognosis.[14,17,18] Therefore, systematic screening of depression in patients with advanced respiratory diseases and chronic respiratory insufficiency is warranted.

[1]Department of Respiratory Medicine, Tampere University Hospital, Tampere, Finland
[2]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[3]Allergy Centre, Tampere University Hospital, Tampere, Finland
[4]Department of Oncology, Palliative Care Unit, Tampere University Hospital, Tampere, Finland

Corresponding Author:
Heidi A. Rantala, MD, Department of Respiratory Medicine, Tampere University Hospital, Tampere, Finland; Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; Elämänaukio, Kuntokatu 2, 33520 Tampere, Finland.
Email: Heidi.Rantala@tuni.fi

Patients with chronic respiratory insufficiency suffer from multimorbidity demanding medical attention. Their proper treatment requires knowledge of individual symptom burdens beyond breathlessness. Previous studies have focused on different advanced pulmonary diseases, but not on an unselected population of chronic respiratory insufficiency.[1,2,9,16] Therefore, studies describing the overall symptom burden, prevalence of depression, or the relationship between depression and other symptoms in patients with chronic respiratory insufficiency are needed.

We aimed to describe the overall symptom burden in subjects with chronic respiratory insufficiency and to assess the association between depression and other symptoms. We also assessed how well a single question on depression as part of the Edmonton symptom assessment system (ESAS) reflects depressive symptoms measured by a more thorough depression scale (DEPS) questionnaire.

Methods

All patients with chronic respiratory insufficiency who visited the respiratory insufficiency clinic of Tampere University Hospital from October 1, 2016, to October 31, 2017, were included in this retrospective study. Information on sex, age, weight, height, living conditions, smoking status, diagnoses, microspirometry results, scores of ESAS and DEPS, and the date of death (follow-up until December 31, 2018) were collected from the medical records. The disease-causing chronic respiratory insufficiency and the need for NIV or LTOT were defined as the primary disease, while all other diseases were considered as comorbidities. The Charlson comorbidity index was calculated for the subjects based on the number and severity of their comorbidities.[19,20]

Questionnaires

In the respiratory insufficiency unit of Tampere University Hospital, patients are asked to complete the ESAS and DEPS in addition to the normal medical assessment. The ESAS was originally developed for assessing the symptoms of patients with advanced cancer in palliative care, but it is a commonly used method for assessing symptoms in patients with many advanced diseases.[21,22] In the ESAS, different symptoms perceived on that day are measured on a numeric rating scale from 0 (no symptoms) to 10 (the worst possible symptoms).[23,24] In our clinic, we use a modified version with 12 questions covering 11 symptoms (pain at rest, pain on movement, tiredness, shortness of breath, loss of appetite, nausea, dry mouth, constipation, depression, anxiety, and insomnia) and general well-being (0 for the best possible well-being and 10 for the worst possible well-being).

The DEPS is a validated, self-assessed screening tool for depression.[25] The DEPS questionnaire consists of 10 questions and provides a total score varying from 1 to 30 points. The suggested cut-offs for depressive symptoms and clinical depression are ≥ 9 and ≥ 12, respectively.[26] The cut-off level of 9 points has a high sensitivity to detect the possibility of depression and is therefore used as a threshold for further diagnostic evaluation of depression.[26–29]

Statistical Analysis

The distributions were nonnormal based on Shapiro–Wilk test and, thus, nonparametric tests were used. Comparisons of different groups were performed by the Mann-Whitney U test or Kruskal–Wallis test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. To evaluate the capacity of the ESAS depression score to predict DEPS ≥ 9, a receiver operating characteristic curve (ROC) analysis was performed. Additionally, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the values were calculated. To assess if the relation between depression and other symptoms is independent of other demographic factors, we conducted a logistic regression multivariate analysis. Statistical significance was set as $P < .05$. Analyses were performed with IBM SPSS Statistics version 26.0. (IBM Corp.).

Ethical Consideration

This study was approved by the Regional Ethics Committee of Tampere University Hospital, Finland (approval code R15180 / December 1, 2015).

Results

Altogether, 270 subjects with chronic hypoxemic or hypercapnic respiratory insufficiency visited the respiratory insufficiency clinic of Tampere University Hospital during the follow-up time. Of those, 226 subjects had completed the ESAS questionnaire. The reasons for missing ESAS results were as follows: inability to complete the questionnaire ($n = 9$), unwillingness to answer the questionnaire ($n = 4$), and technical or unknown reasons ($n = 31$). Of these 226 subjects with ESAS questionnaires, DEPS was available for 208 subjects. The reasons for missing DEPS were as follows: unwillingness to answer the questionnaire ($n = 4$) and technical or unknown reasons ($n = 14$).

The subject characteristics are shown in Table 1. The most common primary diseases causing the need for NIV or LTOT were COPD and obesity-hypoventilation syndrome (OHS). The treatment for respiratory insufficiency was NIV in 92 (40.7%) and LTOT in 85 (37.6%) of the subjects, while 21 (9.3%) of the subjects had both NIV and LTOT. Twenty-two subjects had only portable oxygen, and 1 subject was treated with continuous positive airway pressure (CPAP) due to OHS. Five subjects with respiratory insufficiency refused to use NIV or LTOT. Of the deceased subjects, 59.2% died during the first year after visiting the respiratory insufficiency clinic.

Symptoms measured by ESAS in the whole group and according to the primary disease are shown in Table 2. In

Table 1. Subject Characteristics in all Subjects and According to the Primary Diagnosis Causing Respiratory Insufficiency.

	All subjects ($n = 226$)	COPD ($n = 104$)	OHS ($n = 61$)	Others[a] ($n = 61$)	*P*-value*
Gender, *n* (%)					
Male	130 (57.5)	69 (66.3)	31 (50.8)	30 (49.2)	.046
Female	96 (42.5)	35 (33.7)	30 (49.2)	31 (50.8)	
Age, median (IQR)	72.0 (65.0-79.0)	73.0 (68.3-79.0)	69.0 (61.0-78.0)	71.0 (60.5-80.0)	.009
BMI (kg/m^2), median (IQR)[b]	30.0 (23.8-38.5)	24.6 (20.8-30.7)	42.3 (38.5-49.9)	28.8 (24.9-32.5)	<.001
Smoking status, *n* (%)					
Never-smoker	65 (28.8)	3 (2.9)	23 (37.7)	39 (63.9)	<.001
Ex-smoker	141 (62.4)	94 (90.4)	27 (44.3)	20 (32.8)	
Smoker	19 (8.4)	7 (6.7)	11 (18.0)	1 (1.6)	
Unknown	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.6)	
FEV_1, liters, median (IQR)[c]	1.16 (0.71-1.67)	0.78 (0.57-1.18)	1.60 (1.20-1.95)	1.37 (0.96-1.80)	<.001
Charlson comorbidity index, median (IQR)	2.0 (1.0-3.0)	2.0 (0.0-2.0)	2.0 (1.0-3.0)	1.0 (0.0-2.5)	.032
Died before December 31, 2018, *n* (%)	71 (31.4)	44 (42.3)	7 (11.5)	20 (32.8)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; OHS, obesity-hypoventilation syndrome; IQR, interquartile range; BMI, body mass index; FEV_1, forced vital capacity in 1 s.

*P-value between the subjects with COPD, OHS, and others.

[a]Others consisting of neurological diseases ($n = 14$), thoracic deformity ($n = 14$), interstitial lung diseases ($n = 13$), heart diseases ($n = 12$), sleep apnea ($n = 2$), and others ($n = 6$).

[b]Data were missing in 1 subject: *confined to bed*.

[c]Data were missing in 7 subjects*: lack of cooperation (3), no respiratory disease (4).*

addition to shortness of breath, the most noticeable symptoms were dry mouth (3.0), pain on movement, and tiredness. Subjects with COPD reported more severe shortness of breath, dry mouth, and loss of appetite compared to other groups. Symptom scores for pain at rest were missing in 9 subjects and in other categories in 3 to 6 subjects.

Of the subjects who completed the DEPS questionnaire, 81 (38.9%) scored ≥9 points reaching the cut-off for depressive symptoms. The symptom severities measured by ESAS in the subjects with <9 and ≥9 points in DEPS are shown in Table 3. The proportion of subjects having DEPS ≥9 points did not significantly differ between subjects with different primary diseases (41.7% in COPD, 38.2% in OHS, and 35.1% in other diseases, $P = .72$). All the symptoms were significantly more severe in subjects with DEPS ≥9 compared to those with DEPS <9.

We evaluated the capacity of the ESAS depression score to predict whether DEPS is below 9 or at least 9 points by creating a ROC curve. The area under the ROC curve was 0.840 ($P < .001$) (Figure 1). The sensitivity, specificity, and positive and negative predictive values for ESAS scores to predict DEPS ≥9 are shown in Table 4. If the ESAS depression score was 0, there was an 89% probability that the subject would score below 9 points in DEPS. Similarly, if the subject reported at least 4 points in the ESAS depression score, there was an 89% probability for him/her to score at least 9 points in the DEPS.

To assess if the ESAS depression score is associated with DEPS independently of other ESAS questions and demographic details of subjects, we conducted a logistic regression model with DEPS ≥9 points as the dependent variable and gender, age, use of NIV, and use of LTOT and ESAS depression score as explanatory variables. In this model, only the ESAS depression score was independently associated with DEPS being ≥9 points. We then 1 by 1 added other ESAS variables to the model and only ESAS well-being and insomnia scores separately were associated with DEPS being ≥9 points, but they did not affect the significance of ESAS depression score in predicting DEPS ≥9 points. Further, they were not associated with DEPS being ≥9 points, if included both in the model (Supplemental Table 1). Other ESAS items and other demographic details were not significantly associated with DEPS ≥9 points and did not affect the relation between ESAS depression score and DEPS.

Discussion

We showed a high symptom burden in subjects with chronic respiratory insufficiency. In addition to impaired well-being, the most severe symptoms were shortness of breath, pain on movement, tiredness, and dry mouth. Shortness of breath, dry mouth, and loss of appetite were more severe in subjects with COPD compared to other subjects. Subjects with depressive symptoms measured with the DEPS questionnaire had higher scores in all ESAS categories than those without. Compared to the more thorough DEPS, the single question on depression as part of the ESAS seems to work as a reasonable screening tool for depressive symptoms.

In clinical practice, it would be reasonable to have 1 simple screening tool for both depression and other symptoms. According to the present study, the ESAS could serve as such a tool. We showed that if a subject scores 4 or more in the

Table 2. Scores and Prevalence of Symptoms Measured by the Modified ESAS Questionnaire According to the Primary Diagnosis Causing Respiratory Insufficiency.

	All subjects ($n=226$)		COPD ($n=104$)		OHS ($n=61$)		Others[b] ($n=61$)		
	Prevalence[c] (%)	Score, median (IQR)	Prevalence[c] (%)	Score, median (IQR)	Prevalence[c] (%)	Score, median (IQR)	Prevalence[c] (%)	Score, median (IQR)	*P*-value*
Symptoms									
Pain at rest	54.4	1.0 (0.0-3.0)	50.5	1.0 (0.0-3.0)	62.5	2.0 (0.0-4.0)	52.5	1.0 (0.0-2.0)	.15
Pain on movement	71.8	3.0 (0.0-6.0)	70.3	2.0 (0.0-5.5)	72.9	4.0 (0.0-7.0)	73.3	2.5 (0.0-4.0)	.29
Tiredness	81.4	3.0 (1.0-6.0)	86.1	3.0 (2.0-6.0)	75.9	2.0 (0.8-6.0)	78.7	3.0 (1.0-5.0)	.18
Shortness of breath	84.2	4.0 (2.0-7.0)	95.1	6.0 (3.0-8.0)	74.1	3.0 (0.0-5.0)	75.0	3.0 (0.3-5.0)	<.001
Loss of appetite	49.5	0.0 (0.0-3.0)	62.1	1.0 (0.0-4.0)	34.5	0.0 (0.0-2.0)	42.6	0.0 (0.0-2.0)	.004
Nausea	29.5	0.0 (0.0-1.0)	33.0	0.0 (0.0-1.0)	24.6	0.0 (0.0-0.5)	28.3	0.0 (0.0-1.0)	.60
Dry mouth	80.3	3.0 (1.0-7.0)	87.5	5.0 (2.0-7.0)	67.8	2.0 (0.0-6.0)	80.0	3.0 (1.0-7.0)	.01
Constipation	51.1	1.0 (0.0-3.0)	53.4	1.0 (0.0-4.0)	47.4	0.0 (0.0-2.0)	50.0	1.0 (0.0-3.0)	.47
Depression	54.8	1.0 (0.0-3.5)	56.9	1.0 (0.0-4.0)	51.7	1.0 (0.0-3.3)	54.1	1.0 (0.0-3.0)	.91
Anxiety	52.5	1.0 (0.0-3.0)	55.9	1.0 (0.0-4.0)	46.6	0.0 (0.0-3.0)	52.5	1.0 (0.0-3.0)	.50
Insomnia	64.0	2.0 (0.0-4.0)	70.6	2.0 (0.0-4.0)	54.2	1.0 (0.0-5.0)	62.3	1.0 (0.0-3.0)	.40
Well-being		4.0 (2.0-5.0)		4.0 (2.5-5.0)		3.0 (1.8-5.3)		3.0 (2.0-5.0)	.20

Abbreviations: ESAS, Edmonton symptom assessment system; COPD, chronic obstructive pulmonary disease; OHS, obesity-hypoventilation syndrome.
*P-value for the difference in ESAS scores between the subjects with COPD, OHS, and others.
[b]Others consisting of neurological diseases ($n=14$), thoracic deformity ($n=14$), interstitial lung diseases ($n=13$), heart diseases ($n=12$), sleep apnea ($n=2$), and others ($n=6$).
[c]Prevalence is defined as a proportion of subjects with an ESAS score ≥1.

ESAS depression category, the probability of depressive symptoms according to the DEPS is high. This same cut-off level has also been shown to be useful in detecting clinical depression defined by standardized questionnaires among patients with cancer.[30] According to the logistic regression analysis, the relation between ESAS depression scores is not affected by subjects' characteristics or other ESAS items. Based on the current results, we suggest that in patients scoring 0 on the ESAS depression question, there is probably no need for further evaluation of depression. Those scoring 1 to 3 would need to complete a specific depression questionnaire (eg, the DEPS), while those scoring 4 or more could be referred to

Table 3. Scores and Prevalence of Symptoms Measured by the Modified ESAS Questionnaire According to DEPS Category.

	DEPS <9 ($n=127$)		DEPS ≥9 ($n=81$)		
	Prevalence[a] (%)	Score, median (IQR)	Prevalence[a] (%)	Score, median (IQR)	*P*-value*
Symptoms[b]					
Pain at rest	50.8	1.0 (0.0-3.0)	61.0	2.0 (0.0-4.5)	.02
Pain on movement	66.9	2.0 (0.0-4.0)	84.6	4.5 (1.0-7.0)	.001
Tiredness	73.4	2.0 (0.0-4.0)	97.5	5.0 (3.0-7.0)	<.001
Shortness of breath	76.8	3.0 (1.0-5.0)	94.9	6.0 (3.0-8.0)	<.001
Loss of appetite	39.2	0.0 (0.0-2.0)	68.4	2.0 (0.0-5.0)	<.001
Nausea	19.2	0.0 (0.0-0.0)	50.6	1.0 (0.0-3.0)	<.001
Dry mouth	78.0	3.0 (1.0-5.0)	85.9	6.0 (3.0-8.0)	<.001
Constipation	41.6	0.0 (0.0-2.5)	67.9	2.0 (0.0-5.0)	<.001
Depression	37.6	0.0 (0.0-2.0)	87.3	4.0 (2.0-7.0)	<.001
Anxiety	33.6	0.0 (0.0-1.0)	86.1	4.0 (2.0-7.0)	<.001
Insomnia	51.2	1.0 (0.0-2.0)	83.5	3.0 (1.0-6.0)	<.001
Well-being		3.0 (1.0-5.0)		5.0 (4.0-6.0)	<.001

Abbreviations: ESAS, Edmonton symptom assessment system; DEPS, depression scale; IQR, interquartile range.
*P-value for the difference in medians of DEPS <9 and ≥9.
[a]Prevalence is defined as a proportion of subjects with ESAS score ≥1.
[b]Data were missing in 18 subjects: *unwilling to answer DEPS questionnaire (4), technical or unknown reason (14).*

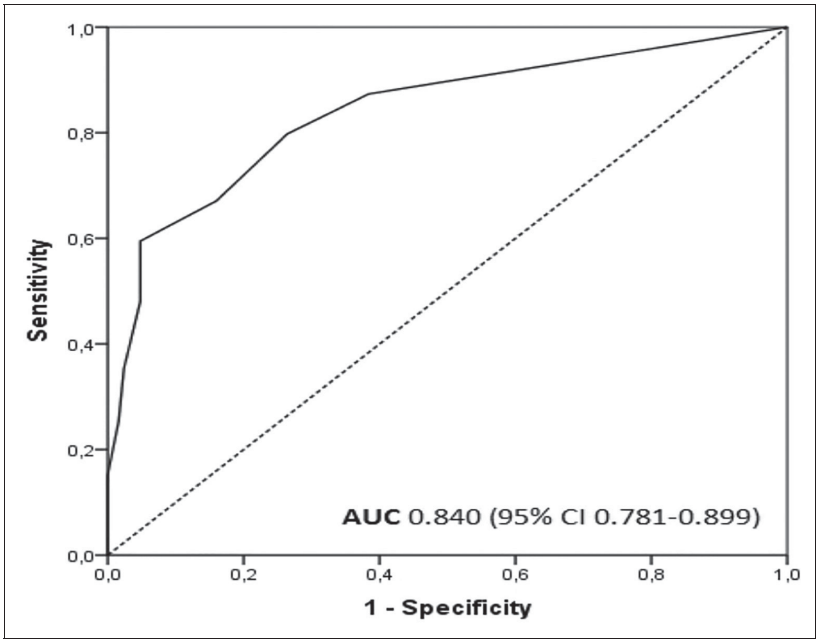


Figure 1. The ROC curve for the ESAS depression score to predict a DEPS score ≥9.
Abbreviations: ROC, receiver operating characteristic; ESAS, Edmonton symptom assessment system.

clinical evaluation of depression. These cut-offs for clinical decision-making should be tested in further prospective studies.

In the present study, the subjects with chronic respiratory insufficiency, especially those with COPD, suffered from a high symptom burden measured with a systematic ESAS questionnaire. In previous studies, the symptoms described have varied according to the study design or disease severity, but they all have reported dyspnea as the main symptom.[2,6,31] Blinderman et al[6] described symptoms in patients with advanced COPD, for whom they did not report LTOT or NIV usage, and the most prevalent symptoms in addition to dyspnea were fatigue, xerostomia, coughing, pain, and anxiety. However, dry mouth was more prevalent in our subjects with chronic respiratory insufficiency than in the Blinderman study.[6] In a recent study by Gainza-Miranda et al,[2] the highest ESAS scores were found in dyspnea and loss of well-being in 60 patients with severe COPD and LTOT with or without NIV. This is in line with our study, but anxiety and depression were even more severe in the study by Gainza-Miranda et al,[2] compared to the subjects with COPD in our study. In a study by Walke et al,[31] patients with severe COPD reported shortness of breath, anxiety, and physical discomfort even more frequently than patients with cancer or chronic heart failure. There are only a few studies concerning symptoms on top of sleepiness in patients with OHS. In a small study evaluating 10 patients with OHS, Baris et al[16] reported depression and anxiety in all patients. In the present study, the number of subjects with a primary diagnosis other than COPD or OHS was too small for any disease-specific conclusions. However, these subjects also suffered from multiple symptoms, and it is therefore essential to screen symptoms comprehensively in all patients with chronic respiratory insufficiency and to integrate symptom-centered palliative care into the treatment.

Table 4. ESAS Depression Scores' Capacity to Predict DEPS ≥9.

ESAS depression score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
≥1	87	62	59	89	72
≥2	80	74	66	85	76
≥3	67	84	73	80	77
≥4	59	95	89	79	81
≥5	48	95	86	74	77
≥6	35	98	90	71	74
≥7	25	98	91	68	70
≥8	15	100	100	65	67
≥9	4	100	100	62	63
10	3	100	100	62	62

Abbreviations: ESAS, Edmonton symptom assessment system; DEPS, depression scale; PPV, positive predictive value; NPV, negative predictive value.
DEPS was filled in 208 subjects.

In the current study, 39% of the subjects with a completed DEPS questionnaire reached the threshold of 9 points for depressive symptoms without a significant difference between the subject groups. Our result is in line with a previous study in a similar patient population showing a prevalence of depressive symptoms of 34%.[29] In a review by Smith and Wrobel,[15] the prevalence of depression varied from 8% to 80% in patients with COPD, exceeding the prevalence found in the general population. Even in mild COPD, depression is reported in ~15% of the patients. Lewis et al[32] found no difference in the prevalence of depression between patients with COPD with or without LTOT as in both patient groups, the prevalence of depression was ~15%. The prevalence of depression in patients with interstitial lung disease varies from 10% to 49%.[3,9,33] In contrast to COPD and interstitial lung disease, there are only a few studies concerning depression in OHS.[16,34]

Higher scores on the DEPS questionnaire were associated with greater symptom scores in all ESAS categories in our subjects. Similar results have been reported among patients with advanced cancer.[35] In COPD, clinically significant depression has been associated with a greater level of dyspnea and with other symptoms of COPD, such as cough, wheezing, and sputum production.[36] Severe pulmonary disease with severe dyspnea can restrict a patient's ability to leave home or take part in activities, leading to social exclusion and later on to depressive symptoms or clinical depression. Moreover, depressive patients are physically less active, have impaired quality of life, and may experience their symptoms more severely than others.[35,37] In addition to higher symptom burden, depression, and depressive symptoms are associated with increased risk of exacerbations, longer hospital stays, more frequent emergency room visits, and shorter survival in COPD.[37,38] Depression may also influence compliance to treatment, and different treatments may influence depression. In a previous study, noncompliant LTOT users with COPD had major depression more often than compliant LTOT users.[39] However, depressive symptoms are shown to decrease after CPAP therapy in OHS and by pulmonary rehabilitation in COPD.[16,34,40] Regardless of the etiology of the chronic respiratory insufficiency, depressive symptoms are associated with many clinically important variables and should trigger a comprehensive symptom evaluation and therapy.

Strengths and Limitations

We presented a real-life study on an unselected sample of subjects with chronic respiratory insufficiency. This study offers practical information on the symptom burden and screening of depressive symptoms in these subjects. The subjects with chronic respiratory insufficiency are a heterogeneous group with different underlying diseases, of which we focused on the most common ones, COPD and OHS, while other subject groups were too small to make conclusions.

We studied the overall symptom burden in these subjects during their treatment. However, we did not have the results of the ESAS questionnaires at the initiation of LTOT or NIV in every subject, which prevented us from evaluating the change in symptoms during the therapy. The ESAS questionnaire used in these subjects did not include questions concerning cough or secretions, which might have been informative in subjects with respiratory disease. Some of the subjects had missing values in the ESAS and the DEPS due to the retrospective nature of the study. Although the proportion of missing questionnaires was limited, it is possible that subjects with depression or without any symptoms were more unwilling to answer, which might have influenced our results. The questionnaires were given to the subjects at the same time when arriving at the clinic, but as they were not asked to fill the forms out in a specific order, the random order may have affected the results. Depressive symptoms in the ESAS were compared with a validated thorough questionnaire for depression (ie, the DEPS). However, we could not compare the results of the ESAS depression score to a clinical diagnosis of depression made by a psychiatrist. The focus of this study was to screen depressive symptoms in all subjects visiting a pulmonary unit to find those needing closer examination of depression.

Conclusion

Systematic assessment with the ESAS questionnaire revealed that subjects with chronic respiratory insufficiency, especially those with COPD, suffer from multiple symptoms beyond breathlessness. The single ESAS depression question seems to serve as a reasonable screening tool for depressive symptoms, which were associated with a higher prevalence and severity of other symptoms. We suggest that there is a need for systematic symptom screening as well as integrated palliative care with psychosocial support for patients with chronic respiratory insufficiency.

Author's Note

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. The literature search was performed by HAR, SLK, LL, and JTL. Data collection was performed by HAR. The study was designed by HAR, SLK, LL, and JTL. Analysis of data was conducted by HAR, SLK, LL, and JTL. The manuscript was drafted by HAR, SLK, LL, and JTL. The review of the manuscript was carried out by HAR, SLK, LL, and JTL. The study was performed in the Department of Pulmonology, Tampere University Hospital, Tampere, Finland. This study was approved by the Regional Ethics Committee of Tampere University Hospital, Finland (approval code R15180 / December 1, 2015).

Acknowledgments

We warmly thank B.M. Anni Hanhimäki from the Faculty of Medicine and Health Technology in Tampere University for her assistance in data collection.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The study was supported by grants from Medical Research Fund of Tampere University Hospital, Väinö and Laina Kivi Foundation, Tampere Tuberculosis Foundation, The Research Foundation of the Pulmonary Diseases, Nummela Foundation, Jalmari and Rauha Ahokas Foundation, and The Finnish Anti-tuberculosis Foundation.

Supplemental Material

Supplemental material for this article is available online.

References

1. Ahmadi Z, Wysham NG, Lundstrom S, Janson C, Currow DC, Ekstrom M. End-of-life care in oxygen-dependent ILD compared with lung cancer: a national population-based study. *Thorax*. 2016;71(6):510-516.
2. Gainza-Miranda D, Sanz-Peces EM, Alonso-Babarro A, et al. Breaking barriers: prospective study of a cohort of advanced chronic obstructive pulmonary disease patients To describe their survival and End-of-life palliative care requirements. *J Palliat Med*. 2019;22(3):290-296.
3. Ryerson CJ, Arean PA, Berkeley J, et al. Depression is a common and chronic comorbidity in patients with interstitial lung disease. *Respirology*. 2012;17(3):525-532.
4. Walke LM, Byers AL, McCorkle R, Fried TR. Symptom assessment in community-dwelling older adults with advanced chronic disease. *J Pain Symptom Manage*. 2006;31(1):31-37.
5. Tsolaki V, Pastaka C, Kostikas K, et al. Noninvasive ventilation in chronic respiratory failure: effects on quality of life. *Respiration*. 2011;81(5):402-410.
6. Blinderman CD, Homel P, Andrew Billings J, Tennstedt S, Portenoy RK. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. *J Pain Symptom Manage*. 2009;38(1):115-123.
7. 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(March):735-740.
8. Kessler R, Partridge MR, Miravitlles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J*. 2011;37(2):264-272.
9. Carvajalino S, Reigada C, Johnson MJ, Dzingina M, Bajwah S. Symptom prevalence of patients with fibrotic interstitial lung disease: a systematic literature review. *BMC Pulm Med*. 2018;18(1):78.
10. Borel J-C, Burel B, Tamisier R, et al. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. Ma X-L, ed. *PLoS One*. 2013;8(1):e52006.
11. Smith MC, Wrobel JP. Epidemiology and clinical impact of major comorbidities in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2014;9:871-888.
12. Patel AR, Patel AR, Singh S, Singh S, Khawaja I. *Global initiative for chronic obstructive lung disease*. Fontana, WI, USA; 2020. www.goldcopd.org.
13. King C, Nathan SD. Identification and treatment of comorbidities in idiopathic pulmonary fibrosis and other fibrotic lung diseases. *Curr Opin Pulm Med*. 2013;19(5):466-473.
14. Miravitlles M, Molina J, Quintano JA, Campuzano A, Pérez J, Roncero C. Factors associated with depression and severe depression in patients with COPD. *Respir Med*. 2014;108(11):1615-1625.
15. Di Marco F, Verga M, Reggente M, et al. Anxiety and depression in COPD patients: the roles of gender and disease severity. *Respir Med*. 2006;100(10):1767-1774.
16. Baris S A, Tuncel D, Ozerdem C, et al. The effect of positive airway pressure therapy on neurocognitive functions, depression and anxiety in obesity hypoventilation syndrome. *Multidiscip Respir Med*. 2016;11(1):1-11.
17. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional associations between clinically relevant depression or anxiety and COPD. *Chest*. 2013;144(3):766-777.
18. Blakemore A, Dickens C, Chew-Graham CA, et al. Depression predicts emergency care use in people with chronic obstructive pulmonary disease: a large cohort study in primary care. *Int J Chron Obstruct Pulmon Dis*. 2019;14:1343-1353.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40-(5):373-383.
20. Charlson ME, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47-(11):1245-1251.
21. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton symptom assessment system (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care*. 1991;7(2):6-9.
22. Hui D, Bruera E. The Edmonton symptom assessment system 25 years later: past, present, and future developments. *J Pain Symptom Manage*. 2017;53(3):630-643.
23. Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton symptom assessment scale. *Cancer*. 2000;88(9):2164-2171.
24. Hannon B, Dyck M, Pope A, et al. Modified Edmonton symptom assessment system including constipation and sleep: validation in outpatients With cancer. *J Pain Symptom Manage*. 2015;49-(5):945-952.
25. Salokangas RKR, Poutanen O, Stengård E. Screening for depression in primary care development and validation of the depression scale, a screening instrument for depression. *Acta Psychiatr Scand*. 1995;92(1):10-16.
26. Poutanen O, Koivisto A-M, Kääriä S, Salokangas RKR. The validity of the depression scale (DEPS) to assess the severity of depression in primary care patients. *Fam Pract*. 2010;27(5):527-534.
27. Sheehan AM, McGee H. Screening for depression in medical research: ethical challenges and recommendations. *BMC Med Ethics*. 2013;14(1):4.
28. Poutanen O, Koivisto A-M, Salokangas RKR. The depression scale (DEPS) as a case finder for depression in various subgroups of primary care patients. *Eur Psychiatry*. 2008;23(8):580-586.
29. Kerminen H, Jämsen E, Jäntti P, Mattila AK, Leivo-Korpela S, Valvanne J. Implementation of a depression screening protocol

among respiratory insufficiency patients. *Clin Respir J*. 2019;13(1):34-42.
30. Boonyathee S, Nagaviroj K, Anothaisintawee T. The accuracy of the Edmonton symptom assessment system for the assessment of depression in patients With cancer: a systematic review and meta-analysis. *Am J Hosp Palliat Med*. 2018;35(4):731-739.
31. Walke LM, Gallo WT, Tinetti ME, Fried TR. The burden of symptoms Among community-dwelling older persons with advanced chronic disease. *Arch Intern Med*. 2004;164(21):2321.
32. Lewis KE, Annandale JA, Sykes RN, Hurlin C, Owen C, Harrison NK. Prevalence of anxiety and depression in patients with severe COPD: similar high levels with and without LTOT. *COPD*. 2007;4(4):305-312.
33. Holland AE, Fiore JF, Bell EC, et al. Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. *Respirology*. 2014;19(8):1215-1221.
34. Bouloukaki I, Mermigkis C, Michelakis S, et al. The association between adherence to positive airway pressure therapy and long-term outcomes in patients With obesity hypoventilation syndrome: a prospective observational study. *J Clin Sleep Med*. 2018;14-(09):1539-1550.
35. Delgado-Guay M, Parsons HA, Li Z, Palmer JL, Bruera E. Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. *Support Care Cancer*. 2009;17(5):573-579.
36. Doyle T, Palmer S, Johnson J, et al. Association of anxiety and depression with pulmonary-specific symptoms in chronic obstructive pulmonary disease. *Int J Psychiatry Med*. 2013;45(2):189-202.
37. Martinez Rivera C, Costan Galicia J, Alcázar Navarrete B, et al. Factors associated with depression in COPD: a multicenter study. *Lung*. 2016;194(3):335-343.
38. Laurin C, Moullec G, Bacon SL, Lavoie KL. Impact of anxiety and depression on chronic obstructive pulmonary disease exacerbation risk. *Am J Respir Crit Care Med*. 2012;185(9):918-923.
39. Kayhan F, Ilik F, Karamanli H, Cemal Pazarli A, Kayhan A. Major depression in long-term oxygen therapy dependent chronic obstructive pulmonary disease. *Perspect Psychiatr Care*. 2018;54(1):6-10.
40. Withers NJ, Rudkin ST, White RJ. Anxiety and depression in severe chronic obstructive pulmonary disease: the effects of pulmonary rehabilitation. *J Cardiopulm Rehabil*. 1999;19(6):362-365.

Supplementary Table 1. Association of DEPS ≥ 9 points with other variables in logistic regression analysis

	HR (95% CI)	P-value
Gender	1.0 (0.4-2.3)	0.996
Age	1.0 (1.0-1.1)	0.094
Usage of NIV	1.5 (0.6-3.7)	0.385
Usage of LTOT	1.1 (0.4-2.7)	0.865
ESAS depression	1.7 (1.4-2.1)	< 0.001
ESAS well-being	1.2 (1.0-1.5)	0.087
ESAS insomnia	1.2 (1.0-1.4)	0.079

DEPS, Depression scale; NIV, noninvasive ventilation; LTOT, long-term oxygen therapy, ESAS, Edmonton Symptom Assessment System

PUBLICATION
II

Dyspnea on exercise is associated with overall symptom burden in patients with chronic respiratory insufficiency.

Rantala Heidi A, Leivo-Korpela Sirpa, Lehto Juho T, Lehtimäki Lauri

Palliative Medicine Reports. 2021; 2:1, 1-6
doi:10.1089/pmr.2020.0112

Publication reprinted with the permission of the copyright holders [Mary Ann Liebert, Inc.].

Palliative Medicine Reports
Volume 2.1, 2021
DOI: 10.1089/pmr.2020.0112
Accepted February 5, 2021

Palliative Medicine Reports
Mary Ann Liebert, Inc. publishers

BRIEF REPORT Open Access

Dyspnea on Exercise Is Associated with Overall Symptom Burden in Patients with Chronic Respiratory Insufficiency

Heidi A. Rantala, MD,[1,2,*] Sirpa Leivo-Korpela, MD, PhD,[1,2] Juho T. Lehto, MD, PhD,[2,3] and Lauri Lehtimäki, MD, PhD[2,4]

Abstract

Background: Patients with chronic respiratory insufficiency suffer from many symptoms together with dyspnea.

Objective: We evaluated the association of dyspnea on exercise with other symptoms in patients with chronic respiratory insufficiency due to chronic obstructive pulmonary disease or interstitial lung disease.

Design: This retrospective study included 101 patients in Tampere University Hospital, Finland. Dyspnea on exercise was assessed with modified Medical Research Council (mMRC) dyspnea questionnaire, and other symptoms were assessed with Edmonton Symptom Assessment System (ESAS) and Depression Scale (DEPS). The study was approved by Regional Ethics Committee of Tampere University Hospital, Finland (approval code R15180/December 1, 2015).

Results: Patients with mMRC 4 (most severe dyspnea) compared with those with mMRC 0–3 reported higher symptom scores on ESAS in shortness of breath (median 8.0 [IQR 6.0–9.0] vs. 4.0 [2.0–6.0], $p < 0.001$), dry mouth (7.0 [4.0–8.0] vs. 3.0 [1.0–6.0], $p < 0.001$), tiredness (6.0 [3.0–7.0] vs. 3.0 [1.0–5.0], $p < 0.001$), loss of appetite (3.0 [0.0–6.0] vs. 1.0 [0.0–3.0], $p = 0.001$), insomnia (3.0 [1.0–7.0] vs. 2.0 [0.0–3.0], $p = 0.027$), anxiety (3.0 [0.0–5.5] vs. 1.0 [0.0–3.0], $p = 0.007$), and nausea (0.0 [0.0–2.0] vs. 0.0 [0.0–0.3], $p = 0.027$). Patients with mMRC 4 were more likely to reach the DEPS threshold for depression than those scoring mMRC 0–3 (42.1% vs. 20.8%, $p = 0.028$).

Conclusions: Patients with chronic respiratory insufficiency need comprehensive symptom screening with relevant treatment, as they suffer from broad symptom burden worsening with increased dyspnea on exercise.

Keywords: chronic obstructive pulmonary disease; chronic respiratory insufficiency; dyspnea on exercise; Edmonton Symptom Assessment System; interstitial lung disease; modified Medical Research Council dyspnea questionnaire

Introduction

Vast majority of patients with chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD) suffer from dyspnea, but only a smaller fraction with advanced disease have chronic respiratory insufficiency, a marker of impaired life expectancy. Dyspnea, which may occur with or without respiratory insufficiency, is a subjective experience of breathing discomfort,[1] whereas chronic respiratory insufficiency is an objective finding defined by hypoxemia (partial pressure of oxygen in arterial gas <8.0 kPa) or hypercapnia (partial pressure of carbon dioxide in blood gas ≥6.0 kPa) caused by disturbance of gas exchange between pulmonary alveoli and circulation or by insufficient ventilation.[2]

Patients with advanced COPD or ILD typically suffer from severe dyspnea,[3–5] which increases with approaching death and is associated with impaired quality of life.[6–8] In addition to dyspnea, patients with COPD and ILD suffer frequently from other symptoms, such as fatigue, weight loss, depression, and anxiety, further impairing their quality of life.[9] Previous studies have

[1]Department of Respiratory Medicine, Tampere University Hospital, Tampere, Finland.
[2]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.
[3]Department of Oncology, Palliative Care Centre, Tampere University Hospital, Tampere, Finland.
[4]Allergy Centre, Tampere University Hospital, Tampere, Finland.

*Address correspondence to: Heidi A. Rantala, MD, Department of Respiratory Medicine, Tampere University Hospital, Elämänaukio, Kuntokatu 2, Tampere 33520, Finland, E-mail: heidi.rantala@tuni.fi

© Heidi A. Rantala *et al.*, 2021; Published by Mary Ann Liebert, Inc. This Open Access article is distributed under the terms of the Creative Commons License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

shown the association of dyspnea and other symptoms in patients with COPD and ILD in general.[3,10,11] However, the overall symptom burden specifically in patients with chronic respiratory insufficiency due to COPD or ILD and increasing dyspnea remains unknown.

Centers managing patients with chronic respiratory insufficiency commonly screen for dyspnea as a target of therapy. However, assessment of other symptoms and their association with increasing dyspnea would be important to offer more comprehensive treatment for these patients.

Our aim was to assess how dyspnea on exercise is associated with overall symptom burden in patients with chronic respiratory insufficiency due to COPD or ILD.

Materials and Methods

This was a retrospective study performed in patients with chronic respiratory insufficiency visiting the respiratory insufficiency clinic of Tampere University Hospital between 1.10.2016 and 31.10.2017. All the patients with chronic respiratory insufficiency due to COPD or ILD, who had filled in the modified Medical Research Council (mMRC) dyspnea questionnaire during the routine visits, were included. Patients' clinical characteristics, diagnoses, mMRC dyspnea scores, Edmonton Symptom Assessment System (ESAS), and Depression Scale (DEPS) were collected from medical records. The Charlson comorbidity index (CCI) was calculated for each patient.[12,13]

Questionnaires

The mMRC questionnaire asks patients to self-report dyspnea in daily activities. The scale varies from 0 to 4: 0 for "I only get breathless with strenuous exercise," 1 for "I get short of breath when hurrying on the level or up a slight hill," 2 for "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level," 3 for "I stop for breath after walking about 100 meters or after a few minutes on the level," and 4 for "I am too breathless to leave the house."[14,15]

ESAS is used for assessing symptoms in many advanced diseases.[16,17] Patients rate different symptoms on a numeric rating scale from 0 (no symptoms) to 10 (the worst possible symptoms).[18,19] We used a modified version with 12 questions covering 11 symptoms and general well-being (0 for the best possible well-being and 10 for the worst possible well-being). The cutoff point for each symptom to be categorized as moderate or severe was ≥4.[20–22]

The DEPS is a validated self-assessed screening tool for depression consisting of 10 questions and provides a total score varying from 1 to 30 points.[23] The suggested cutoffs for depressive symptoms and clinical depression are ≥9 and ≥12, respectively.[24]

Statistical analysis

The five-step mMRC scale was converted to two-step scale by comparing scores 0–3 and 4 to sort out the group with most difficult dyspnea on exercise. Comparisons of different groups were performed by Mann-Whitney *U* test for continuous variables as the distributions were non-normal based on visual estimation, and Pearson's chi-square or Fisher's exact tests for categorical variables.

To assess if the relation between dyspnea on exercise and other symptoms is independent of other clinical factors, we conducted a logistic regression multivariate analysis including also gender, age, body mass index, primary diagnosis for chronic respiratory insufficiency, CCI, and ESAS total score. Statistical significance was set as $p < 0.05$. Analyses were performed with IBM SPSS Statistics version 26.0. (IBM Corp, Armonk, NY).

Ethics approval and consent to participate

This study was approved by the Regional Ethics Committee of Tampere University Hospital, Finland (approval code R15180/December 1, 2015).

Results

During the follow-up time, 128 patients with COPD or ILD and chronic respiratory insufficiency visited the clinic. The mMRC questionnaire was available in 101 patients, among whom ESAS and DEPS questionnaires were available in 98 and 91 patients, respectively. Reasons for the missing ESAS or DEPS questionnaires were unwillingness to answer the questionnaire, inability to complete the questionnaire, and technical or unknown reasons.

The patient characteristics are shown in Table 1. COPD was severe (GOLD grade III: FEV_1 30%–50% predicted) or very severe (GOLD grade IV: FEV_1 <30% predicted)[9] in most (75.2%) of the patients with COPD. Patients in mMRC category 4 were more likely to need help in activities of daily living and had lower FEV_1 and body mass index than those scoring 0–3 in mMRC. The treatment for respiratory insufficiency was oxygen therapy in 81 (80.2%), noninvasive ventilation (NIV) in 10 (9.9%), and both in 6 (5.9%) patients. Four patients (4.0%) refused to use NIV or oxygen therapy despite

Table 1. Patient Characteristics According to the Modified Medical Research Council Dyspnea Scale Category

	All patients	mMRC 0–3	mMRC 4	p^a
Total, *n*	101	55	46	
Male, *n* (%)	65 (64.4)	36 (65.5)	29 (63.0)	0.801
Age, years, median (IQR)	75.0 (70.0–81.0)	74.0 (69.0–80.0)	75.5 (71.0–81.5)	0.141
BMI, kg/m^2, median (IQR)	24.5 (21.1–29.3)	27.0 (22.5–33.2)	23.3 (19.3–27.7)	0.001
Smoking status, *n* (%)				
Never-smoker	9 (8.9)	3 (5.5)	6 (13.0)	0.104
Ex-smoker	89 (88.1)	48 (87.3)	40 (87.0)	
Smoker	4 (4.0)	4 (7.3)	0 (0.0)	
Disease causing the chronic respiratory insufficiency, *n* (%)				
COPD	89 (88.1)	47 (85.5)	42 (91.3)	0.366
ILD	12 (11.9)	8 (14.5)	4 (8.7)	
FEV_1				
Liters, median (IQR)	0.90 (0.60–1.25)	0.98 (0.68–1.48)	0.72 (0.46–1.1)	0.008
% of predicted, median (IQR)	31.0 (23.0–48.5)	34.0 (27.0–54.0)	25.5 (19.0–44.3)	0.003
Charlson comorbidity index, median (IQR)	2.0 (0.0–2.0)	2.0 (0.0–2.0)	2.0 (0.0–2.0)	0.789
Need for help with ADL, *n* (%)	38 (37.6)	9 (16.4)	29 (63.0)	<0.001
Died before 31.12.2018, *n* (%)	48 (47.5)	22 (40.0)	26 (56.5)	0.098

[a]Between the patients in categories mMRC 0–3 and mMRC 4.

ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; ILD, interstitial lung disease; IQR, interquartile range; mMRC, modified Medical Research Council.

chronic respiratory insufficiency. Of the deceased patients, 29 (60.4%) died during the following year after the visit in the clinic.

The symptom severities measured by ESAS in the two mMRC categories are shown in Table 2. In the total study population, shortness of breath and dry mouth were the most severe symptoms. Compared with patients with mMRC 0–3, those with mMRC 4 reported significantly higher scores in shortness of breath, dry mouth, tiredness, loss of appetite, anxiety, insomnia, nausea, and impaired well-being.

A significantly higher proportion of patients with mMRC 4, compared with those scoring 0–3 in mMRC, reached the threshold for moderate or severe symptom (≥4) in shortness of breath, pain on movement, tiredness, loss of appetite, constipation, anxiety, insomnia, and dry mouth. The total ESAS score among patients in mMRC category 4 compared with those in mMRC 0–3 category remained statistically significantly higher also in the logistic regression multivariate analysis accounting for other clinical factors.

The scores of DEPS in the two mMRC categories are shown in Table 3. As compared with patients scoring 0–3 in mMRC, those in mMRC category 4 had higher median DEPS scores and a significantly higher proportion of them reached the threshold for clinical depression.

Discussion

We identified a high symptom burden among patients with chronic respiratory insufficiency due to COPD or ILD. Patients with more severe dyspnea on exercise and scoring 4 in mMRC had more severe symptoms of dry mouth, tiredness, loss of appetite, anxiety, nausea, and insomnia in addition to impaired well-being measured with ESAS, compared with those with mMRC 0–3. Also depression measured with DEPS was more common in patients with mMRC 4 than in patients with mMRC 0–3.

Our finding that patients with COPD or ILD suffer from many symptoms, which worsens by increasing dyspnea on exercise, is in line with previous studies.[25,26] However, although earlier studies have shown that symptoms are worse in those patients with COPD or ILD who suffer from more severe dyspnea,[3,27] this is the first study to assess this specifically in patients with chronic respiratory insufficiency.

Many of the symptoms found in this study, such as fatigue, loss of appetite, and tiredness, may be consequences of an advanced disease.[28] In contrast, some of the symptoms, for example, dry mouth, could be directly associated with dyspnea on exercise as a result of mouth breathing and higher frequency of breathing, but also oxygen therapy or NIV and used medication, for example, inhaled anticholinergics, may provoke dryness of mouth.

Scoring at least 12 points in DEPS questionnaire, the cutoff for depression,[24] was significantly more common in patients with mMRC score 4 than in those with mMRC score 0–3. This is in line with previous studies that have focused on the same relation from the opposite perspective and showed higher levels of dyspnea

Table 2. Median Scores and Proportion of Patients with at Least Moderate Symptoms (≥4 Points) in Edmonton Symptom Assessment System Questionnaire According to Modified Medical Research Council Dyspnea Scale Category

	All ($n=98$)	mMRC 0–3 ($n=55$)	mMRC 4 ($n=43$)	p[a]
ESAS scores[b]				
Pain at rest				
Median (IQR)	0.0 (0.0–3.0)	0.0 (0.0–3.0)	2.0 (0.0–4.0)	0.063
≥4, %	21.9	17.0	27.9	0.198
Pain on movement				
Median (IQR)	2.0 (0.0–6.0)	2.0 (0.0–4.0)	5.0 (0.0–6.0)	0.068
≥4, %	41.7	30.2	55.8	0.011
Tiredness				
Median (IQR)	3.0 (2.0–6.0)	3.0 (1.0–5.0)	6.0 (3.0–7.0)	<0.001
≥4, %	49.0	32.1	69.8	<0.001
Shortness of breath				
Median (IQR)	6.0 (3.0–8.0)	4.0 (2.0–6.0)	8.0 (6.0–9.0)	<0.001
≥4, %	72.2	57.4	90.7	<0.001
Loss of appetite				
Median (IQR)	1.0 (0.0–5.0)	1.0 (0.0–3.0)	3.0 (0.0–6.0)	0.001
≥4, %	28.9	14.8	46.5	0.001
Nausea				
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–0.3)	0.0 (0.0–2.0)	0.027
≥4, %	6.2	3.7	9.3	0.255
Dry mouth				
Median (IQR)	5.0 (2.0–7.0)	3.0 (1.0–6.0)	7.0 (4.0–8.0)	<0.001
≥4, %	60.2	47.3	76.7	0.003
Constipation				
Median (IQR)	1.0 (0.0–4.0)	1.0 (0.0–3.0)	2.0 (0.0–6.0)	0.072
≥4, %	28.9	18.5	41.9	0.012
Depression				
Median (IQR)	1.0 (0.0–4.0)	1.0 (0.0–3.0)	2.0 (0.0–5.0)	0.120
≥4, %	30.2	22.2	40.5	0.053
Anxiety				
Median (IQR)	1.0 (0.0–4.8)	1.0 (0.0–3.0)	3.0 (0.0–5.5)	0.007
≥4, %	32.3	22.2	45.2	0.017
Insomnia				
Median (IQR)	2.0 (0.0–4.0)	2.0 (0.0–3.0)	3.0 (1.0–7.0)	0.027
≥4, %	28.1	18.9	39.5	0.025
Well-being				
Median (IQR)	4.0 (3.0–5.0)	3.0 (2.0–5.0)	5.0 (4.0–6.0)	<0.001
Total score				
Median (IQR)	34.0 (21.0–51.5)	24.0 (15.8–34.8)	44.0 (34.0–63.0)	<0.001

[a]Between the patients in categories mMRC 0–3 and mMRC 4.
[b]Data missing in three patients: *inability to fill in the questionnaire (2), unwillingness to answer the questionnaire (1).*
ESAS, Edmonton Symptom Assessment System.

Table 3. Median Scores and Proportion of Patients with at Least 9 or 12 Points in Depression Scale Questionnaire According to Modified Medical Research Council Dyspnea Scale Category

	All ($n=91$)	mMRC 0–3 ($n=53$)	mMRC 4 ($n=38$)	p[a]
DEPS score, median (IQR)[b]	8.0 (3.0–14.0)	6.0 (2.5–10.5)	9.5 (4.8–18.5)	0.025
DEPS ≥9 points, *n* (%)	41 (40.6)	20 (37.7)	21 (55.3)	0.097
DEPS ≥12 points, *n* (%)	27 (26.7)	11 (20.8)	16 (42.1)	0.028

[a]Between patients in categories mMRC 0–3 and mMRC 4.
[b]Data missing in 10 patients: *inability to complete in the questionnaire (2), unwillingness to answer DEPS questionnaire (3), technical or unknown reason (5).*

and other symptoms in patients with COPD suffering from anxiety and depression.[29,30] Dyspnea has also been associated with higher depression scores in patients with ILD.[10] In a previous study on an unselected population of patients with chronic respiratory insufficiency, one third of the patients suffered from depressive symptoms and a quarter from depression,[31] being less than in this study focusing only on patients with COPD or ILD causing respiratory insufficiency.

The patients with mMRC score 4 have, by definition, restricted ability to leave home or take part in activities, which may lead to social exclusion and depression. This further underlines the importance of screening

depression in patients with chronic respiratory insufficiency to find those patients who will benefit from the treatment of depression.

Strengths and limitations

This was a retrospective study performed in patients with chronic respiratory insufficiency due to COPD or ILD, offering practical information on symptom burden of these patients. Owing to the retrospective nature of the study, there were some questionnaire data missing. This may have biased the sample to those with less severe symptoms, and thereby underestimated the total symptom burden of the patient population. Medical treatment of the underlying pulmonary disease and treatment of chronic respiratory insufficiency may affect the relationship between dyspnea on exercise and other symptoms, but we were not able to assess this effect in our cross-sectional setting.

Further long-term follow-up studies would provide more information on how the relationship between dyspnea on exercise and other symptoms develop during the course of the disease.

Conclusions

In patients with chronic respiratory insufficiency due to pulmonary disease increasing dyspnea on exercise is associated with higher overall symptom burden, especially symptoms such as dry mouth, tiredness, loss of appetite, anxiety, nausea, depression, and insomnia. Therefore, these patients need a comprehensive symptom screening and management, including psychosocial support and early integrated palliative care.

Authors' Contributions

Each author (H.A.R., S.L.-K., J.T.L., and L.L.) contributed substantially to this study by participating in literature search, study design, data analysis, article preparation, and article review. H.A.R. carried out the data collection. All authors approved the final version of this article. The study was performed in Department of Pulmonology, Tampere University Hospital, Tampere, Finland.

Acknowledgment

We warmly thank B.M. Anni Hanhimäki from the Faculty of Medicine and Health Technology in Tampere University for her assistance in data collection. Published Preprint in Research Square, Posted September 22, 2020, DOI: 10.21203/rs.3.rs-73163/v1.

Funding Information

The study was supported by grants from Medical Research Fund of Tampere University Hospital, Väinö and Laina Kivi Foundation, Tampere Tuberculosis Foundation, The Research Foundation of the Pulmonary Diseases, Nummela Foundation, Jalmari and Rauha Ahokas Foundation, and The Finnish Anti-Tuberculosis Foundation.

Author Disclosure Statement

No competing financial interests exist.

References

1. Meek PM, Schwartzstein RM, Adams L, et al.: Dyspnea. Am J Respir Crit Care Med 1999;159:321–340.
2. Roussos C, Koutsoukou A: Respiratory failure. Eur Respir J 2003; 22(Supplement 47):3s–14s.
3. Rajala K, Lehto JT, Sutinen E, et al.: mMRC dyspnoea scale indicates impaired quality of life and increased pain in patients with idiopathic pulmonary fibrosis. ERJ Open Res 2017;3:00084-02017.
4. Gainza-Miranda D, Sanz-Peces EM, Alonso-Babarro A, et al.: Breaking barriers: Prospective study of a cohort of advanced chronic obstructive pulmonary disease patients to describe their survival and end-of-life palliative care requirements. J Palliat Med 2019;22:290–296.
5. Walke LM, Byers AL, McCorkle R, et al.: Symptom assessment in community-dwelling older adults with advanced chronic disease. J Pain Symptom Manage 2006;31:31–37.
6. Currow DC, Smith J, Davidson PM, et al.: Do the trajectories of dyspnea differ in prevalence and intensity by diagnosis at the end of life? A consecutive cohort study. J Pain Symptom Manage 2010;39:680–690.
7. Rajala K, Lehto JT, Sutinen E, et al.: Marked deterioration in the quality of life of patients with idiopathic pulmonary fibrosis during the last two years of life. BMC Pulm Med 2018;18:172.
8. Morris D, Galicia-Castillo M: Dying with dyspnea in the hospital. Am J Hosp Palliat Care 2015;34:132–134.
9. Global Initiative for Chronic Obstructive Lung Disease: https://goldcopd.org/2021-gold-reports/. (Last Accessed January 22, 2021).
10. Ryerson CJ, Berkeley J, Carrieri-Kohlman VL, et al.: Depression and functional status are strongly associated with dyspnea in interstitial lung disease. Chest 2011;139:609–616.
11. Martinez Rivera C, Costan Galicia JJJ, Alcázar Navarrete B, et al.: Factors associated with depression in COPD: A multicenter study. Lung 2016; 194:335–343.
12. Charlson ME, Pompei P, Ales KL, et al.: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–383.
13. Charlson ME, Szatrowski TP, Peterson J, et al.: Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–1251.
14. Bestall JC, Paul EA, Garrod R, et al.: Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581–586.
15. Mahler DA, Wells CK: Evaluation of clinical methods for rating dyspnea. Chest 1988;93:580–586.
16. Bruera E, Kuehn N, Miller MJ, et al.: The Edmonton Symptom Assessment System (ESAS): A simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6–9.
17. Hui D, Bruera E: The Edmonton Symptom Assessment System 25 years later: Past, present, and future developments. J Pain Symptom Manage 2017;53:630–643.
18. Chang VT, Hwang SS, Feuerman M: Validation of the Edmonton Symptom Assessment Scale. Cancer 2000;88:2164–2171.
19. Hannon B, Dyck M, Pope A, et al.: Modified Edmonton Symptom Assessment System including constipation and sleep: Validation in outpatients with cancer. J Pain Symptom Manage 2015;49:945–952.
20. Serlin RC, Mendoza TR, Nakamura Y, et al.: When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995;61:277–284.

21. Selby D, Cascella A, Gardiner K, et al.: A single set of numerical cutpoints to define moderate and severe symptoms for the Edmonton Symptom Assessment System. J Pain Symptom Manage 2010;39:241–249.
22. Oldenmenger WH, de Raaf PJ, de Klerk C, et al.: Cut points on 0–10 Numeric Rating Scales for Symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: A systematic review. J Pain Symptom Manage 2013;45:1083–1093.
23. Salokangas RKR, Poutanen O, Stengård E: Screening for depression in primary care Development and validation of the Depression Scale, a screening instrument for depression. Acta Psychiatr Scand 1995;92: 10–16.
24. Poutanen O, Koivisto A-M, Kääriä S, et al.: The validity of the Depression Scale (DEPS) to assess the severity of depression in primary care patients. Fam Pract 2010;27:527–534.
25. Walke LM, Gallo WT, Tinetti ME, et al.: The burden of symptoms among community-dwelling older persons with advanced chronic disease. Arch Intern Med 2004;164:2321.
26. Smith TA, Ingham JM, Jenkins CR: Respiratory failure, noninvasive ventilation, and symptom burden: An observational study. J Pain Symptom Manage 2019;57:282.e1–289.e1.
27. Elbehairy AF, McIsaac H, Hill E, et al.: Impact of a specialized ambulatory clinic on refractory breathlessness in subjects with advanced COPD. Respir Care 2020;65:444–454.
28. Smith AK, Currow DC, Abernethy AP, et al.: Prevalence and outcomes of breathlessness in older adults: A national population study. J Am Geriatr Soc 2016;64:2035–2041.
29. Doyle T, Palmer S, Johnson J, et al.: Association of anxiety and depression with pulmonary-specific symptoms in chronic obstructive pulmonary disease. Int J Psychiatry Med 2013;45:189–202.
30. Wajnberg A, Ornstein K, Zhang M, et al.: Symptom burden in chronically ill homebound individuals. J Am Geriatr Soc 2013;61:126–131.
31. Kerminen H, Jämsen E, Jäntti P, et al.: Implementation of a depression screening protocol among respiratory insufficiency patients. Clin Respir J 2019;13:34–42.

Cite this article as: Rantala HA, Leivo-Korpela S, Lehto JT, and Lehtimäki L (2021) Dyspnea on exercise is associated with overall symptom burden in patients with chronic respiratory insufficiency, *Palliative Medicine Reports* 2:1, 48–53, DOI: 10.1089/pmr.2020.0112

Abbreviations Used

ADL = activities of daily living
BMI = body mass index
COPD = chronic obstructive pulmonary disease
CPAP = continuous positive airway pressure
DEPS = Depression Scale
ESAS = Edmonton Symptom Assessment System
FEV_1 = forced expiratory volume in one second
ILD = interstitial lung disease
IQR = interquartile range
mMRC = modified Medical Research Council
NIV = noninvasive ventilation

Publish in Palliative Medicine Reports

- Immediate, unrestricted online access
- Rigorous peer review
- Compliance with open access mandates
- Authors retain copyright
- Highly indexed
- Targeted email marketing

liebertpub.com/pmr

PUBLICATION III

Predictors of impaired survival in patients with long-term oxygen therapy

Rantala Heidi A, Leivo-Korpela Sirpa, Lehtimäki Lauri, Lehto Juho T

Respiratory Care 2019 Nov; 64 (11): 1401-1409
doi:10.4187/respcare.06615

Republished with permission of [Daedalus Enterprises Inc], from [Predictors of Impaired Survival in Subjects With Long-Term Oxygen Therapy; Heidi A Rantala, Sirpa Leivo-Korpela, Lauri Lehtimäki and Juho T Lehto, Vol. 64, 11, year of copyright 2021]; http://rc.rcjournal.com/content/early/2019/03/26/respcare.06615.

Predictors of Impaired Survival in Subjects With Long-Term Oxygen Therapy

Heidi A Rantala, Sirpa Leivo-Korpela, Lauri Lehtimäki, and Juho T Lehto

BACKGROUND: The need for long-term oxygen therapy (LTOT) is usually a sign of advanced disease, which could trigger advance care planning. However, LTOT is used in patients with different characteristics and multiple diagnoses beyond COPD. We studied the factors associated with survival in an unselected sample of subjects who started LTOT. METHODS: We conducted a retrospective study that included 195 subjects for whom LTOT was initiated in Tampere University Hospital from January 1, 2012, to December 31, 2015, and followed up until December 31, 2017. RESULTS: The most frequent diseases that caused the need for LTOT were COPD and interstitial lung diseases. Most of the subjects (69%) died during the study period; the median survival time was 2.2 y. The subjects with interstitial lung disease as a primary disease for LTOT had a shorter survival time (median 0.9 y) compared with those with COPD (median 2.4 y, $P < .001$). Survival was shorter in the subjects ages >75 y (median 1.4 y) compared with those who were ages ≤75 y (median 2.8 y, $P = .001$) and also in those who required help with daily activities (median 1.2 y) compared with those who did not (median 3.3 y, $P < .001$). In multivariate analysis, a diagnosis of interstitial lung disease (hazard ratio 2.1, 95% CI 1.4–3.2), Charlson comorbidity index (hazard ratio 1.26, 95% Cl 1.11–1.43), and required help in activities of daily living (hazard ratio 2.1, 95% CI 1.4–3.1) were associated with impaired survival. CONCLUSIONS: The survival of the subjects who started LTOT varied greatly. The subjects with interstitial lung disease and those who required assistance with activities of daily living were at risk of dying in ~1 y, which suggested that advance care planning should be directed especially to these patients. *Key words: chronic hypoxemia; long-term oxygen therapy; interstitial lung disease; chronic obstructive pulmonary disease; activities of daily living; survival.* [Respir Care 2019;64(11):1401–1409. © 2019 Daedalus Enterprises]

Introduction

Chronic hypoxemia is a common feature in many end-stage respiratory diseases. Long-term oxygen therapy (LTOT) can be used to treat hypoxemia, but the effects of LTOT on survival and precise indications for it have been assessed only in subjects with COPD. LTOT prolongs survival and is recommended in patients with COPD who have severe hypoxemia, defined as $P_{aO_2} \leq 55$ mm Hg or P_{aO_2} between 55 and 60 mm Hg in the presence of complicating factors, such as peripheral edema, polycythemia (hematocrit ≥ 55%) or pulmonary hypertension.[1-3] There

Dr Rantala and Dr Leivo-Korpela are affiliated with the Department of Respiratory Medicine, Tampere University Hospital, Tampere, Finland. Dr Rantala, Dr Leivo-Korpela, Dr Lehtimäki, and Dr Lehto are affiliated with the Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland. Dr Lehtimäki is affiliated with the Allergy Centre, Tampere University Hospital, Tampere, Finland. Dr Lehto is affiliated with the Palliative Care Unit, Department of Oncology, Tampere University Hospital, Tampere, Finland.

The study was supported by grants from Medical Research Fund of Tampere University Hospital, Väinö and Laina Kivi Foundation, Tampere Tuberculosis Foundation, The Research Foundation of the Pulmonary Diseases, Nummela Foundation, Jalmari and Rauha Ahokas Foundation, and The Finnish Anti-tuberculosis Foundation.

The authors have disclosed no conflicts of interest.

Correspondence: Heidi A Rantala MD, Department of Respiratory Medicine, Tampere University Hospital, Faculty of Medicine and Health Technology, Tampere University, Teiskontie 35, 33521 Tampere, Finland. E-mail: Heidi.Rantala@tuni.fi.

DOI: 10.4187/respcare.06615

is clear evidence for LTOT usage in patients with COPD and with these criteria, but LTOT does not seem to improve survival in patients with COPD and with moderate hypoxemia only.[4-7]

Although the best evidence for the use of LTOT is based on studies in subjects with COPD, LTOT is also recommended in many other diseases that cause hypoxemia (interstitial lung disease, cystic fibrosis, pulmonary hypertension, and cardiac failure) even though there is no clear evidence of its effectiveness on survival or alleviation of symptoms.[3] In many diseases, chronic respiratory insufficiency and hypoxemia develop at the late stages of the disease, when the life expectancy of the patient is limited.[8-10] Therefore, the clinical decision to initiate LTOT should be concomitantly considered with timely advance care planning and palliative care consultation. However, the individual prognosis in patients who receive LTOT is difficult to estimate due to considerable variation in the rate of progression among different pulmonary diseases and to the effects of other factors, such as age and comorbidities. At the moment, there is little information regarding which factors among patients on LTOT are associated with their prognosis in clinical practice. Our aim was to study the factors associated with survival in subjects for whom LTOT was initiated in a real-life setting.

QUICK LOOK

Current knowledge

Long-term oxygen therapy (LTOT) prolongs survival in patients with COPD and severe hypoxemia. It is also used in several other diseases that cause hypoxemia, although there is no clear evidence of its effectiveness. The need for LTOT is considered a marker of advanced disease, but there is no current knowledge about which factors are associated with poor survival among these patients in a real-life setting.

What this paper contributes to our knowledge

The overall survival of subjects with LTOT was poor but varied greatly. The subjects who had interstitial lung disease as the primary disease that caused the need for LTOT or needed help in activities of daily living were more likely to die during the first year after the onset of LTOT. The Charlson comorbidity index was associated with worse overall survival as well.

Methods

Patients

All the patients who were started on LTOT in the respiratory insufficiency unit of the Tampere University Hospital from January 1, 2012, to December 31, 2015, were included in this study. The subjects were followed up until death or December 31, 2017.

Data Collection

All medical records, including notes of the nurses, were reviewed. The collected characteristics of the subjects included age, sex, weight, height, living conditions, working status, smoking status, medication, diagnoses, and date of death. Results of spirometry, arterial blood gases, and nocturnal or daytime oxygen saturation were recorded as well. According to the comorbidities, the Charlson comorbidity index was calculated for each subject based on the disease severity.[11,12] For subjects with COPD, the Global Initiative for Chronic Obstructive Lung Disease stages for the severity of the air-flow limitation were defined.[13] The subjects were considered to require assistance in activities of daily living (ADL) if they needed continuous help from a family member who worked as a caregiver, received home care services (eg, dietary services, ablution, dressing, or medication), or permanently stayed in a nursing home or community hospital. The disease that caused the need for initiation of LTOT was defined as the primary disease, whereas all other diseases were considered comorbidities.

Statistical Analysis

Based on a visual estimation, many of the distributions were non-normal, and nonparametric tests were used. A comparison of different groups was performed by using the Mann-Whitney Test for continuous variables and the Pearson chi-square test or Fisher exact test for categorical variables. The Kaplan-Meier method and the Cox proportional hazard regression analysis were used for survival estimation. Statistical significance was set as $P < .05$. Analyses were performed with IBM SPSS Statistics version 22.0 (Armonk, NY).

Ethical Consideration

This study was approved by the regional ethics committee of Tampere University Hospital, Finland (approval R15180/1.12.2015).

Results

Altogether 195 subjects started LTOT during the study period and were included. Characteristics of the subjects are shown in Table 1. Most subjects (68%) smoked before the start of LTOT, and the median pack-years among smokers was 40 (interquartile range [IQR] 20–50). Almost two

Table 1. Subject Characteristics

Characteristic	Value
Sex, *n* (%)	
Males	121 (62.1)
Females	74 (37.9)
Age	
Median (IQR) y	74.0 (67.0–81.0)
≤75 y, *n* (%)	113 (57.9)
>75 y, *n* (%)	82 (42.1)
Body mass index, median (IQR) kg/m^2*	27.7 (23.1–33.2)
Need for help with ADL, *n* (%)	
No	105 (53.8)
Yes	90 (46.2)
Smoking status, *n* (%)	
Never-smoker	60 (30.8)
Ex-smoker	133 (68.2)
Smoker	1 (0.5)
Unknown	1 (0.5)
FEV_1†	
Median (IQR) L	1.30 (0.96–1.82)
Median (IQR) % of predicted	51.0 (36.5–64.5)
FVC‡	
Median (IQR) L	2.49 (1.86–3.06)
Median (IQR) % of predicted	72.0 (57.0–84.0)
P_{aO_2} with room air, median (IQR) mm Hg§	51.7 (47.3–55.5)
Oxygen flow, median (IQR) L/min	1.5 (1.0–2.0)
Primary disease that caused the need for LTOT, *n* (%)	
COPD	92 (47.2)
Interstitial lung diseases	44 (22.6)
Heart diseases	18 (9.2)
Obesity-hypoventilation syndrome	18 (9.2)
Other	23 (11.8)
Comorbidities, *n* (%)	
Hypertension	120 (61.5)
Heart diseases	112 (57.4)
Cerebrovascular diseases	13 (6.7)
Diabetes	60 (30.8)
COPD	18 (9.2)
Asthma	27 (13.8)
Sleep apnea	38 (19.5)
Neurologic diseases	33 (16.9)
Renal diseases	18 (9.2)
Rheumatic diseases	18 (9.2)
Cancer	38 (19.5)
Others	49 (25.1)
No comorbidities	9 (4.6)
Charlson comorbidity index, median (IQR)	2.0 (1.0–3.0)

* Data were missing in 3 subjects: confined to bed i.e. unable to perform measurements because of tetraplegia or muscle dystrophy.
† Data were missing in 18 subjects: lack of co-operation i.e. subject didn't understand instructions because of Alzhemer disease or schizophrenia etc. (9), acute illness i.e. respiratory infections and pulmonary embolisms. (8), data not available (1).
‡ Data were missing in 29 subjects: only microspirometry available (11), data same as stated in part † (18).
§ Data were missing in 42 subjects: $P_{aO_2} < 60$ mm Hg or saturation < 92% with supplemental oxygen (31), nocturnal or exertional desaturation (8), other reasons (3).
IQR = interquartile range
ADL = activities of daily living
LTOT = long-term oxygen therapy

thirds of subjects on LTOT were men. Of the subjects with COPD, 3.3, 27.2, 43.5, and 26.1% belonged to Global Initiative for Chronic Obstructive Lung Disease stages 1, 2, 3 and 4, respectively. Interstitial lung disease and COPD were the most-common diseases that cause the need for LTOT. Of the subjects with interstitial lung disease, 58% had idiopathic pulmonary fibrosis (IPF). Eighteen subjects had obesity-hypoventilation syndrome, and 16 of these (89%) used CPAP or noninvasive ventilation, together with LTOT, whereas the remaining 2 subjects only received LTOT due to nonadherence with CPAP or noninvasive ventilation. All the subjects had an oxygen concentrator, and 60 of them (30.8%) also had ambulatory oxygen therapy. Overall, the subjects had a median of 3 comorbidities, and cardiovascular diseases were the most common. Continuous help at home was needed by 68 of the subjects (35%), whereas 22 (11%) permanently stayed in a nursing home or a community hospital.

Survival

During the study period, 133 subjects (69%) died, and the median (IQR) survival time of the total study sample was 2.2 (0.8–4.4) y. The subjects with interstitial lung disease as the primary disease had a shorter survival time (median [IQR] 0.9 [0.4–2.2] y) compared with subjects with COPD (median [IQR] 2.4 [1.1–4.5] y, $P < .001$). In addition, age > 75 y and the need for help with ADL were associated with shorter survival (Fig. 1). Among the subjects with COPD Global Initiative for Chronic Obstructive Lung Disease stages were not significantly associated with survival ($P = .77$) Fifty-six subjects (29%) died during the first year after the initiation of LTOT. The characteristics of the subjects who died in, or survived, over the first year are shown in Table 2. Those who died during the first year were older, needed help more often with ADL, and had lower body mass index (BMI). The 1-y survival rate was lower in the subjects with interstitial lung disease (47%) compared with those with COPD (79%) ($P < .001$) as the primary disease. None of the subjects with obesity-hypoventilation syndrome as their primary disease died in the first year.

Factors Associated With Overall Survival

The factors associated with subjects' survival time are presented in Table 3. In univariate analysis, older age, the need for help in ADL, lower BMI, interstitial lung disease, the Charlson comorbidity index, and heart (coronary artery disease or heart failure) or neurologic diseases as comorbidities were associated with shorter survival. In contrast, sleep apnea as a comorbidity was associated with longer survival. In multivariate analysis, the need for help with ADL. Charlson comorbidity index, and interstitial lung

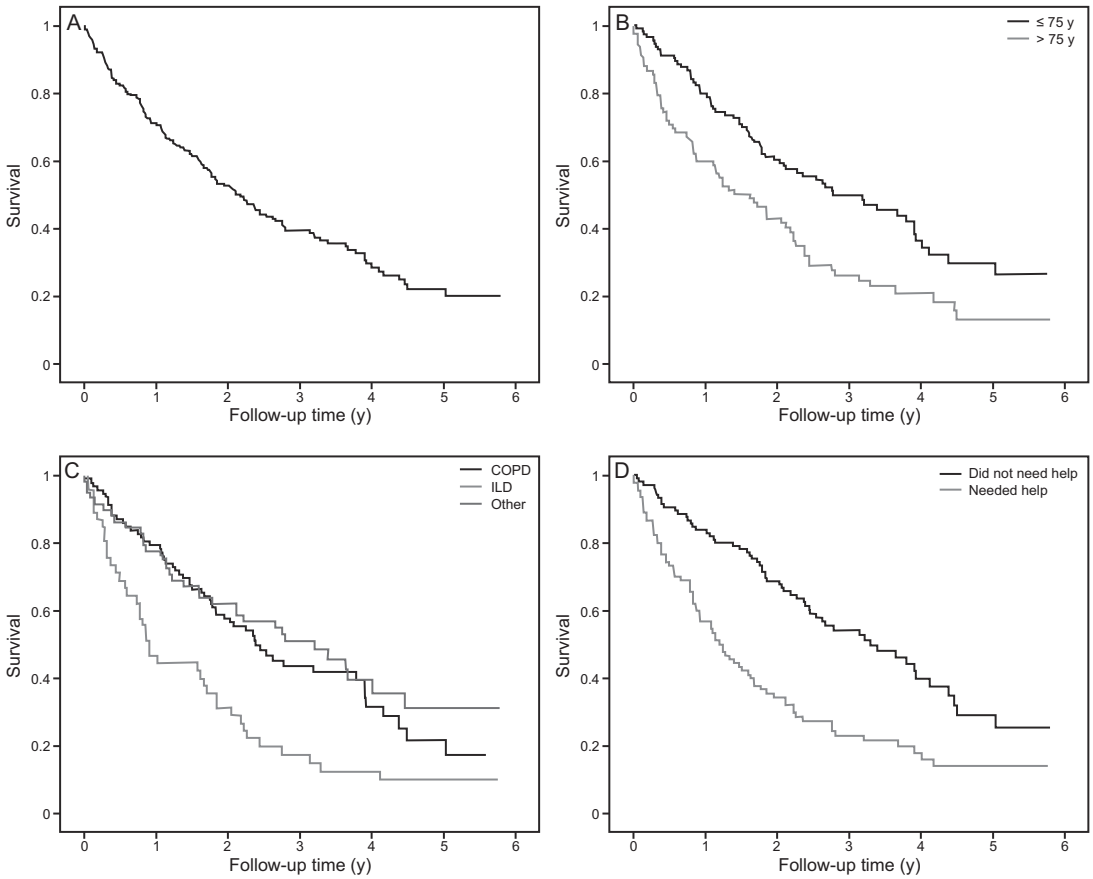


Fig. 1. A: Overall survival after the initiation of long-term oxygen therapy in the total study sample. B: In subjects ages >75 y (median 1.4 [IQR 0.4–3.1] y) and ≤75 y (median 2.8 [IQR 1.1–NA] y), $P = .001$. C: According to primary disease, COPD (median 2.4 [IQR 1.1–4.5] y), ILD (median 0.9 [IQR 0.4–2.2] y), or other (median 3.2 [IQR 1.1–5.8] y), $P < .001$ between COPD and ILD. D: According to the need for help in activities of daily living, did not need help (median 3.3 [IQR 1.7–5.8] y) and needed help (median 1.2 [QR 0.4–2.8] y), $P < .001$. IQR = interquartile range; ILD = interstitial lung disease, NA = not available.

disease as the underlying need for LTOT remained independently associated with shorter survival (Table 3).

Discussion

We presented a real-life study in an unselected sample of subjects for whom LTOT was prescribed and initiated. The median survival of the total sample was ~2 y, but this varied significantly among different subject groups. The subjects with interstitial lung disease had significantly shorter survival than did those with COPD, and more than half of the subjects with interstitial lung disease died during the first year after initiation of LTOT. The need for help in ADL, a higher Charlson comorbidity index, and interstitial lung disease as a primary disease that necessitated LTOT were independently associated with poorer survival.

The subjects on LTOT who needed constant help with ADL had worse overall and 1-y survival compared with those who managed by themselves or needed only occasional help. It seemed that the limited general performance status better reflected the risk of death than did lung function or blood gas levels in a nonselected subject sample with LTOT. To our knowledge, this was the first study to show the association between the need for help in ADL and survival among subjects with LTOT, although the need for help in ADL is associated with worse survival among subjects with interstitial lung disease or COPD in general.[14,15] Leuchte et al[14] showed that subjects with IPF (with or without LTOT) who

Table 2. Subject Characteristics According to 1 Year Survival After the Initiation of LTOT

Characteristic	Died during the 1st Year	Survived Over 1 Year	*P**
Total, *n*	56	139	
Sex, *n* (%)			.17
Males	39 (69.6)	82 (59.0)	
Females	17 (30.4)	57 (41.0)	
Age			
Median (IQR) y	78.5 (68.0–85.0)	72.0 (66.0–79.0)	.004
≤75 y, *n* (%)	23 (41.1)	90 (64.7)	.002
>75 y, *n* (%)	33 (58.9)	49 (35.3)	
Body mass index, median (IQR) kg/m^2	25.5 (22.9–29.9)	28.6 (23.2–33.9)	.03
Need for help with ADL, *n* (%)			<.001
No	17 (30.4)	88 (63.3)	
Yes	39 (69.6)	51 (36.7)	
Smoking status, *n* (%)			.61
Never-smoker	21 (37.5)	39 (28.1)	
Ex-smoker	35 (62.5)	98 (70.5)	
Smoker	0 (0.0)	1 (0.7)	
Not known	0 (0.0)	1 (0.7)	
FEV_1			
Median (IQR) L	1.47 (1.04–1.95)	1.28 (0.91–1.79)	.10
Median (IQR) % of predicted	57.0 (40.0–66.0)	47.0 (35.0–63.0)	.039
FVC			
Median (IQR) L	2.32 (1.91–3.00)	2.56 (1.82–3.09)	.58
Median (IQR) % of predicted	70.0 (55.8–86.3)	72.5 (57.3–83.8)	.77
P_{aO_2} with room air, median (IQR) mm Hg	54 (46.5–58.5)	57.4 (48.0–54.8)	.25
Oxygen flow, median (IQR) L/min	2.0 (1.0–2.0)	1.5 (1.0–2.0)	.54
Primary disease that caused the need for LTOT, *n* (%)			<.001
COPD	19 (33.9)	73 (52.5)	.02
Interstitial lung disease	24 (42.9)	20 (14.4)	<.001
Heart diseases	8 (14.3)	10 (7.2)	.12
Obesity-hypoventilation syndrome	0 (0.0)	18 (12.9)	.005
Other	5 (8.9)	18 (12.9)	.43
Comorbidities, *n* (%)			
Hypertension	34 (60.7)	86 (61.9)	.88
Heart diseases	35 (62.5)	77 (55.4)	.36
Cerebrovascular diseases	4 (7.1)	9 (6.5)	>.99
Diabetes	18 (32.1)	42 (30.2)	.79
COPD	7 (12.5)	11 (7.9)	.32
Asthma	4 (7.1)	23 (16.5)	.09
Sleep apnea	9 (16.1)	29 (20.9)	.45
Neurologic diseases	10 (17.9)	23 (16.5)	.83
Renal diseases	7 (12.5)	11 (7.9)	.32
Rheumatic diseases	5 (8.9)	13 (9.4)	.93
Cancer	11 (19.6)	27 (19.4)	.97
Others	13 (23.2)	36 (25.9)	.70
No comorbidities	2 (3.6)	7 (5.0)	>.99
Charlson comorbidity index, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–2.0)	.09

LTOT = long-term oxygen therapy
IQR = interquartile range
ADL = activities of daily living

needed help in ADL had worse survival compared to those who didn't need help in ADL.

Similarly, in the subjects with COPD (no mention of the possible use of LTOT), difficulties in ADL were associated with worse survival in a study by Liu et al.[15] The need for help in ADL probably reflected poor performance status and high morbidity, which are features of poor prognosis in many diseases.[16] In the current study, 83.3% of

Table 3. Factors Associated With Survival in Cox Regression Analysis

Factor	Univariate Analysis		Multivariate Analysis*	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex				
Females	Ref.		ND	
Males	1.02 (0.72–1.45)	.92	ND	ND
Age (continuous)	1.03 (1.01–1.05)	.001	ND	ND
Age (categorical)				
≤75 y	Ref.		Ref.	
>75 y	1.81 (1.29–2.55)	.001	1.31 (0.90–1.90)	.15
Body mass index, kg/m^2	0.97 (0.95–0.99)	.007	0.97 (0.94–1.01)	.11
Need for help in ADL				
No	Ref.		Ref.	
Yes	2.22 (1.57–3.14)	<.001	2.10 (1.44–3.06)	<.001
Smoking status				
Never-smoker	Ref.		ND	
Ex-smoker	0.98 (0.68–1.42)	.92	ND	ND
FEV_1				
L	1.11 (0.84–1.48)	.47	ND	ND
% of predicted	1.01 (1.00–1.02)	.09	ND	ND
FVC				
L	0.96 (0.78–1.19)	.73	ND	ND
% of predicted	1.00 (0.99–1.01)	.48	ND	ND
P_{aO_2} with room air, mm Hg	7.7 (6.15–9.53)	.86	ND	ND
Oxygen flow, L/min	0.99 (0.82–1.18)	.87	ND	ND
Primary disease that caused the need for LTOT				
COPD	Ref.		Ref.	
Interstitial lung disease	2.20 (1.46–3.29)	<.001	2.08 (1.36–3.17)	.001
Heart diseases	1.25 (0.65–2.38)	.50	1.33 (0.69–2.57)	.40
Obesity-hypoventilation syndrome	0.42 (0.19–0.92)	.031	0.49 (0.20–1.24)	.13
Other	0.98 (0.57–1.73)	.98	1.08 (0.60–1.94)	.81
Comorbidities†				
Hypertension	0.93 (0.66–1.31)	.68	ND	ND
Heart diseases	1.49 (1.04–2.12)	.03	0.94 (0.63–1.39)	.75
Cerebrovascular diseases	1.66 (0.92–3.02)	.09	ND	ND
Diabetes	1.03 (0.71–1.49)	.88	ND	ND
COPD	1.11 (0.63–1.97)	.72	ND	ND
Asthma	0.73 (0.43–1.23)	.24	ND	ND
Sleep apnea	0.40 (0.23–0.70)	.001	1.54 (0.84–2.83)	.16
Neurologic diseases	1.53 (1.00–2.32)	.048	1.00 (0.63–1.56)	.98
Renal diseases	1.64 (0.99–2.73)	.057	ND	ND
Rheumatic diseases	0.66 (0.35–1.27)	.21	ND	ND
Cancer	1.07 (0.69–1.65)	.78	ND	ND
Others	1.20 (0.81–1.75)	.36	ND	ND
No comorbidities	0.98 (0.46–2.13)	.98	ND	ND
Charlson comorbidity index	1.24 (1.11–1.39)	<.001	1.26 (1.11–1.43)	<.001

* Variables significantly associated with survival ($P < .05$) in univariate analysis, and all primary diagnoses were included.
† HR in comparison with subjects without the comorbidity in question.
HR = hazard ratio
Ref. = Reference
ND = no data
ADL = activities of daily living
LTOT = long-term oxygen therapy

the patients who couldn't perform any kind of lung function measurements (spirometry nor microspirometry) and 72.4% of those who could only perform microspirometry were in need of help with ADL, which was probably associated with poor performance status and which prevented the completion of spirometry. Due to this association, our statistical analysis may not have been sensitive enough to detect the association between poor lung function and poor survival. Further, the lack of an association between baseline P_{aO_2} and survival might have been because the baseline P_{aO_2} was not necessarily related to the forthcoming progression rate of the disease or deterioration of the patient.

In addition, a relatively high proportion of our subjects (46%) who started LTOT needed help with ADL, which, to our knowledge, has not previously been clearly reported. In a study by Okubadejo et al,[17] subjects with advanced COPD and on LTOT were reported as less independent with ADL than those not on LTOT, but the actual proportion of subjects who needed help with ADL was not reported. Thus, coping with ADL should be discerned in every patient who starts LTOT as an estimation of survival and social support.

The median survival of the subjects with COPD who received LTOT was reported to be approximately 2–3 y,[8,9] whereas, in a recent study on subjects with interstitial lung disease and on LTOT, the survival was only 8.4 months.[10] Our results were well in line with these numbers, but we were able to show this difference in a single center clinical study as well. More than half of our subjects with interstitial lung disease had a diagnosis of IPF, which further explained the poor survival of this subject group because the median survival after a diagnosis of IPF is only approximately 2–4 y.[18-22] Our results highlighted the importance of a primary diagnosis in patients with LTOT as a clinical tool in estimating prognosis. Further, there is no clear evidence for the beneficial role of LTOT on survival or symptom alleviation in patients with interstitial lung disease or IPF.[23]

In the univariate analysis, FEV_1 was significantly higher in the subjects who died during the first year, but this was not significant in the multivariate analysis. This was probably explained because the subjects with interstitial lung disease had shorter survival than those with COPD, whereas COPD as an obstructive disease is associated with lower FEV_1. Our results were in line with previous studies that showed that, although the decline in lung function indices does predict worse survival in interstitial lung disease and COPD, impaired exercise capacity is more closely associated with mortality.[24,25]

Also, younger age and higher BMI in our subjects with LTOT were associated with better survival in univariate but not in multivariate analysis. We suggest that the better survival in subjects with highed BMI was partly explained by the survivors being more likely to have obesity-hypoventilation syndrome rather than a progressive lung disease as the main reason for initiation of LTOT. Unfortunately, the small number of subjects with obesity-hypoventilation syndrome prevented us from evaluating this group in detail. Most of the subjects with obesity-hypoventilation syndrome also had noninvasive ventilation or CPAP in addition to LTOT, as recommended in the guidelines.[3] However, lower BMI has been associated with poorer survival in several advanced diseases, such as COPD[5,26-28] and IPF,[29] which might also explain the association between shorter survival and lower BMI in univariate analysis.

Most of our subjects had comorbidities, of which heart and neurologic diseases were associated with shorter overall survival in univariate analysis. In previous studies, comorbidities were shown to be associated with impaired survival in COPD and interstitial lung disease.[30,31] However, other factors, such as lung function and poor performance status, have been more closely related to prognosis.[32] Similarly, the relation of any single comorbidity to mortality disappeared in the multivariate analysis of our data, which indicated that other factors were more important regarding survival. The multimorbidity index (Charlson comorbidity index), in turn, was associated with shorter survival in univariate analysis and also in multivariate analysis. We suggested that the total burden of comorbidities might be more closely related to poor survival than a single disease as a comorbidity.

Advance care planning and palliative care are recommended as integral parts of the treatment of patients with advanced cardiopulmonary diseases.[13,33] However, recent studies showed that advance care planning conversations are uncommon in patients with chronic respiratory disease.[34,35] The benefits of integrated palliative care in patients with COPD or interstitial lung disease include better control of dyspnea, fewer emergency department visits during the last year of life, and an opportunity for patients to die at home instead of in the hospital.[36,37] However, a recent study showed that subjects with interstitial lung disease and on LTOT still receive lower-quality end-of-life care compared with subjects with cancer.[15] One of the key questions in clinical practice is the suitable timing of advance care planning and integrated palliative care. The need for LTOT is usually a sign of advanced disease, but our study showed the heterogeneity of subjects on LTOT. Based on our results, the initiation of LTOT should be considered a trigger for advance care planning discussions and palliative care consultations, especially in patients with interstitial lung disease or those who continuously need help with ADL.

Strengths and Limitations

We presented data on all subjects who were started on LTOT in a single university hospital during the study period. This allowed us to compare prognostic factors in an unselected subject sample and to give practical information for physicians who are taking care of the patients with LTOT. However, the study sample was relatively small, and, therefore, statistical power may not be sufficient to detect weak associations, especially among subjects with diseases other than COPD and interstitial lung disease (eg, obesity-hypoventilation syndrome). Due to the retrospective nature of the study, we were not able to study all the possible factors that influenced the prognosis of the subjects. The need for help with ADL was defined by using strict criteria, which probably found subjects who needed major help but might have omitted those with lesser impairment in self-care. Further, our analysis included data on important factors, for example, lung function, only at baseline, and we thus were not able to study the predictive ability of changes in these variables during LTOT.

Conclusions

The median overall survival among a real-life sample of subjects started on LTOT was relatively short but with considerable variation. The most important clinical predictors of poor survival were interstitial lung disease as the underlying disease that necessitated LTOT, the need for help with ADL, and multiple comorbidites. We suggest that these factors could be used by clinicians as triggers for advance care planning and palliative care consultations.

REFERENCES

1. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980;93(3):391-398.
2. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet 1981;1(8222):681-686.
3. Hardinge M, Annandale J, Bourne S, Cooper B, Evans A, Freeman D, et al. British Thoracic Society guidelines for home oxygen use in adults. Thorax 2015;70(Suppl 1):i1-43.
4. COPD Working Group. Long-term oxygen therapy for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser 2012;12(7):1-64.
5. Górecka D, Gorzelak K, Sliwiński P, Tobiasz M, Zieliński J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax 1997;52(8):674-679.
6. Long-Term Oxygen Treatment Trial Research Group, Albert RK, Au DH, Blackford AL, Casaburi R, Cooper JA, Jr, et al. A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation. N Engl J Med 2016;375(17):1617-1627.
7. Ekström M, Ringbaek T. Which patients with moderate hypoxemia benefit from long-term oxygen therapy? Ways forward. Int J Chron Obstruct Pulmon Dis 2018;13:231-235.
8. Ahmadi Z, Sundh J, Bornefalk-Hermansson A, Ekström M. Long-term oxygen therapy 24 vs 15 h/day and mortality in chronic obstructive pulmonary disease. PLoS One 2016;11(9):e0163293.
9. Gulbas G, Gunen H, In E, Kilic T. Long-term follow-up of chronic obstructive pulmonary disease patients on long-term oxygen treatment. Int J Clin Pract 2012;66(2):152-157.
10. Ahmadi Z, Wysham NG, Lundström S, Janson C, Currow DC, Ekström M. End-of-life care in oxygen-dependent ILD compared with lung cancer: a national population-based study. Thorax 2016;71(6):510-516.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383.
12. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47(11):1245-1251.
13. From the global strategy for the diagnosis, management and prevention of COPD, global initiative for chronic obstructive lung disease (GOLD) 2017. Available at https://goldcopd.org. *Accessed March 24, 2018.*
14. Leuchte HH, Mernitz P, Baezner C, Baumgartner RA, von Wulffen W, Neurohr C, Behr J. Self-report daily life activity as a prognostic marker of idiopathic pulmonary fibrosis. Respiration 2015;90(6):460-467.
15. Liu Y, Croft JB, Anderson LA, Wheaton AG, Presley-Cantrell LR, Ford ES. The association of chronic obstructive pulmonary disease, disability, engagement in social activities, and mortality among US adults aged 70 years or older, 1994-2006. Int J Chron Obstruct Pulmon Dis 2014;9:75-83.
16. Stineman MG, Xie D, Pan Q, Kurichi JE, Zhang Z, Saliba D, et al. All-cause 1-, 5-, and 10-year mortality in elderly people according to activities of daily living stage. J Am Geriatr Soc 2012;60(3):485-492.
17. Okubadejo AA, O'Shea L, Jones PW, Wedzicha JA. Home assessment of activities of daily living in patients with severe chronic obstructive pulmonary disease on long-term oxygen therapy. Eur Respir J 1997;10(7):1572-1575.
18. Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis: a population-based cohort study. Chest 1998;113(2):396-400.
19. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 2000;162(6):2213-2217.
20. King TE Jr, Schwarz MI, Brown K, Tooze JA, Colby TV, Waldron JA Jr, et al. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. Am J Respir Crit Care Med 2001;164(6):1025-1032.
21. Mura M, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, et al. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. Eur Respir J 2012;40(1):101-109.
22. King TE Jr, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet 2011;378(9807):1949-1961.
23. Bell EC, Cox NS, Goh N, Glaspole I, Westall GP, Watson A, Holland AE. Oxygen therapy for interstitial lung disease: a systematic review. Eur Respir Rev 2017;26(143). pii: 160080.
24. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J 2004;23(1):28-33.

25. Puhan MA, Siebeling L, Zoller M, Muggensturm P, ter Riet G. Simple functional performance tests and mortality in COPD. Eur Respir J 2013;42(4):956-963.
26. Cao C, Wang R, Wang J, Bunjhoo H, Xu Y, Xiong W. Body mass index and mortality in chronic obstructive pulmonary disease: a meta-analysis. PLoS One 2012;7(8):e43892.
27. Guo Y, Zhang T, Wang Z, Yu F, Xu Q, Guo W, et al. Body mass index and mortality in chronic obstructive pulmonary disease: a dose-response meta-analysis. Medicine (Baltimore) 2016;95(28):e4225.
28. Marti S, Muñoz X, Rios J, Morell F, Ferrer J. Body weight and comorbidity predict mortality in copd patients treated with oxygen therapy. Eur Respir J 2006;27(4):689-696.
29. Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. Chest 2007;131(5):1448-1453.
30. Ekström MP, Jogréus C, Ström KE. Comorbidity and sex-related differences in mortality in oxygen-dependent chronic obstructive pulmonary disease. PLoS One 2012;7(4):e35806.
31. Schwarzkopf L, Witt S, Waelscher J, Polke M, Kreuter M. Associations between comorbidities, their treatment and survival in patients with interstitial lung diseases - a claims data analysis. Respir Res 2018;19(1):73.
32. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350(10):1005-1012.
33. Selecky PA, Eliasson CA, Hall RI, Schneider RF, Varkey B, McCaffree DR, American College of Chest Physicians. Palliative and end-of-life care for patients with cardiopulmonary diseases: American College of Chest Physicians Position Statement. Chest 2005; 128(5):3599-3610.
34. Jabbarian LJ, Zwakman M, van der Heide A, Kars MC, Janssen DJA, van Delden JJ, et al. Advance care planning for patients with chronic respiratory diseases: a systematic review of preferences and practices. Thorax 2018;73(3):222-230.
35. Rush B, Hertz P, Bond A, McDermid RC, Celi LA. Use of palliative care in patients with end-stage COPD and receiving home oxygen: national trends and barriers to care in the United States. Chest 2017; 151(1):41-46.
36. Kalluri M, Claveria F, Ainsley E, Haggag M, Armijo-Olivo S, Richman-Eisenstat J. Beyond idiopathic pulmonary fibrosis diagnosis: multidisciplinary care with an early integrated palliative approach is associated with a decrease in acute care utilization and hospital deaths. J Pain Symptom Manage 2018;55(2):420-426.
37. Brinkman-Stoppelenburg A, Rietjens JA, van der Heide A. The effects of advance care planning on end-of-life care: a systematic review. Palliat Med 2014;28(8):1000-1025.

Copyright of Respiratory Care is the property of Daedalus Enterprises, Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

PUBLICATION IV

Survival and end-of-life aspects among subjects on long-term noninvasive ventilation.

Rantala Heidi A, Leivo-Korpela Sirpa, Kettunen Siiri, Lehto Juho T, Lehtimäki Lauri

European Clinical Respiratory Journal. 2020 Nov 5;8(1): 1840494
doi:10.1080/20018525.2020.1840494

Publication reprinted with the permission of the copyright holders.
https://www.tandfonline.com/doi/full/10.1080/20018525.2020.1840494

EUROPEAN CLINICAL RESPIRATORY JOURNAL
2020, VOL. 8, 1840494
https://doi.org/10.1080/20018525.2020.1840494

Taylor & Francis
Taylor & Francis Group

OPEN ACCESS Check for updates

Survival and end-of-life aspects among subjects on long-term noninvasive ventilation

Heidi A. Rantala [a,b], Sirpa Leivo-Korpela [a,b], Siiri Kettunen[b], Juho T. Lehto [b,c] and Lauri Lehtimäki [b,d]

[a]Department of Respiratory Medicine, Tampere University Hospital, Tampere, Finland; [b]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [c]Palliative Care Centre and Department of Oncology, Tampere University Hospital, Tampere, Finland; [d]Allergy Centre, Tampere University Hospital, Tampere, Finland

ABSTRACT

Background: The need for noninvasive ventilation (NIV) is commonly considered a predictor of poor survival, but life expectancy may vary depending on the underlying disease. We studied the factors associated with decreased survival and end-of-life characteristics in an unselected population of subjects starting NIV.

Methods: We conducted a retrospective study including 205 subjects initiating NIV from 1/1/2012-31/12/2015 who were followed up until 31/12/2017.

Results: The median survival time was shorter in subjects needing help with activities of daily living than in independent subjects (hazard ratio (HR) for death 1.7, 95% CI 1.2–2.6, $P = 0.008$) and was also shorter in subjects on long-term oxygen therapy (LTOT) than in those not on LTOT (HR for death 2.8, 95% CI 1.9–4.3, $P < 0.001$). There was marked difference in survival according to the disease necessitating NIV, and subjects with amyotrophic lateral sclerosis or interstitial lung disease seemed to have the shortest survival. The two most common diseases resulting in the need for NIV were chronic obstructive pulmonary disease (COPD) and obesity hypoventilation syndrome (OHS). The median survival time was 4.4 years in COPD subjects, but the median survival time was not reached in subjects with OHS (HR for death COPD vs. OHS: 3.2, 95% CI 1.9–5.5, $P < 0.001$). Most of the deceased subjects (55.6%) died in the hospital, while only 20.0% died at home. The last hospitalization admission leading to death occurred through the emergency room in 44.4% of the subjects.

Conclusions: Survival among subjects starting NIV in this real-life study varied greatly depending on the disease and degree of functional impairment. Subjects frequently died in the hospital after admission through the emergency department. A comprehensive treatment approach with timely advance care planning is therefore needed, especially for those needing help with activities of daily living and those with both NIV and LTOT.

ARTICLE HISTORY
Received 21 February 2020
Accepted 19 October 2020

Keywords
Chronic respiratory insufficiency; noninvasive ventilation; chronic obstructive pulmonary disease; obesity hypoventilation syndrome; activities of daily living; long-term oxygen therapy; survival

Introduction

Chronic hypercapnia commonly occurs in the late stages of pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), some neuromuscular disorders and, by definition, obesity hypoventilation syndrome (OHS) [1]. It has been shown that the treatment of hypoventilation with noninvasive ventilation (NIV) in patients with OHS [2] or amyotrophic lateral sclerosis (ALS) [3,4] improves survival [5], reduces sleepiness and decreases daytime $PaCO_2$ [6]. Although the overall benefit of long-term NIV for patients with COPD is under debate, the use of NIV has been shown to improve survival and reduce readmissions among patients with persistent hypercapnia after acute exacerbation of COPD [7]. There are international guidelines for the initiation of NIV in patients with COPD [8,9] and OHS [1,10], but the criteria are not strict, leaving room for clinical judgment. The use of NIV may also be beneficial in patients with hypoventilation due to other diseases, such as thoracic deformation. As the list of diseases causing chronic hypoventilation is long and there are no uniform criteria for the initiation of NIV, the real-life sample of patients initiating NIV is heterogeneous, with different underlying diseases and comorbidities.

End-of-life care and advance care planning are usually recommended if the patient is at considerable risk of dying in the next 12 months [11]. Timely advance care planning improves patient care and decreases unnecessary treatments and hospital

CONTACT Heidi A. Rantala Heidi.Rantala@tuni.fi Department of Respiratory Medicine, Tampere University Hospital, Tampere, Finland, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland, Tampere, 33520, Finland

Supplemental data for this article can be accessed here.

© 2020 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

admissions [12]. In subjects with neuromuscular diseases, such as ALS, hypoventilation is a sign of advanced disease [4]. The overall survival of patients with COPD on NIV is difficult to estimate as a consequence of the substantial impact of comorbidities [13]. As patients treated with NIV form a heterogeneous group, the need for NIV cannot be uniformly used as an indicator of poor prognosis. Therefore, it would be useful to identify relevant prognostic factors to guide the appropriate timing of advance care planning and arrangements for end-of-life care in everyday practice.

Our aim was to identify the factors associated with decreased survival and end-of-life characteristics in subjects in whom NIV was initiated in a real-life setting in an unselected patient population of a respiratory insufficiency clinic.

Materials and methods

Subjects

All subjects who started NIV, excluding 11 subjects with only sleep apnoea, between 1 January 2012, and 31 December 2015, in the respiratory insufficiency unit of Tampere University Hospital were included in this study. Tampere University Hospital provides care for the 530 000 inhabitants of Pirkanmaa County. All the subjects were treated in an acute pulmonary ward or respiratory insufficiency unit at the time of initiation of NIV, and they visited the respiratory insufficiency unit 1–3 months after the initiation of NIV and approximately once or twice per year thereafter. The decision to initiate NIV was made on clinical grounds by the attending pulmonologist, who applied the relevant guidelines [2,4,8,14]. The subjects were followed up until death or 31 December 2017.

Data collection

All the medical records of the subjects were reviewed. The collected information included sex, age, weight, height, living conditions, smoking status, primary diagnoses, information about comorbidities, do not resuscitate orders and decisions regarding end-of-life care. We also collected the results of spirometry and arterial or capillary blood gas analysis and the usage hours and settings of NIV recorded by nurses or doctors. The median daily usage hours from the device memory card were registered at every control for the time period between the previous and current visits. The disease necessitating NIV was defined as the primary disease, while all the other diseases were considered comorbidities. Diagnoses of COPD and OHS were made by the attending physician of the respiratory insufficiency unit in compliance with the current guidelines [1,15]. The Charlson comorbidity index was calculated for the subjects based on the number and severity of their comorbidities [16,17]. A subject was defined as needing help with activities of daily living (ADL) if he or she needed daily help from a family member working as a caregiver, received home care services provided by social services (e.g., dietary services, ablutions, dressing or medication) or permanently resided in a nursing home or a community hospital.

All the death certificates of the subjects who died before 31 December 2017 were reviewed. The collected information included the date and cause of death, place of death, do not resuscitate orders and end-of-life care decisions. An end-of-life care decision was defined as a recorded decision to start comfort-only end-of-life care or symptom-centred palliative care.

Statistical analysis

Almost all of the continuous variables were non-normally distributed based on visual estimation; thus, nonparametric tests were used. Comparisons of categorical variables were performed with the Mann–Whitney U test or Kruskal–Wallis test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. The Kaplan–Meier method and Cox regression were used for survival estimation. All comorbidities affecting more than five subjects (hypertension, cardiovascular diseases, diabetes, asthma, previous cancer and sleep apnoea) and age were included in the Cox multivariate analysis conducted in subjects with COPD or OHS. Statistical significance was set at $P < 0.05$. Analyses were performed with IBM SPSS Statistics versions 22.0 and 26.0 (IBM Corp, Armonk, NY).

Ethics consideration

This study was approved by the Regional Ethics Committee of Tampere University Hospital, Finland (approval code R15180/1 December 2015).

Results

A total of 205 subjects started long-term NIV during the study period and were included. The characteristics of the subjects are shown in Table 1. The most common diseases necessitating NIV were COPD and OHS. Three out of eight subjects with ILD initiated NIV with

concomitant LTOT due to hypercapnia ≥8 kPa and five subjects with ILD initiated NIV as part of palliative treatment for dyspnoea. Of the subjects included in the analysis, 135 (65.9%) started NIV during an acute exacerbation or airway infection, but they all fulfilled the criteria for long-term NIV after the resolution of the acute event. Altogether, 62 (30.2%) of all the included subjects and 26 (49.1%) of the subjects with COPD were treated with long-term oxygen therapy (LTOT) concomitantly with NIV. Of all the subjects who discontinued NIV during the follow-up period, 33 (16.1%) subjects discontinued due to lack of motivation or insufficient usage hours (<4 h per 24 h), and 14 (6.8%) subjects did not fulfil the criteria for NIV anymore. Furthermore, of those who discontinued NIV, 29 (60.0%) discontinued it during the first year, 6 (20.7%) of whom had COPD, 17 (58.6%) of whom had OHS and 6 (20.7%) of whom had other diagnoses. The median partial pressure of pCO_2 was 8.1 kPa (IQR 7.0–9.5) at the initiation of NIV, and at the first control, it was reduced to 6.1 kPa (IQR 5.4–6.7). The detailed settings of NIV, usage data and values of pCO_2 are shown in Supplementary Table 1. The most common comorbidities were cardiovascular diseases, hypertension and diabetes. Of all the subjects, 56 (27.3%) needed daily help at home, and 15 (7.3%) permanently resided in a nursing home or a community hospital.

Baseline characteristics in the subjects with COPD, OHS and other diagnoses are presented in Table 2. As expected, subjects with COPD had a more prominent smoking history, while subjects with OHS were more likely to be obese and more often suffered from concomitant sleep apnoea. Of those subjects with OHS, 20 (20.6%) also had mild or moderate COPD as a comorbidity.

Survival

Almost half (43.9%) of the subjects died during the study period. Needing help with ADL was associated with worse survival than being independent (hazard ratio for death (HR) 1.7, 95% CI 1.2–2.6, $P = 0.008$) (Figure 1(a)). Lung function or discontinuation of NIV therapy were not significantly associated with survival. In the total study sample, subjects who used LTOT concomitantly with NIV had worse survival than those who did not use LTOT (HR 2.8, 95% CI 1.9–4.3, $P < 0.001$) (Figure 1(b)).

There were marked differences in survival between subjects with different diseases, and the median survival was significantly longer in subjects with OHS (median not reached) than in those with COPD (median of 4.4 yrs., IQR 1.4–5.3, $P < 0.001$) (Figure 1(c)). The numbers of subjects in each of the other disease groups were relatively small, and detailed survival data in these groups are presented in Supplementary Figure 1. Survival was shortest in subjects with interstitial lung diseases and ALS.

Due to the small numbers of subjects in other disease groups, Cox multivariate analysis was conducted only in subjects with COPD and OHS (Supplementary Table 2). In subjects with COPD, hypertension (HR 6.4 (95% CI 2.4–-17.2, $P < 0.001$)) and older age (HR 1.1 (95% CI 1.0–1.2, $P = 0.011$)) were significantly associated with worse survival, while diabetes (HR 0.2 (95% CI 0.1–0.6, $P = 0.002$)) and previous cancer (HR 0.1 (95% CI 0.02–0.5, $P = 0.006$)) were associated with longer survival. None of the comorbidities in the survival analysis were associated with the survival time among subjects with OHS.

End-of-life characteristics

Of the subjects who died, 87.8% had do not resuscitate orders, and 43.3% had end-of-life care decisions (Table 3). The do not resuscitate decision was made a median of 199 days before death (IQR 43–642 days), and the medians were 171 days (IQR 35–506), 144 days (IQR 20–665) and 387 days (IQR 97–697) among subjects with COPD, OHS and other diagnoses, respectively ($P = 0.344$). The exact date of the DNR decision was missing in 24 subjects. Fifty-six percent of all the deceased subjects died in the hospital, and one-fifth died at home. Of those who died at the hospital, 86.0% had a do not resuscitate order, and 40.0% had an end-of-life care decision, while these proportions were 83.3% and 38.9%, respectively, among those who died at home. Forty-four percent of the subjects arrived via the emergency department for their last hospital admission before death. There was no difference in do not resuscitate orders or end-of-life care decisions between subjects who arrived via the emergency department for the last hospitalization before death and those who did not. The most common causes of death were COPD and heart disease.

Discussion

In this retrospective study on subjects with NIV due to respiratory insufficiency, the need for help with ADL and simultaneous LTOT were associated with shortened survival, while subjects with COPD had worse survival than those with OHS. Among the comorbidities, hypertension was associated with decreased survival in subjects with COPD. Decisions reflecting the recognition of the approach of the end-of-life period

Table 1. Subject characteristics.

Sex, *n* (%)	
Males	120 (58.5)
Females	85 (41.5)
Age, Median (IQR) y	67.0 (60.3–75.1)
< 65 y, *n* (%)	85 (41.5)
65–75 y, *n* (%)	74 (36.1)
> 75 y, *n* (%)	46 (22.4)
Body mass index, Median (IQR) (kg/m^2)*	33.2 (25.5–43.3)
<18.5, *n* (%)	11 (5.5)
18.5–24.9, *n* (%)	35 (17.5)
25.0–29.9, *n* (%)	32 (16.0)
30.0–34.9, *n* (%)	29 (14.5)
35.0–39.9, *n* (%)	33 (16.5)
>40.0, *n* (%)	60 (30.0)
Need for help with ADL, *n* (%)	
No	134 (65.4)
Yes	71 (34.6)
Smoking status, *n* (%)	
Never-smoker	69 (33.7)
Ex-smoker	89 (43.4)
Smoker	46 (22.4)
Not known	1 (0.5)
Pack years, Median (IQR) y	30.0 (15.0–50.0)
FEV_1 †	
Median (IQR) L	1.23 (0.86–1.83)
Median (IQR) % of predicted	45.5 (33.0–59.0)
FVC ‡	
Median (IQR) L	2.30 (1.60–2.78)
Median (IQR) % of predicted	61.0 (49.0–71.5)
FEV_1/FVC, Median (IQR) ‡	0.67 (0.48–0.77)
pCO_2, Median (IQR) kPa	8.2 (7.1–9.6)
Primary disease that caused the need for NIV, *n* (%)	
Obesity hypoventilation syndrome	97 (47.3)
COPD	53 (25.9)
Amyotrophic lateral sclerosis	10 (4.9)
Other neurological disease than amyotrophic lateral sclerosis	17 (8.3)
Thoracic deformity	14 (6.8)
Interstitial lung diseases	8 (3.9)
Other §	6 (2.9)
Comorbidities, *n* (%)	
Hypertension	127 (62.0)
Cardiovascular diseases	117 (57.1)
Sleep Apnea	87 (42.4)
Diabetes	85 (41.5)
Asthma	48 (23.4)
COPD	26 (12.7)
Cancer	31 (15.1)
Neurological diseases	20 (9.8)
Renal diseases	19 (9.3)
Rheumatic diseases	15 (7.3)
Others	99 (48.3)
No comorbidities	12 (5.9)
Charlson Comorbidity Index, Median (IQR)	1.0 (1.0–2.0)

* Data missing in five subjects due to being confined to bed (tetraplegia, multiple sclerosis, spinocerebellar ataxia or otherwise poor general condition (2)).

† Data missing in 20 subjects: lack of co-operation (tetraplegia, muscle dystrophy or subject didn't understand instructions because of e.g. Alzheimer's disease) in ten subjects and spirometry was not conducted in nine subjects as the disease was not a lung disease and missing values in one subject.

‡ Data missing in 40 subjects: only microspirometry available (20) and same reasons as for FEV_1† (20)

§ Consisting of central hypoventilation due to opioids (n = 1), bronchiolitis obliterans (n = 1), severe asthma (n = 1), tracheobronchomalacia (n = 1), vocal cord dysfunction (n = 1), chronic pleuritis (n = 1)

IQR, interquartile range; ADL, activities of daily living; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; pCO_2, partial pressure of carbon dioxide; NIV, noninvasive ventilation; COPD, chronic obstructive pulmonary disease

were commonly made, but many of the subjects still died in the hospital.

The median survival time in subjects with COPD (4.4 yrs.) was slightly better than that identified in a study by Blankenburg et al. (3.9 yrs.), while a relatively long survival of OHS subjects was found in both studies[18]. Subjects with other diagnoses showed very variable prognoses in our study. Furthermore, there were very limited numbers of subjects in these groups, precluding the drawing of firm conclusions. However, subjects with amyotrophic lateral sclerosis and interstitial lung disease had poor survival, which is in line with previous studies [19,20]. Among subjects with chronic hypoventilation, those with COPD, amyotrophic lateral sclerosis and interstitial lung diseases could benefit from timely advance care planning.

To our knowledge, this is the first study to evaluate the association between needing help with ADL and survival in subjects with NIV. Impairment in ADL has been previously shown to affect survival in the general elderly population [21], and patients with COPD have more difficulties with ADL than those without COPD [22]. However, those previous studies did not report the usage of NIV. Coping with ADL should be assessed among patients needing domiciliary NIV because needing help with ADL is common and is associated with worse survival.

Most of the subjects starting NIV, especially those with OHS, had several comorbidities, of which cardiovascular diseases, hypertension, diabetes and sleep apnoea were the most common. In contrast to the findings in some previous studies, cardiovascular diseases were not associated with decreased survival among subjects with COPD in our study [13,23,24]. However, hypertension was associated with poor survival in subjects with COPD in our results. In a previous study by Mannino et al., hypertension was common in subjects with at least severe COPD; hypertension was only slightly associated with impaired survival, while cardiovascular disease had a larger effect on survival [24]. We suggest that subjects with hypertension could actually have undiagnosed cardiovascular disease and a higher risk of cardiovascular events. Subjects with COPD and diabetes or previous non-metastatic cancer had better survival than those without. This somewhat unexpected finding might be due to better health behaviours in subjects with diabetes and cancer survivors. Although our results may also be partly due to the lack of power or coincident results related to multiple statistical testing, they highlight the need for comprehensive care of patients treated with

Table 2. Subject characteristics in subjects with COPD, obesity-hypoventilation syndrome or other diagnoses as the cause for initiation of noninvasive ventilation.

	COPD	OHS	Others	P-value
Total, *n*	53	97	55	
Sex, *n* (%)				
Males	35 (66.0)	56 (57.7)	29 (52.7)	0.364
Females	18 (34.0)	41 (42.3)	26 (47.3)	
Age, Median (IQR) y	69.0 (63.7–73.9)	66.3 (58.4–75.1)	65.9 (58.9–76.7)	0.523
< 65 y, *n* (%)	18 (34.0)	42 (43.3)	25 (45.5)	0.194
65–75 y, *n* (%)	25 (47.2)	35 (36.1)	14 (25.5)	
>75 y, *n* (%)	10 (18.9)	20 (20.6)	16 (29.1)	
Body mass index, Median (IQR) (kg/m^2)*	25.9 (21.4–31.2)	43.5 (37.4–48.8)	25.5 (21.5–28.9)	<0.001
<18.5, *n* (%)	7 (13.2)	0 (0.0)	4 (7.8)	
18.5–24.9, *n* (%)	16 (30.2)	0 (0.0)	19 (37.3)	
25.0–29.9, *n* (%)	13 (24.5)	0 (0.0)	19 (37.3)	
30.0–34.9, *n* (%)	11 (20.8)	14 (14.6)	4 (7.8)	
35.0–39.9, *n* (%)	6 (11.3)	24 (25.0)	3 (5.9)	
>40.0, *n* (%)	0 (0.0)	58 (60.4)	2 (3.9)	
Need for help with ADL, *n* (%)				
No	40 (75.5)	72 (74.2)	22 (40.0)	<0.001
Yes	13 (24.5)	25 (25.8)	33 (60.0)	
Smoking status, *n* (%)				
Never-smoker	0 (0.0)	40 (41.2)	29 (52.7)	<0.001
Ex-smoker	30 (56.6)	35 (36.1)	24 (43.6)	
Smoker	23 (43.4)	21 (21.6)	2 (3.6)	
Not known	0 (0.0)	1 (1.0)	0 (0.0)	
Pack years, Median (IQR) y	45.0 (35.0–54.0)	25.0 (10.0–40.0)	15.0 (7.0–30.0)	<0.001
FEV_1 †				
Median (IQR) L	0.81 (0.68–1.06)	1.65 (1.13–1.98)	1.27 (0.94–2.11)	<0.001
Median (IQR) % of predicted	29.0 (21.0–40.0)	53.0 (43.0–62.3)	47.0 (33.5–66.5)	<0.001
FVC ‡				
Median (IQR) L	2.44 (2.00–2.74)	2.27 (1.72–2.84)	1.66 (1.20–2.53)	0.012
Median (IQR) % of predicted	66.0 (55.0–77.0)	62.0 (52.0–73.0)	51.0 (39.0–66.0)	0.002
FEV_1/FVC, Median (IQR) ‡	0.41 (0.27–0.50)	0.70 (0.63–0.77)	0.77 (0.67–0.89)	<0.001
pCO_2, Median (IQR) kPa	8.4 (7.9–10.4)	8.6 (7.4–10.0)	7.3 (6.2–8.6)	<0.001
Comorbidities, *n* (%)				
Hypertension	28 (52.8)	71 (73.2)	28 (50.9)	0.007
Cardiovascular diseases	32 (60.4)	60 (61.9)	25 (45.5)	0.124
Diabetes	18 (34.0)	56 (57.7)	11 (20.0)	<0.001
COPD		20 (20.6)	5 (9.1)	0.001
Asthma	11 (20.8)	25 (25.8)	12 (21.8)	0.745
Sleep Apnoea	6 (11.3)	72 (74.2)	9 (16.4)	<0.001
Neurological diseases	2 (3.8)	10 (10.3)	8 (14.5)	0.164
Renal diseases	5 (9.4)	9 (9.3)	5 (9.1)	1.000
Rheumatic diseases	3 (5.7)	6 (6.2)	6 (10.9)	0.545
Cancer	8 (15.1)	16 (16.5)	7 (12.7)	0.824
Others	22 (41.5)	53 (54.6)	24 (43.6)	0.221
No comorbidities	4 (7.5)	0 (0.0)	8 (14.5)	<0.001
Charlson Comorbidity Index, Median (IQR)	1.0 (0.0–2.0)	2.0 (1.0–3.0)	1.0 (0.0–2.0)	0.001

* Data missing in five subjects due to being confined to bed (tetraplegia, multiple sclerosis, spinocerebellar ataxia or otherwise poor general condition (2)).
† Data missing in 20 subjects: lack of co-operation (tetraplegia, muscle dystrophy or subject didn't understand instructions because of e.g. Alzheimer's disease) in nine subjects and spirometry was not conducted in ten subjects as the disease was not a lung disease and missing values in one subject.
‡ Data missing in 40 subjects: only microspirometry available (20) and same reasons as for FEV_1† (20)
COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation sdr; IQR, interquartile range; ADL, activities of daily living; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; pCO_2, partial pressure of carbon dioxide; COPD, chronic obstructive pulmonary disease

NIV, with a focus on comorbidities and not just hypoventilation.

The subjects in this study were adherent to NIV, with a median of 6 h. Our results are in line with those of the study by Blankenburg et al., although the discontinuation percentages in subjects with COPD and OHS in our study were slightly lower [18]. Moreover, discontinuation was not associated with survival in the subjects in the current study, even though discontinuation has previously been shown to be associated with worse survival in subjects with OHS [25]. Our finding might be related to the tendency of subjects with milder disease and better prognosis to perceive less subjective gain from the treatment, making them more likely to discontinue NIV, although again, the lack of a significant association between survival and the discontinuation of NIV may also be due to the relatively small study population. In our study, the decrease in pCO_2 after the initiation of NIV was quite good even with relatively low pressures, especially in subjects with COPD, compared to what is usually recommended [26,27], and this might be related to

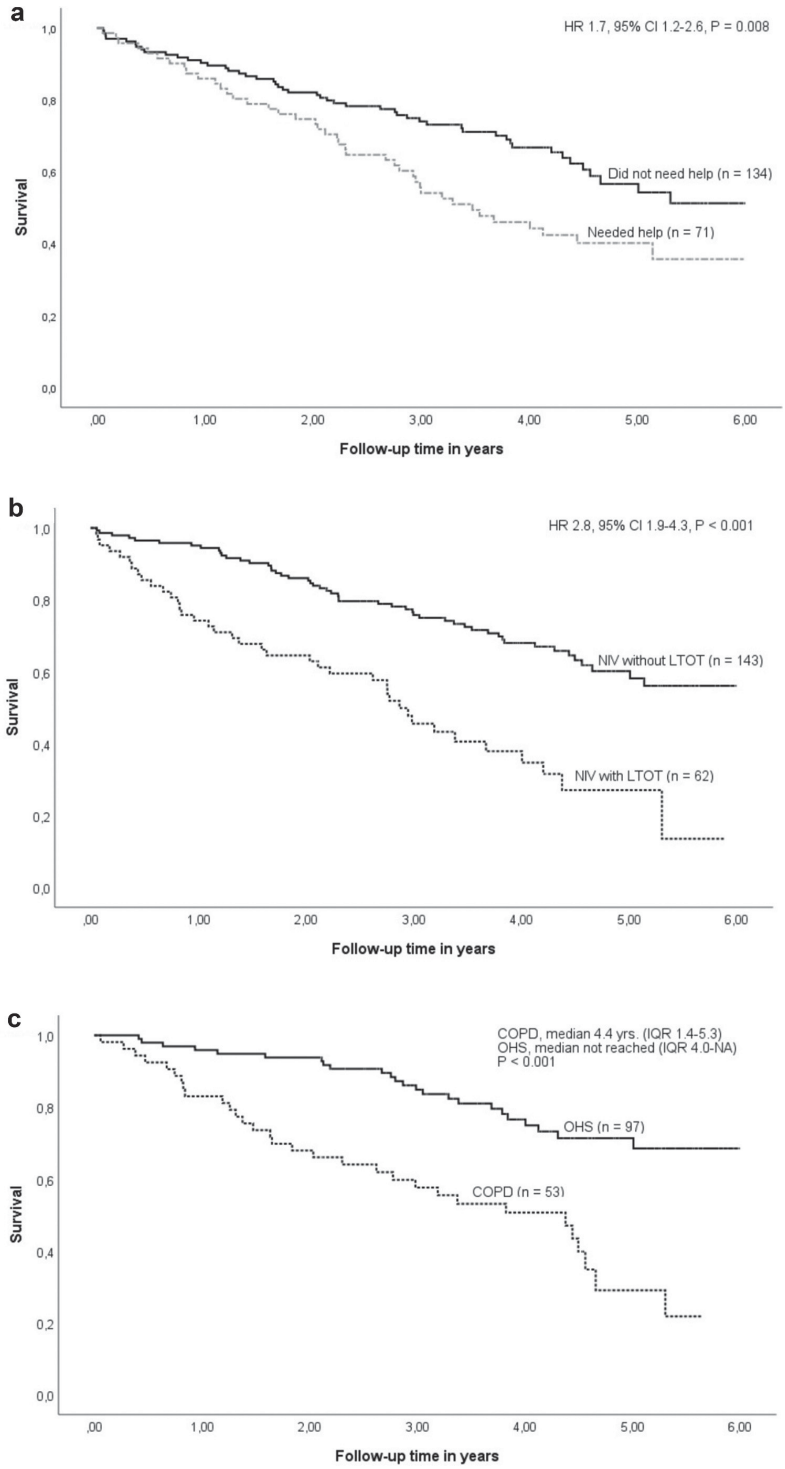


Figure 1. Kaplan-Meier survival curve for overall survival in the total study sample according to the need for assistance with activities of daily living (A), according to the concomitant use of long-term oxygen therapy with NIV (B) and after the initiation of noninvasive ventilation according to the primary diagnosis for noninvasive ventilation in subjects with OHS and COPD (C).NIV, noninvasive ventilation; LTOT, long-term oxygen therapy; HR; hazard ratio; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; IQR, interquartile range; NA, not available.

Table 3. Characteristics related to end-of-life among the deceased subjects according to primary diagnosis.

	COPD	OHS	Others	P-value
Total, *n*	53	97	55	
Died before 31.12.2017, *n* (% of all)	31 (58.5)	24 (24.7)	35 (63.6)	<0.001
DNR decision before death, *n* (%) †	30 (96.8)	18 (75.0)	31 (88.6)	0.053
End-of-life care decision before death, *n* (%)	12 (38.7)	11 (45.8)	16 (45.7)	0.814
Place of death, *n* (%)				
Hospital	17 (54.8)	17 (70.8)	16 (45.7)	0.907
Home	7 (22.6)	3 (12.5)	8 (22.9)	
Nursing home	3 (9.7)	1 (4.2)	3 (8.6)	
Hospice	2 (6.5)	2 (8.3)	4 (11.4)	
Emergency	2 (6.5)	1 (4.2)	3 (8.6)	
Not known	0 (0.0)	0 (0.0)	1 (2.9)	
Cause of death, *n* (%)				
COPD	23 (74.2)	2 (8.3)	1 (2.9)	<0.001
Heart diseases	4 (12.9)	9 (37.5)	4 (11.4)	
Interstitial lung disease	0 (0.0)	0 (0.0)	8 (22.9)	
Cancer	4 (12.9)	3 (12.5)	3 (8.6)	
Neurological diseases	0 (0.0)	1 (4.2)	13 (37.1)	
Chronic respiratory failure	0 (0.0)	4 (16.7)	1 (2.9)	
Pneumonia or other infection	0 (0.0)	1 (4.2)	1 (2.9)	
Other	0 (0.0)	4 (16.7)	4 (11.4)	
Admission through the emergency for the last hospitalization before death, *n* (%)	13 (41.9)	11 (45.8)	16 (45.7)	0.941

† 39 (49.4%) had also end-of-life care decision
COPD, chronic obstructive lung disease; OHS, obesity hypoventilation sdr; DNR, do not resuscitate

the fact that NIV was initiated in approximately 60% of subjects in an acute setting.

In the total study sample, those subjects needing LTOT in addition to NIV had worse survival than those who did not need LTOT, and this was also found when subjects with COPD and OHS were analysed separately. This is to be expected, as being hypercapnic is a sign of a pathological process that decreases gas exchange. To our knowledge, there have been no previous studies assessing whether the use of LTOT is associated with survival in patients with COPD who also use NIV. In contrast, a previous study by Murphy et al. showed that survival was better in subjects with concomitant NIV with LTOT than in subjects with only LTOT after the acute exacerbation of COPD [7]. However, our results are in line with those of one previous study by Priou and colleagues, in which hypoxemia among patients with OHS and NIV was also associated with worse survival than the absence of hypoxemia [28].

Our study showed that the majority of the deceased subjects had do not resuscitate orders, which is in line with the findings in the study by Raskin et al. [29]. However, only half of our subjects had end-of-life care decisions, although our numbers are higher than those previously reported by European respiratory care units [30]. Many of the subjects in this study died in the hospital, and only one-fifth of them died at home, which was also found in a study by Gruneir et al. [31]. In contrast, 85% of the 60 patients with advanced COPD died at home or in the palliative care unit in a recent study by Gainza-Miranda et al., highlighting the different practices in the arrangements of palliative care in the context of advanced respiratory insufficiency [32]. In addition, almost half of the subjects arrived via the emergency room for their last hospitalization prior to death in our study. When discussing do not resuscitate orders with a patient, the physician should also consider broader advance care planning discussions, including arrangements for end-of-life care, to avoid unnecessary hospitalization before death.

More than half of the subjects with COPD died in our study; thus, the management of these subjects should focus on slowing down the progression of COPD. In contrast, we found that comorbidities were a common cause of death in subjects with OHS, as shown in previous studies [25,33]. This highlights the importance of a comprehensive therapeutic approach to comorbidities in patients with OHS.

Strengths and limitations

The strength of the study is the unselected subject sample with NIV, which means that the findings provide practical information to physicians caring for similar patients. Due to the retrospective nature of the study, consistent baseline settings of NIV were lacking, and the criterion for the initiation of NIV slightly differed due to the heterogeneity of the subject population and the clinical decisions made by the attending pulmonologist. A minority of the subjects with OHS (20/97) also had COPD, but none of them had severe obstruction, and hypoventilation was thus considered to be primarily due to OHS. Due to missing lung function tests, the association

between FEV_1/FVC and survival could not be analysed. The need for assistance with ADL was defined by using strict criteria, ensuring an accurate definition of those who needed help, although the criteria might have excluded subjects with minor impairment.

Conclusions

Survival in a real-life sample of subjects with NIV varied depending on the primary disease, need for help with ADL and use of LTOT. In addition, hypertension in subjects with COPD was associated with shortened survival. Most of the subjects died in the hospital after being admitted through the emergency department, although most of them had a do not resuscitate order or end-of-life care decision. Among patients treated with NIV, a comprehensive treatment approach with timely advance care planning is needed, and clinicians should pay attention to the underlying primary diagnosis, functional impairment and comorbidities.

Disclosure statement

The authors declare that there are no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This study was supported by grants from Medical Research Fund of Tampere University Hospital, Väinö and Laina Kivi Foundation, Tampere Tuberculosis Foundation, The Research Foundation of the Pulmonary Diseases, Nummela Foundation, Jalmari and Rauha Ahokas Foundation, and The Finnish Anti-tuberculosis Foundation.

Notes on contributors

Heidi Rantala is a specialist in Respiratory Medicine working at Tampere University Hospital. Her PhD project focuses on management of patients with chronic respiratory insufficiency.

Sirpa Leivo-Korpela is a PhD, specialist in Respiratory Medicine working at Tampere University Hospital and her research interest covers chronic respiratory insufficiency and palliative care in respiratory diseases.

Siiri Kettunen is an MD conducting research on chronic respiratory insufficiency.

Juho T. Lehto is a Professor of Palliative Medicine at Tampere University and his research interest covers palliative care in respiratory diseases.

Lauri Lehtimäki is an Associate Professor of Respiratory Medicine at Tampere University and his research interest covers chronic airway diseases.

Authorship statement

Literature search: Rantala, Leivo-Korpela, Kettunen, Lehto, Lehtimäki

Data collection: Rantala, Kettunen

Study design: Rantala, Leivo-Korpela, Lehto, Lehtimäki

Analysis of data: Rantala, Leivo-Korpela, Lehto, Lehtimäki

Manuscript preparation: Rantala, Leivo-Korpela, Lehto, Lehtimäki

Review of manuscript: Rantala, Leivo-Korpela, Kettunen, Lehto, Lehtimäki

Data availability statement

Data available on request from the authors

ORCID

Heidi A. Rantala http://orcid.org/0000-0001-9597-5553
Sirpa Leivo-Korpela http://orcid.org/0000-0002-1324-6718
Juho T. Lehto http://orcid.org/0000-0001-8519-7372
Lauri Lehtimäki http://orcid.org/0000-0003-1586-4998

References

[1] Mokhlesi B, Kryger MH, Grunstein RR. Assessment and management of patients with obesity hypoventilation syndrome. Proc Am Thorac Soc. 2008;5(2):218–225.
[2] Budweiser S, Riedl SG, Jörres RA, et al. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. J Intern Med. 2007;261(4):375–383.
[3] Kleopa KA, Sherman M, Neal B, et al. Bipap improves survival and rate of pulmonary function decline in patients with ALS. J Neurol Sci. 1999;164(1):82–88.
[4] Bourke SC, Tomlinson M, Williams TL, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol. 2006;5(2):140–147.
[5] Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care. 2010;55(10):134–135.
[6] Masa JF, Corral J, Caballero C, et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea. Thorax. 2016;71(10):899–906.
[7] Murphy PB, Rehal S, Arbane G, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation. JAMA. 2017;317(21):2177.
[8] Goldberg A, Leger P, Hill N, et al. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD,

and nocturnal hypoventilation—A consensus conference report. Chest. 1999;116(2):521–534.
[9] Ergan B, Oczkowski S, Rochwerg B, et al. European respiratory society guidelines on long-term home non-invasive ventilation for management of COPD. Eur Respir J. 2019;54(3):1901003.
[10] Mokhlesi B, Masa JF, Brozek JL, et al. Evaluation and management of obesity hypoventilation syndrome. An official American thoracic society clinical practice guideline. Am J Respir Crit Care Med. 2019;200(3):e6–e24.
[11] Boyd K, Murray SA. Recognising and managing key transitions in end of life care. BMJ. 2010;341(sep16 2):c4863.
[12] Brinkman-Stoppelenburg A, Rietjens JA. van der Heide A. The effects of advance care planning on end-of-life care: A systematic review. Palliat Med. 2014;28(8):1000–1025.
[13] Smith M, Wrobel J. Epidemiology and clinical impact of major comorbidities in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2014;9:871–888.
[14] Windisch W, Geiseler J, Simon K, et al. German national guideline for treating chronic respiratory failure with invasive and non-invasive ventilation – Revised edition 2017: PART 2. Respiration. 2018;96(2):171–203.
[15] Global Initiative for Chronic Obstructive Lung Disease. published in Fontana, WI, USA; [cited 2020 Jun 8] Available from: www.goldcopd.org
[16] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–383.
[17] Charlson ME, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245–1251.
[18] Blankenburg T, Benthin C, Pohl S, et al. Survival of hypercapnic patients with COPD and obesity hypoventilation syndrome treated with high intensity non invasive ventilation in the daily routine care. Open Respir Med J. 2017;11(1):31–40.
[19] Sancho J, Martínez D, Bures E, et al. Bulbar impairment score and survival of stable amyotrophic lateral sclerosis patients after noninvasive ventilation initiation. ERJ Open Res. 2018;4(2):00159–02017.
[20] King CS, Nathan SD. Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities. Lancet Respir Med. 2017;5(1):72–84.
[21] Stineman MG, Xie D, Pan Q, et al. All-cause 1-, 5-, and 10-year mortality in elderly people according to activities of daily living stage. J Am Geriatr Soc. 2012;60(3):485–492.
[22] Liu Y, Croft J, Anderson L, et al. The association of chronic obstructive pulmonary disease, disability, engagement in social activities, and mortality among US adults aged 70 years or older, 1994–2006. Int J Chron Obstruct Pulmon Dis. 2014;9:75.
[23] Boudestein LCM, Rutten FH, Cramer MJ, et al. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. Eur J Heart Fail. 2009;11(12):1182–1188.
[24] Mannino DM, Thorn D, Swensen A, et al. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J. 2008;32(4):962–969.
[25] Castro-Añón O, LA PDL, De la Fuente Sánchez S, et al. Obesity-hypoventilation syndrome: increased risk of death over sleep apnea syndrome. Atkin SL, ed. PLoS One. 2015;10(2):e0117808.
[26] Dreher M, Storre JH, Schmoor C, et al. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax. 2010;65(4):303–308.
[27] Köhnlein T, Windisch W, Köhler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014;2(9):698–705.
[28] Priou P, Hamel J-F, Person C, et al. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. Chest. 2010;138(1):84–90.
[29] Raskin J, Vermeersch K, Everaerts S, et al. Do-not-resuscitate orders as part of advance care planning in patients with COPD. ERJ Open Res. 2018;4(1):00116–02017.
[30] Nava S, Sturani C, Hartl S, et al. End-of-life decision-making in respiratory intermediate care units: a European survey. Eur Respir J. 2007;30(1):156–164.
[31] Gruneir A, Mor V, Weitzen S, et al. Where people die: a multilevel approach to understanding influences on site of death in America. Med Care Res Rev. 2007;64(4):351–378.
[32] Gainza-Miranda D, Sanz-Peces EM, Alonso-Babarro A, et al. Breaking barriers: prospective study of a cohort of advanced chronic obstructive pulmonary disease patients to describe their survival and end-of-life palliative care requirements. J Palliat Med. 2019;22(3):290–296.
[33] Borel J-C, Burel B, Tamisier R, et al. Comorbidities and mortality in hypercapnic obese under domiciliary non-invasive ventilation. Ma X-L, ed. PLoS One. 2013;8(1):e52006.

Supplementary Table 1. Details of the settings, usage and achieved pCO_2 levels in subjects with noninvasive ventilation.

	COPD	**OHS**	**Others**	***P*-value***
Total, *n*	53	97	55	
IPAP, cmH_20, Median (IQR) †	16.0 (12.0-17.5)	18.0 (16.0-20.0)	14.0 (12.0-15.0)	<0.001
EPAP, cmH_20, Median (IQR) †	6.0 (6.0-8.0)	10.0 (8.0-10.0)	6.0 (6.0-8.0)	<0.001
Average usage per day during the first year,				
hours, Median (IQR) ‡	6.0 (4.0-8.0)	6.0 (4.0-7.5)	5.5 (3.4-8.3)	0.904
pCO_2 at the initiation, kPa, Median (IQR)	8.4 (7.9-10.4)	8.6 (7.4-10.0)	7.3 (6.2-8.6)	<0.001
pCO_2 at the first follow-up, kPa, Median (IQR) § ¥	6.2 (5.5-6.9)	6.0 (5.4-6.6)	6.2 (5.7-6.8)	0.201

* Between subjects with COPD and Obesity-hypoventilation syndrome.

† Data missing in 3 subjects.
‡ Nine subjects died before the first follow-up visit in stable state and data missing in 8 subjects.
§ Nine subjects died before the first follow-up visit in stable state, data missing in one subject, data not analyzed in six subjects due to not having used the device.
¥ Median length of the first follow-up was 42 days (IQR 35-63).

pCO_2, partial pressure of carbon dioxide; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; IQR, interquartile range; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure

Supplementary Table 2. Association of age and comorbidities on survival among subjects with COPD and OHS in Cox multivariate analysis.

	COPD		OHS	
	HR (95% CI)	***P-value***	**HR (95 % CI)**	***P-value***
Age at the initiation of NIV	1.1 (1.0-1.2)	0.011	1.0 (1.0-1.1)	0.082
Comorbidities				
Hypertensio	6.4 (2.4-17.2)	<0.001	1.1 (0.4-3.2)	0.868
Cardiovascular diseases	1.2 (0.5-3.0)	0.627	2.8 (0.9-8.5)	0.079
Diabetes	0.2 (0.1-0.6)	0.002	0.7 (0.3-1.7)	0.393
Asthma	0.5 (0.2-1.7)	0.289	1.8 (0.7-4.5)	0.239
Previous cancer	0.1 (0.02-0.5)	0.006	0.8 (0.3-2.6)	0.748
Sleep apnea	0.7 (0.2-2.5)	0.599	0.4 (0.2-1.1)	0.081

NIV, noninvasive ventilation; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; HR, hazard ratio

Supplementary Figure