Health-related quality of life and its association with mortality in patients receiving long-term mechanical ventilation

Heidi Øksnes Markussen

Thesis for the degree of Philosophiae Doctor (PhD)
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SCIENTIFIC ENVIRONMENT

This thesis was completed at the Department of Global Public Health and Primary Care, Faculty of Medicine and Dentistry, University of Bergen. The clinical research environment was mainly the Department of Thoracic Medicine at Haukeland University Hospital and the Norwegian National Advisory Unit for long-term mechanical ventilation (LTMV), as well as the national and international network for LTMV and respiratory care.

My supervisor was Professor, RN, Gerd Karin Natvig, Department of Global Public Health and Primary Care, University of Bergen. Professor Natvig was the head of the research group Life Phenomena and Quality of Life, of which I was a member, and has been the head of the Nursing Science Section, Department of Global Public Health and Primary Care.

Dr. Med., associate professor, Sverre Lehmann at the Institute of Internal Medicine, and member of the Bergen Respiratory Research Group, Institute of Internal Medicine, University of Bergen was co-supervisor. He is a specialist in pulmonary medicine and the leader of the Obstructive Lung Diseases, Respiratory Failure and Sleep-related Diseases Section, the leader of research on LTMV at the Norwegian National Advisory Unit, the Department of Thoracic Medicine, Haukeland University Hospital.

Associate professor and biostatistician, Roy Miodini Nilsen, at the University of West Norway was co-supervisor. He was previous a biostatistician at the Centre for Clinical Research, Haukeland University Hospital.

During my PhD work, I completed the doctorate courses at the Department of Global Public Health and Primary Care, University of Bergen. I have participated in scientific network meetings and research conferences run by the Life Phenomena and Quality of Life Research Group, the Bergen Respiratory Research Group, the Norwegian Nursing Association, the European Respiratory Care Association, the European Respiratory Society and the American Association for Respiratory Care.

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I would also like to acknowledge the supervision from Professor Astrid Wahl and Professor Berit Rokne during my master thesis, which was the starting point and inspiration for the PhD work.

My first meeting with patients having severe respiratory insufficiency receiving mechanical ventilation was as a nurse in the Thoracic Department at Haukeland Hospital in 1985. In the 80's and 90's many of these patients were transferred from the Intensive Care Unit (ICU) to the Thoracic ward. The ICU had succeed to help the patients to overcome critical acute illness, trauma or surgery complications, but some of the patients were still dependent on a ventilator. Our knowledge in treatment of patients with severe respiratory insufficiency was limited and the municipal health care service had limited resources to care for these patients. Thus, some of these patients stayed at the Thoracic ward treated with a ventilator usually used at ICU patients for years. To maintain the patients' quality of life in this setting was difficult.

The establishment of the National centre of excellence in home mechanical ventilation and the Norwegian registry for long-term mechanical ventilation (LTMV) had a huge impact of the knowledge in treatment in this field. MD Jan Grepstad, MD Ove Fondenes and RN Sølvi Flaten, were among the key persons in establishing the centre. Previous head of the Department of Thoracic Medicine, Professor Amund Gulsvik and Head Nurse Liv Digranes were also important in the process of preparing establishing a National Centre for home mechanical ventilation. Later heads of the department, MD Sverre Sørenson, MSc Inger-Johanne Haaland Wang, MD Alf H Andreassen, MD Kathan Al-Azawy and acting head of Thoracic department today, Kjetil Sævartveit have all contributed to development of the care for patients with severe chronic respiratory failure and I am very grateful for their efforts and work.

I would also like to thank the Norwegian advisory unit for LTMV and all participants in the national LTMV network for positive inspiration and support during the project. Especially MD and leader Ove Fondenes, who has a unique engagement for LTMV patients and who generously shares his knowledge in the field; always having the patients best interest in mind.

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My deepest gratitude goes to my family, especially my sister, Eva and brother Otto, my husband Arild, our daughter Mari, sons Even and Simon and daughter in law, Daisy and my grandchild Thomas, thank you for love and support in work and in life.

ABBREVIATIONS

AARC	American Association for Respiratory Care
ALS	Amyotrophic lateral sclerosis
ANOVA	Analysis of variance
BiPAP	Bi-level positive airway pressure
BMI	Body Mass Index
CHRF	Chronic hypercapnic respiratory failure
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Disease Questionnaire
CWD	Chest wall disease
EPAP	Expiratory positive airway pressure
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
HR	Hazard ratio
HRQoL	Health-related quality of life
IPAP	Inspiratory positive airway pressure
LTMV	Long-term mechanical ventilation
LTOT	Long-term oxygen therapy
MFR-28	Maugeri Foundation Respiratory Failure Questionnaire
NIPPV	Non invasive positive pressure ventilation
NIV	Non-invasive ventilation
NMD	Neuromuscular disease
OHS	Obesity-hypoventilation syndrome
$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of arterial oxygen
RCT	Randomized controlled trial
SD	Standard deviation
SF-36	Short-Form 36 Questionnaire
SRI	Severe Respiratory Insufficiency Questionnaire
SGRQ	St George's Respiratory Questionnaire
WHO	The World Health Organization
95% CI	95 percent Confidence Interval

ABSTRACT

Background: Long-term mechanical ventilation (LTMV) is a treatment option for patients with severe chronic respiratory failure. The treatment is carried out in patients' home or in a nursing home, and can completely or partially compensate for their breathing failure. The majority of patients receive ventilation through a mask covering the nose or both mouth and nose (non-invasive), while a small percentage receive ventilation through a tracheostomy, which is an opening in the neck leading directly to the trachea (invasive). The main goal with LTMV is to maintain or increase quality of life and to prolong survival. Previous research examining quality of life and health-related quality of life (HRQoL) in this group have used a large number of different questionnaires, none of which has been sensitive to the specific challenges of living with LTMV. There is limited knowledge about the long-term outcome of LTMV on quality of life, factors associated with changes in HRQoL and the association with mortality.

Aims: The overall aim of this thesis was to provide new knowledge about HRQoL in patients treated with LTMV in a six-year follow-up study. To achieve the overall aim, we had to provide a validated Norwegian version of a specific questionnaire to measure HRQoL in patients treated with LTMV. The main aims were to examine changes in HRQoL in patients receiving LTMV, to examine factors associated with changes in HRQoL in relation to socio-demographic background variables, treatment variables and respiratory variables, and to examine mortality in LTMV patients and the associations between HRQoL and mortality.

Materials and methods: This thesis was based on data from the Norwegian LTMV Register in West Norway, the Norwegian Patient Register, the Cause of Death Register, and data on patient-reported outcome measures.

In 2008, all the potential eligible adult patients on the LTMV Register in three counties in West Norway were requested to participate in the study. Data from this register and the Short Form-36 (SF-36) generic questionnaire were used to examine the psychometric properties of the Norwegian version of the Severe Respiratory Insufficiency (SRI) questionnaire, a specific HRQoL instrument developed together with patients treated with LTMV. All the patients were followed up from 2008 to 2014. Changes in HRQoL in the patients still treated with LTMV were measured by the SRI questionnaire, in relation to socio-demographic background variables, treatment variables and respiratory variables.

Mortality and the ability of the SRI questionnaire to predict mortality were measured by adjusting for socio-demographic variables, including age and education level, clinical variables including main disease group, and treatment variables including hours per day on LTMV, time since initiation of LTMV and comorbidity. Data concerning comorbidity was collected from the Norwegian Patient Register and data on mortality was confirmed by the Cause of Death Register.

Results: Out of 193 potential patients on the Norwegian LTMV Register, 127 people (66%) agreed to participate in the study in 2008. The patients were categorized into groups according to neuromuscular diseases, chronic obstructive pulmonary diseases, obesity hypoventilation syndrome and chest wall diseases. The mean age was 61.5 years (SD 15.6) and 68 (53.5%) of the patients were male. The most patients received LTMV via a nasal or mouth mask (92%) and 8% received LTMV via a tracheostomy. The Norwegian version of the SRI questionnaire had good reliability and validity. The reliability of was confirmed by Cronbach Alpha between 0.68 and 0.88 for the subscales and 0.94 for the SRI sum score. The validity was confirmed by high correlations between subscales on the SF-36 and SRI questionnaires. In addition, the validity was supported by that the SRI questionnaire was able to confirm known a priori differences among patients receiving LTMV (Paper I).

After six years, 60 patients were still receiving LTMV and confirmed their participation in the follow-up study. HRQoL improved significantly in the majority of the patients according to the total SRI sum score and in four subdomains of the SRI questionnaire. Patients reported satisfaction with training, while follow-up from healthcare professionals was associated with changes in HRQoL. Side effects of the treatment such as facial soreness were associated with lower SRI scores and thus changes in HRQoL. Older age was associated with lower HRQoL on SRI physical functioning subscales. Lung function, as measured by high forced vital capacity, was associated with improved HRQoL on the SRI social functioning subscale (Paper II).

During the 80-month follow-up period, 52 participants died. The highest mortality rate was among patients with chronic obstructive pulmonary disease (75%), followed by patients with neuromuscular disease (46%), obesity hypoventilation syndrome (31%) and chest wall disease (25%). Lower SRI sum scores in 2008 were associated with a higher mortality risk after adjustment for age, education level, time since initiation of LTMV, hours per day on LTMV, comorbidity and disease category. In addition, according to the SRI questionnaire, physical functioning, psychological well-being and social functioning remained significant risk factors for mortality after covariate adjustment (Paper III).

Conclusions: Based on quality of life as a conceptual framework, this thesis has provided new important knowledge on HRQoL in patients receiving LTMV from a six-year perspective. Improved HRQoL in the majority of the patients also provides new insights for patients and healthcare professionals. Improvements in the subscale related to overall satisfaction with life, reduced anxiety related to breathing, greater capacity among patients to cope with their condition, and contact and relationship with other people are clinically important. There was also an absence of deterioration in the SRI subscales related to physical functioning, respiratory complaints and attendant symptoms, and sleep during six years of ongoing LTMV. From a healthcare perspective, it important that professionals have the potential to influence their

patients' HRQoL by helping to reduce side effects and improve training and follow-up. A greater awareness of the strong association between HRQoL measured by SRI and mortality provides important new knowledge to healthcare professionals and political decision makers responsible for the treatment and care of people treated with LTMV. These results highlight the need to identify patients with low HRQoL and initiate interventions to improve HRQoL. Future research should focus on developing effective interventions to assist patients in living with LTMV as well as improving HRQoL and prognosis for treatment.

LIST OF PUBLICATIONS

The dissertation is based on the following papers:

I. Markussen H, Lehmann S, Nilsen RM, Natvig GK (2015). The Norwegian version of the Severe Respiratory Insufficiency Questionnaire. Int J Nurs Pract. 21(3):229-38. doi: 10.1111/ijn.12256. PMID: 24762168.

II. Markussen H, Lehmann S, Nilsen RM, Natvig GK (2018). Factors associated with change in health-related quality of life among individuals treated with long-term mechanical ventilation, a 6-year follow-up study. J Adv Nurs.74 (3):651-665. doi: 10.1111/jan.13472. PMID: 28983937.

III. Markussen H, Lehmann S, Nilsen RM, Natvig GK (2019). Health-related quality of life as predictor for mortality in patients treated with long-term mechanical ventilation. BMC Pulm Med. 11;19(1):13. doi: 10.1186/s12890-018-0768-4. PMID: 30635052.

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1. INTRODUCTION

1.1 Background

The main purpose of long-term mechanical ventilation (LTMV) is to improve quality of life and extend life expectancy (1-3). The indication for treatment is hypoventilation and chronic hypercapnic respiratory failure (CHRF), while LTMV implies that patients are dependent on mechanical ventilation for at least four hours a day for more than six weeks (4). LTMV is initiated for a variety of disorders and is performed in patients' home or nursing facilities. Previous research has shown that patients with hypoventilation who are not treated with LTMV have a very low quality of life (5) and high mortality (6-8). Patients' underlying conditions are most often incurable and side effects are reported in the case of both invasive and non-invasive LTMV (4, 9, 10). Therefore, it is crucial to gain knowledge about quality of life among patients receiving LTMV. Quality of life is fundamental to the human health experience and a frequently used outcome of health workers' research and practice, aiming to maintain and restore a person's overall experience of well-being (11) and a good life (12, 13). However, the definition of quality of life lacks accuracy, and there is no common universal definition or measurement of the concept (12, 13). The Severe Respiratory Insufficiency (SRI) questionnaire, which specifically aims to measure health-related quality of life (HRQoL) in patients receiving LTMV (14), was originally developed in close collaboration with LTMV patients. The SRI questionnaire has good psychometric properties (10, 14-17) and is based on a definition of HRQoL including functional capacities, psychological well-being and social relations (10). This thesis has used the framework and understanding of HRQoL as reflected in the SRI questionnaire.

LTMV is most commonly a lifelong treatment. However, a few studies have examined the long-term changes in HRQoL during ongoing LTMV, while no studies have examined it using a specific questionnaire for this patient group. Follow-up studies have examined HRQoL before treatment compared to one year after initiating LTMV by using the SRI questionnaire (10, 18-20), and two years after initiating LTMV using

a generic questionnaire (21). To the best of our knowledge, the only previous cohort study covering a period of more than five years among patients receiving LTMV found improvements in symptoms such as anxiety, depression, poor sleep quality and nocturnal dyspnoea (22).

Results from previous studies with different measures of health and quality of life have shown that these measures were prognostic factors for mortality. These findings were obtained from patients with cancer measured by a cancer-specific scale (23), COPD patients with measures of health status such as St George's Respiratory Questionnaire (SGRQ) and the Maugeri Foundation Respiratory Failure (MFR-28) questionnaire (24), and among patients with idiopathic pulmonary fibrosis measured by SGRQ (25). Thus, the rationale for this thesis was to gain new knowledge of the impact of long-term treatment on HRQoL and the predictors for change in HRQoL using the specific SRI questionnaire, as well as to provide new insights into the capacity of HRQoL to predict mortality in people treated with LTMV.

1.2 LTMV treatment

Definitions, indications and prevalence of LTMV

In the US and Canada, "ventilator-assisted individual" (VAI) or "vent user," rather than "patient", is often used to describe a person who is chronically dependent on a mechanical ventilator (26). "Home mechanical ventilation" is also a frequently used term for LTMV. The term LTMV is used in the Norwegian guidelines for LTMV and may be more in line with international practice (4). We also use LTMV in the current thesis, as well as "patient", "ventilator user" and "ventilator-assisted individual".

Hypoventilation causing CHRF often develops gradually, depending on the underlying disease, comorbidity and other factors. As ventilatory control in all humans is reduced during sleep, the earliest signs of hypoventilation occur in sleep. The symptoms of sleep-disordered breathing are, however, most evident during daytime, consisting of

extensive sleepiness, poor concentration, impaired cognitive functioning and, in some patients, headache, particularly in the morning (27). As the disorder progresses to daytime hypercapnia, symptoms related to mechanical imbalance develop, such as breathlessness and tachypnoea.

CHRF patients treated with LTMV were categorized into neuromuscular disease (NMD), chronic obstructive pulmonary disease (COPD), obesity hypoventilation syndrome (OHS) and chest wall disease (CWD) (10, 28, 29). Initially, LTMV was a treatment for patients with NMD (30, 31), a heterogeneous category concerning pathogenesis, disease progression, degree of muscle weakness and ventilator dependency.

The worldwide prevalence of LTMV has increased rapidly in the last decade due to the more comfortable use of non-invasive ventilation via a mask or a mouthpiece (31, 32). The most recent prevalence estimate of non-invasive LTMV in Europe was 6.6/100,000 inhabitants (28); however, the estimate varies widely between European countries, partly due to an extensive lack of high-quality registries for this treatment (28). The prevalence was 12.9/100,000 in Canada (33), 9.9 and 12.0/100,000 in Australia and New Zealand, respectively (34), and 63/100,000 in Lombardy, a major region of Italy (35). In 2012, around 11,000 patients were treated with LTMV in the US (26), with a shift towards non-invasive LTMV and wider indications for treatment in recent years (32). In Norway, the prevalence was 19.9/100,000 as of 31 December 2007 (36) and 46/100,000 in 2017 (37), with similar incidences to those on the Swedish register (38).

In 2018 congenital muscular dystrophies constituted 8% of new patients treated with LTMV, while patients with acquired NMD including amyotrophic lateral sclerosis (ALS), post-polio syndrome and spinal cord injury comprised 20% of the new LTMV patients (39). People with COPD accounted for one third of LTMV users in Europe in 2005 (28), while an almost identical percentage of patients was diagnosed with COPD among European countries in 2016, albeit with a wide range of variance between the countries (40). In Norway, from 2002 to 2018, approximately 25% of the patients

treated with non-invasive LTMV had lung disease, mainly COPD (39). OHS refers to the fastest-growing group of LTMV users worldwide (31) and the largest group of new patients in Norway in 2017 (37).

Basic principles and outcomes of LTMV treatment

Mechanically assisted ventilation refers to the use of a mechanical device to provide ventilator support for patients in order to fully or partially compensate for failure in ventilation and normalization of blood gases (41). The most commonly used objective measure for impaired ventilation is increased arterial carbon dioxide tension ($PaCO_2$) and decreased arterial oxygen tension (PaO_2) (42). LTMV provides assistance with inspiration and decreases the work of breathing by unloading the respiratory muscles, leading to increased tidal and minute ventilation and improved gas exchange (43).

Symptoms of hypoventilation improve considerably by LTMV, with a relapse in symptoms occurs upon discontinuation of treatment. Better one-year survival and improvement in some subscales in generic HRQoL have been found in ALS patients treated with non-invasive LTMV (6). However, the outcome of LTMV will depend on the basic underlying disease, the course of disease, and the extent of treatment requirements, as well as on a number of factors related to patients' overall situation (4). Individuals receiving LTMV are also heterogeneous in terms of pathophysiology, degree of ventilator dependency, and prognosis (4, 31).

Ventilation modes

Ventilation modalities

The origins of modern LTMV can be traced back about five centuries (44). In the late 19th century, ventilators based on negative pressure ventilation (NPV) appeared, using sub-atmospheric pressure which was delivered around the body of the patient to replace or augment the work performed by the respiratory muscles. The "iron lung"

was developed and used extensively during the polio epidemics of the 1930s and 1950s. Negative pressure ventilation, in the form of "body ventilators" or "shield ventilators", is still available, but rarely used today. Originally, positive pressure ventilators (PPVs) were developed for use during anaesthesia (41). Early PPV ventilators delivered breaths according to a pre-set volume in addition to a pre-set back-up respiratory rate and inspiratory time. These ventilators worked regardless of any inspiratory effort from the patient and were therefore often uncomfortable and poorly endured by the patient (43). In the 1980s, pressure support and pressure-controlled ventilation were introduced. Bi-level positive airway pressure (BiPAP) ventilators provided non-invasive positive pressure ventilation in a wide variety of settings (41). In this mode, which is the most frequently used ventilation in LTMV today, the practitioner selects an inspiratory positive airway pressure (IPAP) and an expiratory positive airway pressure (EPAP) to be delivered by the ventilator. The patient triggers an inspiration from the ventilator, or the ventilator delivers an inspiration if the patient's spontaneous breathing rate falls below a pre-set back-up rate. The ventilator's ability to respond automatically to their breathing was reported as important or very important to 91% of LTMV patients (29). Newer modes of ventilation are able to combine aspects of both volume and pressure modes (43).

Non-invasive and invasive LTMV modes

LTMV can be applied invasively via a tracheostomy (an opening in the neck with access to the trachea) and non-invasively via a mask or a mouthpiece. In 2017, 98% of Norwegian LTMV users started the treatment in the non-invasive mode (37), while, in 2008, at the baseline of this thesis, about 92% of the patients received LTMV in the non-invasive mode(4, 36). The interfaces (i.e., the connection between the patient and the ventilator) used in non-invasive ventilation are nasal masks, nasal pillows, oral masks or mouthpieces, or masks covering both mouth and nose. When selecting an interface, it is important to evaluate the fit and air leaks as well as the patient comfort because these influence patient compliance with LTMV. Other aspects to consider include the volume of dead space (volume not included in the ventilation), the position of the interface exhalation port, and finally the type of ventilator to be used (45).

A problem in LTMV might be treatment-related inconvenience or side effects (4, 9, 17, 46). Most side effects are the result of a mismatch between the natural human airway and the artificial airway, but can also occur from the ventilator as a synchronization problem between the patient's own breath and the ventilator-given breath. Mask discomfort is reported by up to 50% of patients receiving non-invasive LTMV (9, 10, 27), such as facial and/or nasal erythema, skin soreness or ulcerations (27). Intentional air leaks are incorporated into the ventilator circuits and necessary for CO_2 removal. Unintentional leaks around the edge of the interface or through the mouth can cause problems of various levels of concern, ranging from eye irritation and dry mouth to an inability to trigger inspiration (27). Other side effects might be dryness of nose, throat or the bronchial tree, epistaxis, ear or sinus pain, gastric insufflation or distension, belching or flatulence, and nausea/vomiting. Sleep-related problems such as late sleep onset and/or sleep disruption (i.e., insomnia) can also occur, sometimes caused by noise from the ventilator (27).

Invasive ventilation is an option when a person has a high degree of ventilator dependency and/or problem with secretion (4, 43). The non-invasive mode is however physiologically more favourable and preferred whenever possible (4, 9). The patients then avoids risks and complications that are associated with a tracheostomy (4).

Organization of the initiating, training and follow-up in LTMV

Major treatment advancements and quality improvements in care from specialist and primary healthcare services have influenced the lives for patients with hypoventilation and CHRF in recent decades in Norway. One example is that of a patient with hypoventilation successfully discharged from the hospital Ullevål, where he had lived his life continuously for 26 years (47). The Norwegian Centre of Excellence in Home Mechanical Ventilation was established in 2003, later renamed the National Advisory Unit for Long Term Mechanical Ventilation (48). The main goal for the centre was to increase or maintain quality of life in LTMV patients (3, 4). Since its beginning, the centre's work has been organized as a decentralized national multi- and

interdisciplinary network, in line with recommendations for the organization of the treatment and care for patients receiving LTMV (49). Dissemination and sharing of knowledge in the field of LTMV are the focus areas for the national network, initially organized by part-time employers from different parts of Norway all having in common the fact that their main employment is within the specialist healthcare service. The unit was reorganized in 2011 into the model that exists today. It includes a central cohort of staff in Bergen and four regional resource groups. The network also includes LTMV user representatives, whose presence is legally anchored in the law on patient and user rights (§3-1), referring to patients' or users' right to participation (50).

A description of the usual routines in Norway for the start and follow-up of LTMV treatment in line with the national guidelines is as follows:

Adaptation and training in the use of the ventilator takes place in the hospital ward, outpatient clinic and, in some cases, patients' home. Lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC)) and arterial blood gases are routinely tested and measured, respectively. In selected cases, the clinicians apply advanced recordings such as transcutaneous CO_2 monitoring, and even more seldom in combination with polysomnography. Downloading the compliance data retrieved from the ventilator's software allows for the ventilator settings to be evaluated and confirmed; furthermore, nurses with specialist expertise perform controls of masks and equipment. A few patients need life-sustaining LTMV 24/7 and about 10% of LTMV patients need an assistant continuously (4). The care needs of patients with LTMV vary greatly with the underlying disease, comorbid conditions and ventilator dependency (4). In 2017, about 62% of the specialized healthcare services in Norway offered home visits to adult LTMV users requiring life-sustaining treatment (37). The municipalities are responsible, both economically and practically, for the daily care of LTMV patients. Healthcare professionals, paraprofessionals and family caregivers perform the care (4).

Respira is an association for LTMV users, connected to the Norwegian National Association for Heart and Lung Diseases. The goal of Respira is to spread knowledge

about LTMV and establish a network of LTMV users to share experiences, as well as to protect the interests of LTMV users and share information about new research in the field of LTMV (51).

1.3 Quality of life

Quality of life is becoming an increasingly used concept in daily life and in research (13). The concept was introduced in the 1950s, as part of the social and cultural criticism of materialism (52). Disciplines such as the social sciences often address objective measures including welfare, life conditions, living arrangements and economic status in their understanding of quality of life (13, 53, 54). Quality of life has been and remains one of the core concepts in nursing (55, 56).

Most commonly, quality of life has been considered as a multidimensional concept, including satisfaction with life and well-being, physical, psychological and social sub dimensions (57-61). A common way to understand overall quality of life is by satisfaction with life, an approach used by the Organization for Economic Cooperation and Development (OECD) (62, 63) and the European Union (EU) (64) and recommended by the Norwegian Health Directorate (65) to derive knowledge of the general population's subjective life satisfaction. This understanding of quality of life has also been present in research on quality of life in patients receiving LTMV (22, 66, 67). Satisfaction with life includes a wide range of a people's experiences and emotions and has been perceived as an overall quality of life term (68). It has also been seen as a degree to which a person positively evaluates her/his overall quality of life (69).

The World Health Organization (WHO) (1995) defines quality of life in terms of individuals' perception of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns (70). It is a broad concept, which includes people's physical health, psychological state, level of independence, social relationships, personal beliefs and

relationships with the environment (70). This definition includes both positive and negative facets of life, is multidimensional and recognizes that quality of life is subjective; further, it concerns people's global evaluations of behaviours, states and capacities, as well as satisfaction versus dissatisfaction, all of which inform quality of life (70).

According to Moons and colleagues (2010), there are some important requirements for quality of life studies. The first criterion is to define the quality of life term used in the study (71). Secondly, researchers are required to state the domains of quality of life that they have assessed. Thirdly, researchers are required to justify the reason(s) for choosing the questionnaire they use. Fourthly, researchers are required to state whether they measure overall quality of life or HRQoL. Therefore, a distinction between overall quality of life and HRQoL should be made clear. The last requirement is that researchers explicitly state the indicators and determinants of quality of life that they have assessed in their research. Researchers have to describe how they have measured quality of life itself , and how they have measured influencing factors (71). Despite many years of research within quality of life a resent systematic review (2019) concluded that researchers still have to pay closer attention to methodological and conceptual clarity of quality of life (72).

Health-related quality of life

To distinguish between quality of life and the requirements of clinical practice and research, the term HRQoL is frequently used (13). The term is used when the purpose is to gain knowledge of issues that are most relevant in a clinical setting, but excludes aspects of quality of life that are not directly related to health, such as politics, religion and culture. The term includes components of the physical state, functional capacities, social relations and psychological well-being (73). However, due to the absence of any agreed definition of HRQoL, most researchers describe what they incorporate in the concept by their choice of instrument. The concept has been developed in order to focus on aspects of a person's subjective experience which relate directly and

indirectly to health, disease, disability and impairment (74), as well as the effectiveness of treatment (54).

HRQoL can address both generic problems and condition- or disease-specific problems (75) and be categorized into generic HRQoL and specific HRQoL (76).

Generic HRQoL is not specific to any disease or health condition; rather, it is used to measure HRQoL in the general healthy population. The advantages of the generic HRQoL approach is that the non-specific character of the concept allows for a broad application and usefulness in terms of comparing HRQoL a different groups of patients and the general population (73, 76). However, this broad understanding of HRQoL can also be a disadvantage because it does not include the specific and important aspects of life among those with CHRF and severe respiratory insufficiency who are receiving LTMV.

Condition-specific HRQoL addresses the specific elements that affect the lives of people with a given condition and is often used to focus on the effect or outcome of a specific condition, disease or treatment (75). The advantages of this approach is it provides more detailed information on how the condition influences HRQoL (76). Thus, this approach is useful when the aim is to examine changes in HRQoL over time (73). Condition-specific HRQoL can provide a measure for evaluating the benefits and the burden of modern medical treatment, while reflecting the most relevant problems associated with a disease or treatment (13). Patients with CHRF usually have breathlessness and symptoms of severe respiratory insufficiency, which affect their daily lives. Therefore, it is important to choose questionnaires for addressing these symptoms (73).

1.4 Questionnaires for patients receiving LTMV

A large number of instruments exists; therefore, researchers need to explain the reasons for choosing to use a particular questionnaire.

Overall quality of life questionnaires

Overall quality of life measures offer advantages due to their ability to capture core aspects of quality of life. However, in our opinion, they are not sufficiently sensitive and responsive to identify specific aspects of the lives of people who are dependent on LTMV.

One example of such a questionnaires is the Satisfaction with Life Scale (SWLS), which was developed to measure global life satisfaction (77). This scale has been used to measure life satisfaction in individuals with Duchene muscular dystrophy (DMD) who are treated with LTMV (66, 78).

Satisfaction with life may also be measured by one single item such as, "How would you rate your overall quality of life?", which has shown to be a valid and reliable measure compared to scores from multidimensional questionnaires (13, 79), for example, the Cantril Ladder. Another kind of measure of quality of life is based on the WHO's definition (80) and has been used to measure the impact of mechanical ventilation on quality of life after discharge from the intensive care unit (ICU) (81) and in COPD patients (82), as well as the effects of lung function reduction on quality of life (83). We were not able to identify whether this has been used with people receiving LTMV.

HRQoL questionnaires

HRQoL questionnaires mainly consist of two categories of questionnaire, the generic questionnaire and the condition-specific questionnaire.

Generic HRQoL questionnaires

The advantage of generic questionnaires is that they focus on wide aspects of HRQoL; thus, they are suitable to compare HRQoL between disease groups and the general population (13). Some of the generic HRQoL questionnaires reference values appropriate to the general population (13, 73). This applies to SF-36, which was

developed from the medical outcome study, based on the WHO's definition of health (84, 85). The concept of health was defined by the WHO (1947) as not only absence of disease and infirmity, but also one state of complete physical, mental and social well-being (86). This concept of health is similar albeit narrower than the definition of quality of life from the WHO, as it lacks the specific aspects of culture and value systems included in it. This is a multidimensional questionnaire which has been referred to as a health measure, a quality of life measure and a generic HRQoL measure (87). By adding the subjective personal judgement of health, it is common to use the SF-36 as a measure of HRQoL. It has been widely used among patients receiving LTMV (6, 21, 46, 87-92) and shown to differentiate between the underlying diseases leading to CHRF (93). However, the non-specific nature of the generic HRQoL questionnaire might lead to insufficient sensitivity and responsiveness in relation to the specific problems and symptoms among patients with CHRF who are receiving LTMV (10).

Condition- and disease-specific HRQoL questionnaires

Condition- and disease-specific questionnaires have been developed for a large number of different conditions and diagnoses (76). The main advantages of using condition- or disease-specific HRQoL instruments is that they are more likely to be responsive to the detection of sometimes small, but clinically significant, changes in specific HRQoL.

The SRI questionnaire is a condition-specific HRQoL instrument developed by Windisch and colleagues (2003) in the German language. The development process is well documented and involved pulmonologists specialized in LTMV, psychologists specialized in quality of life and open interviews with patients receiving LTMV about subjective descriptions of their daily lives (14). The SRI, which was initially developed to assess HRQoL in patients with chronic respiratory failure, due to various underlying diseases, who are receiving LTMV, was validated by a survey including patients with NMD, COPD, OHS and CWD, such as idiopathic kyphoscoliosis and post-tuberculosis sequelae. Patients' view on those aspects that are important to their

HRQoL determined a significant part of the content of the SRI questionnaire; thus, it was derived directly by involving the target group for the questionnaire. The items were then incorporated into physical, social and psychological health domains. Physical health included impairments in terms of physical functioning and capability due to breathlessness and severe respiratory problems. Items asking about well-being and anxieties covered the psychological domain of HRQoL. Items related to "anxiety" were specifically related to respiratory problems such as "fear of breathlessness". Items concerning limitations in social relationships and activities due to respiratory symptoms reflected social aspects of HRQoL. The first version of the SRI questionnaire included 80 items. Thereafter, items were excluded if they were similar to remaining items or did not meet the criterion of a minimal item-scale correlation of 0.30. After this item evaluation, 49 items passed the selection process (14). The minimal clinically important difference of the SRI questionnaire ranged from five and seven points in patients with severe but stable COPD (94). The use of the SRI questionnaire has expanded widely since 2008 and, according to the European Respiratory Society's handbook for non-invasive ventilation (2015), both this and the MRF-28 questionnaires provide the backbone for research on HRQoL in patients treated with LTMV (17).

Other questionnaires used for patients receiving LTMV

The MRF-28 was primarily developed for use in patients with respiratory failure secondary to pulmonary disease or CWD. The conception included 152 identified items from several different questionnaires, 28 of which items correlated with patients' perceptions of overall health. Three specific factors were identified: daily activities, cognitive function and invalidity. Despite the fact that MRF-28 has been used in some studies to measure quality of life in patients treated with LTMV (95, 96), this questionnaire does not apply a multidimensional approach which ought to be included in a specific HRQoL questionnaire.

The Chronic Respiratory Disease (CRQ) questionnaire has been used in several studies among patients treated with LTMV (95, 97, 98). It contains four aspects of patients' lives: dyspnoea, fatigue, emotional function, and mastery, however, as it does not include physical function, it does not apply a multidimensional approach to the measurement of quality of life.

The SGRQ, which was developed to measure health status among those with chronic airflow limitation (99), has been used in studies involving COPD patients treated with LTMV (89, 100). It is mainly a measure of symptoms caused by the disease and includes questions concerning to what degree these symptoms affect the daily activities of patients.

Thus, as these questionnaires (MFR28, CRQ and SGRQ) lack important aspects of quality of life measures, we consider the SRI questionnaire to be the most appropriate instrument for studying specific HRQoL in patients receiving LTMV.

Psychometric testing of a questionnaire

The psychometric testing of a questionnaire includes examining evidence for reliability, validity, sensitivity and responsiveness (101). It consists of a number of stages, where the tester is trying to gather evidence that the instrument produces useful measurements according to the intended purpose of the questionnaire (13). The selected test group should be as representative as possible in relation to the target population.

The reliability refers to the accuracy of information obtained in a study and to what extent the measurement is free from measurement error (101). The internal consistency of a questionnaire is a statistical expression of the degree to which the different questions measure parts of the same. The most common statistical method for measuring internal consistency is Cronbach's alpha. The range of values is from 0 to 1, with coefficients above 0.70 generally regarded as acceptable (102). Internal consistency uses item correlation to assess the homogeneity of multi-item scales.

Validation of an instrument is a process for determining whether it measures what is intended (102). Validity includes three main aspects: content validity, criterion validity and construct validity (13). Construct validity is the most important condition that must be fulfilled in the validation process. It firstly involves creating a hypothetical model before describing the constructs being assessed and postulating their relationship.

Sensitivity is the ability to identify differences between groups, which is one of the most important characteristics of a condition- and disease-specific questionnaire (13); for example, the SRI questionnaire discriminates between the different underlying diagnoses among LTMV patients (14). Responsiveness is related to sensitivity and refers to the ability of a measurement to detect changes as well as to the validity of a changed score (101); for example, the responsiveness of the SRI questionnaire in the detection of changes in HRQoL after commencement of non-invasive LTMV was better than that of the generic questionnaire, SF-36 (10).

Translations, cultural adaptations and validations of the SRI questionnaire have been produced in the most commonly used languages worldwide, including Chinese (103), Spanish (104), English (105), Portuguese (106) and Japanese (107). The SRI questionnaire has also been translated and transculturally adapted into French (108) and Turkish (109), but there have been no validation studies in these languages. The psychometric quality of the specific SRI questionnaire has been well documented in several studies (10, 14-17, 73, 110). A validation study re-examined the internal structure of SRI specifically for COPD patients (111). According to the study, the psychometric condition was better in the case of SRI, compared to the MRF-28 and Clinical COPD questionnaires, as well as the CRQ, in a study of patients with severe COPD who were being treated with non-invasive LTMV (15). The SRI questionnaire addresses some of the shortcomings in the generic and other questionnaires and seems to be a more sensitive HRQoL questionnaire for people treated with LTMV (110). Further, SRI shows the best performance in terms of predicting mortality among patients receiving LTMV, compared to other HRQoL questionnaires (16).

1.5 Previous research

For the present review, we mainly included studies measuring HRQoL using the SRI questionnaire. However, as only a few follow-up studies using the questionnaire have been performed, we also included studies on HRQoL using other questionnaires in the literature review. Survival and mortality have been the primary outcome in some randomized controlled trials (RCTs) (6, 19, 20, 89, 96, 112). We carried out a literature search for this thesis prior to the study in 2008 and several systematic literature searches were subsequently performed with the assistance of library staff from the University of Bergen. The latest literature search was performed in May 2019.

HRQoL among patients receiving LTMV

HRQoL among patients receiving LTMV measured by RCT

The results from RCTs involving patients with COPD and CHRF receiving non-invasive LTMV have shown a trend of improved HRQoL (19) as well as improved HRQoL (18, 20). Importantly, the patients in these RCTs also received LTMV in the ventilator mode, which includes a higher ventilator inspiratory pressure also known as a "high-intensity mode" (18, 20). Another RCT compared rehabilitation alone versus non-invasive LTMV in addition to rehabilitation among patients with COPD (95). In this study, the SRI questionnaire identified improved HRQoL in COPD patients who were receiving non-invasive LTMV in addition to rehabilitation (95).

McEvoy and colleagues (2009) found differences in HRQOL, as measured by SF-36, in patients receiving LTMV and a control group, with the patients in the intervention group reporting impaired HRQoL (106). In the RCT by Kohnlein and colleagues (2014), the SRI summary scale score improved significantly after one year in favour of the intervention group, which was receiving highly intensive LTMV. Changes in SF-

36 scores did not differ significantly between the intervention group and the control group, apart from the general health subscale of SF-36. The RCT by Murphy and colleagues (2017) measured HRQoL using the SRI questionnaire. After six weeks, the patients receiving both LTMV and long-term oxygen treatment (LTOT) reported significantly better HRQoL when measured by SRI, compared to those receiving LTOT only.

Burke and colleagues (2006) performed one of the few RCTs which has compared non-invasive LTMV with no LTMV treatment among patients with NMD. After one year, the patients with good bulbar function (swallow and speech function) reported significant improvements in HRQoL, as measured by the SF-36 subscales, mental health, energy vitality and general health. The ALS subgroup with severe bulbar function reported no significant HRQoL, as measured by SF-36.

Masa and colleagues (2015) compared the efficacy of different treatment alternatives for patients with OHS without obstructive sleep apnoea (OSA). After two months, there was significant improvement in the SF-36 mental health sum scale in the group that received non-invasive LTMV in addition to lifestyle modification compared to the group comprising patients who received lifestyle modification (113).

Follow-up studies

A one-year follow-up study of HRQoL, as measured by SRI, showed significant improvement across all SRI subscales, except for physical functioning, among patients with NMD and OHS who were receiving non-invasive LTMV. Significant improvements were found across all the SRI subscales except for the social relationship subscale (10). The highest improvement was in the attendant symptoms and sleep subscales in patients with NMD and OHS. The patients with NMD reported being less susceptible to sleep disturbances after starting with LTMV, as the attendant symptoms and sleep domain increased from 46 out of 100 prior to the initiation of non-invasive LTMV to 70 out of 100 one year after receiving LTMV. The patients with OHS reported that the attendant symptoms and sleep domain increased from 36 prior to the initiation of non-invasive LTMV to 67 one year after initiating LTMV.

NMD patients reported significant less anxiety after starting non-invasive LTMV, as the SRI anxiety subscale increased from 44 to 57 after one year of receiving non-invasive LTMV. Patients with COPD reported significant improvements in their respiratory complaints subscale from 38 to 56 one year after initiating LTMV (10). Patients with restrictive thoracic diseases reported significant improvement in physical functioning as this domain increased from 38 to 51 one year after initiating non-invasive LTMV (10).

A two-years follow-up study using the SF-36 questionnaire identified improved HRQoL among patients with COPD, OHS and RTD, but not in patients with NMD, where 10 of 11 patients had ALS (21). The deterioration in HRQoL is possible explained by the progressive nature of the ALS course.

Potential predictors of change in HRQoL among patients receiving LTMV

Disease-dependent differences in SRI subscales have been identified (114), and disease-dependent improvements in HRQoL were found in single subscales of the SRI questionnaire (10). In studies among patients treated with LTMV, older age has been associated with impaired HRQoL, when measured by the SF 36 (108) and SRI (147) questionnaires. The total hours per day of receiving LTMV was a significant independent predictor of the improvement in HRQoL, when measured by the SF-36, in patients with OHS, COPD and RTD (21).

A cohort measured HRQoL in difficult-to-wean patients, with and without a ventilator, after discharge from the ICU (115). SRI showed lower HRQoL in ventilator-dependent versus weaned patients, with lower SRI scores for physical functioning and feelings of fear, but with similar scores in social functioning, relations and mental health. Conversely, SF-36 scores in the physical domains and mental health showed no different between patients with a ventilator or who were weaned at discharge from the ICU (115).

Concerning synchrony between the patient and the ventilator, patients ranked highest the “smoothness” or “natural feeling” of breathing, being able to fall asleep and the comfort of the mask (29). The SRI questionnaire was used to evaluate the impact of ventilator modality, such as by comparing average volume assured pressure support (AVAPS) versus pressure support (PS). No influence on HRQoL was found in patients with OHS (116, 117); nor did patients report differences in HRQoL, when measured by SRI, after adding a high back-up rate in addition to high ventilator pressure in COPD patients receiving LTMV (118). Ventilator modality did not influence HRQoL when measured by SRI (118). A recent systematic review concluded that different positive airway pressure modalities appear to be equally effective in improving HRQoL outcomes in patients with OHS (119).

Lower lung function measures, including an obstructive pattern from the FEV_1/FVC ratio (114), are independently predicting lower SRI scores in patients receiving LTMV (120). Whether nasal or face masks were used or additional long-term oxygen therapy was applied, no influence was found in the SRI sum scores in patients treated non-invasively (121).

Mortality in patients treated with LTMV

In the work on Norwegian guidelines for LTMV, the Norwegian Institute of Public Health ordered three systematic reviews of the effect of LTMV (122-124). The primary outcomes in these reviews were life prolongation, quality of life, hospitalization and sleep.

The conclusion from these systematic reviews is that LTMV may be associated with improved survival in CWD and DMD patients, as well as in ALS patients with good bulbar function (122, 125). Mortality did not seem to differ between DMD patients who were invasively and non-invasively ventilated (124). The Norwegian systematic reviews did not find any benefit in terms of the survival of COPD patients treated with non-invasive LTMV (123). A systematic review and meta analyses involving stable

and recently hospitalized COPD patients could not prove any reduction in mortality in the case of domiciliary non-invasive LTMV, compared to usual care alone (126). However, there is too little evidence to draw any conclusions on the potential survival benefits of high-pressure non-invasive LTMV settings (126) Among patients with OHS, no controlled studies of the effect of LTMV on mortality were identified (122).

In a RCT performed by Bourke and colleagues (2006), 13 out of 22 patients (59%) with ALS died in the group that received non-invasive LTMV, compared to 16 out of 19 patients (84%) in the group receiving standard care without LTMV during one year of follow-up or until death (6). For the total study sample, the median survival for the LTMV group participants was 48 days longer than the standard care group participants (219 days versus 171 days) (127). In patients with normal or moderately impaired bulbar function, there was a significant improvement: 205 days' longer survival compared to the standard care group (127). In ALS participants with poor bulbar function, LTMV did not confer survival advantage (6, 127). An Australian cohort study reported significantly increased survival among ALS patients with bulbar onset disease who were treated with non-invasive LTMV, compared to ALS patients with bulbar onset who were not receiving LTMV (128). Among Norwegian ALS patients treated with invasive LTMV, the median survival was 74.8 months and, in patients treated with non-invasive LTMV, it was 15.4 months (129).

Without LTMV, the survival among young patients with DMD is very poor: patients with FVC<1 l had a five-year mortality rate at 92% (130). In a retrospective cohort, an analysis of 835 patients with DMD found that the mean age for respiratory deaths among those without LTMV was 17.7 years, while the mean age for those treated with LTMV increased to 27.9 years (131).

Several RCTs have examined non-invasive LTMV as an intervention to address mortality in COPD patients (19, 20, 89, 96, 112, 132). LTMV provided no survival benefit compared to standard care in patients with prolonged hypercapnia after acute respiratory failure (96, 132). Conversely, McEvoy and colleagues (2009) found significantly improved one-year mortality in COPD patients who received both LTMV

and LTOT, compared to those receiving LTOT only. Importantly, the surviving patients reported impaired HRQoL (89). In a group of COPD patients with hypercapnia in their habitual phase, 12 out of 102 (12%) died among those randomized to high-intensity LTMV after one year, compared to 31 out of 93 (33%) in the ordinary care group (112). In COPD patients with hypercapnia which persisted two weeks or more after treatment for acute respiratory failure, 16 out of 36 patient (44%) died in the high-intensity-plus-LTOT group, compared to 19 out of 28 (68%) in those treated with LTOT only (20). Based on these RCTs, Duiverman (2018) stated that non-invasive LTMV is a cost-effective treatment for COPD patients, as only five COPD patients with CHRF need to be treated with non-invasive LTMV to avoid one death (133).

An uncontrolled four-year follow-up study in patients with OHS, found that three out of 54 patients (5.5%) died in the group treated with non-invasive LTMV, while seven out of 15 patients (46%) died among those who did not want to continue LTMV treatment (7). No significant differences in age, body mass index (BMI) and baseline blood gases were found between the two groups, but more women and higher rates of psychiatric problems were found in those who refused LTMV (7). Survival in the CWD category has been reported two cohort studies (134, 135), based on the Swedish LTMV Register. Among patients with kyphoscoliosis, 32% died in the group treated with LTMV, compared to 76% in the group treated with LTOT (134). In a 10-year cohort of patients with CWD caused by tuberculosis sequelae, 60% died in the LTMV group compared to 87% in the LTOT-only group (135).

Potential predictors for mortality in LTMV patients

A variety of factors has been examined as predictors of death in LTMV patients other than the underlying cause of disease (31, 67, 121, 136-138), such as socio-demographic variables, comorbidities (including body weight and nutrition), lung function and blood gases, ventilator treatment settings and interface strategies, treatment commencement in an elective or acute setting, and ways of organizing the

follow-up. Finally, a few studies have reported on the association between HRQoL and mortality in LTMV patients.

Older age (24, 128, 137, 139) is associated with mortality. Sex might have an influence on mortality among LTMV patients as men with ALS had a 46% greater mortality rate than women (140) and DMD affect almost exclusively men (141). Even if women had a more severe condition when OHS was diagnosed; no gender difference in survival rates was found in OHS treated with LTMV (142). Socio-economic status such as the level of education has been shown to be associated with mortality in patients with chronic disease (143). Married patients experienced longer survival after initiation of non-invasive LTMV than non-married patients (144).

Comorbidity has been identified as a predicting factor for mortality in LTMV patients with NMD (136), COPD (145) and CWD (146), while cardiovascular comorbidities remained the only factor independently associated with a higher risk of death in patients with OHS (136, 147).

Higher BMI has been associated with mortality in LTMV patients (121, 148). However, no association between baseline BMI and mortality in patients with OHS treated with LTMV was identified (149). In addition, obesity was a good prognostic factor for COPD patients using non-invasive LTMV (150). Good enteral nutrition was associated with longer survival in the case of ALS patients (151) and of DMD patients treated with LTMV (131).

Low FVC has been associated with mortality in LTMV patients with OHS (152) and in a population with mixed diagnoses treated with LTMV or LTOT (138). However, another study found no difference in baseline spirometry values between survivors and deceased (67). $PaCO_2$ assessed by arterial blood gases is the most important monitoring parameter for patients treated with LTMV (17), with a decreasing level of $PaCO_2$ having been suggested as an explanation of improved survival in COPD patients (20, 112). However, improvement in $PaCO_2$ did not seem to be associated with an improved survival in COPD patients treated with non-invasive LTMV (153).

The ventilation strategy, “high-intensity” LTMV, which is a combination of higher IPAP and back-up rate, with the aim of decreasing $PaCO_2$, can explain the reduced mortality in COPD patients with CHRF who are treated with non-invasive LTMV (20, 112, 149). However, a marked reduction in cardiac output in “high-intensity” ventilation mode has been reported (154). However, this study used very high IPAP (mean IPAP of 28 cmH_2O), while cardiac output was measured over a short period but clinical relevance was not investigated (154). Another study where the patients received non-invasive LTMV for a longer period found no change in cardiac output or clinical cardiac outcomes. However, both of these two studies had a small sample (133). New studies to better understand the pathophysiological changes occurring in patients using “high-intensity” LTMV are needed (155).

The influence of invasive versus non-invasive LTMV has revealed some contradictory results. Longer survival was reported in cohort studies involving patients with DMD using non-invasive LTMV and mechanically assisted coughing, compared to DMD patients receiving LTMV via a tracheostomy (156, 157). Conversely, the risk of death among patients with DMD was not associated with the use of invasive versus non-invasive LTMV in a 12-year prospective cohort study (158).

Follow-up by a multidisciplinary ALS team was associated with mortality (144), while the size of the treatment centre or regional treatment prevalence did not influence mortality in LTMV patients (137). Starting LTMV in an acute setting was also found to be a negative predictor of survival (137). The proportion of elective commencement of LTMV in Norway has increased in recent last years (it was 77% in NMD patients in 2017) (37).

Another aspect is that life expectancy at birth in Norway has improved by two years since 2005 (it was 82.4 years in 2015), and has remained two years higher compared to the average in other OECD countries (63).

HRQoL measured by SRI has been associated with mortality in LTMV patients (121, 148). In the study by Budweiser and colleagues (2007), the SRI scores was associated with mortality in all patients except for those with COPD (121). The study from Oga

and colleagues (2017) found that SRI scores was associated with mortality in LTMV patients with COPD or pulmonary tuberculosis sequelae (148). The associations between HRQoL measured by SRI and mortality were investigated for up to three years (121, 148). Other health measures have also shown to predict mortality in LTMV patients with COPD (24) and with NMD and CWD (67). However, the SRI scores showed the most significant predicting ability for mortality in patients receiving LTMV in comparison to other health status measures (16).

1.6 Gaps in knowledge: a summary

As described above, there is highly limited knowledge on the relation between HRQoL and living with LTMV from a lifelong perspective. The treatment is both time- and cost-consuming and can causes side effects. Therefore, it is important to address whether or not acceptable condition-specific HRQoL follows the prolongation of life gained by LTMV. If LTMV increases burdens without maintaining or increasing HRQoL, this would be an ethical concern (73). Quality of life and survival have shown consistent trends in terms of improvement after initiating LTMV in studies covering a period of up to one or two years, but an essential question is for how long does this trend continue?

Previously, there has been no specific HRQoL questionnaire sensitive enough for patients with severe respiratory insufficiency validated for use in Norwegian LTMV patients. In earlier research, a huge number of different questionnaires was used, but they were not sufficiently sensitive and responsive to address the specific challenges of living with LTMV, influence on HRQoL. The SRI questionnaire is a specific HRQoL instrument developed by and for patients treated with LTMV and has shown good psychometric qualities. No study worldwide has examined long-term HRQoL in people receiving LTMV by using an instrument that is specific to such a population. Knowledge is also lacking on factors associated with changes in HRQoL among these

patients, especially the importance of factors that healthcare professionals can influence directly.

The SRI questionnaire predicts mortality in LTMV patients; however, these studies have only lasted up to three years and reported contradictory results concerning in which group of LTMV patients the association exists.

2. AIMS OF THE THESIS

With quality of life as a conceptual framework, this thesis aimed to provide new knowledge about the SRI questionnaire as a HRQoL instrument in patients receiving LTMV.

We addressed all research questions in three papers using data from self-administered questionnaires and register-based data from Western Norway.

Paper I addressed the following research questions:

(i) Is the reliability and the validity of the Norwegian version of the SRI questionnaire sufficient for use in HRQoL research and clinical practice among Norwegian patients receiving LTMV?
(ii) Does the Norwegian version of the SRI questionnaire differentiate between generally accepted differences between patients receiving LTMV?

Paper II addressed the following research questions:

(i) Does HRQoL change for people receiving LTMV from baseline in 2008 to 2014 according to the SRI subscales and sum score?
(ii) Do socio-demographic, clinical or patient-reported variables explain changes in HRQoL in people receiving LTMV?

Paper III addressed the following research questions:

(i) How is the association between HRQoL measured by the SRI questionnaire at baseline and all-cause mortality in people receiving LTMV over 80 months of follow-up?
(ii) How was mortality in patients treated with LTMV from 2008 to 2014?

3. MATERIAL AND METHODS

3.1 Study populations (Papers I to III)

In this section, I will describe the main study population and how we recruited patients with regard to the papers in this thesis.

LTMV Register

The Norwegian LTMV Register was the basis for patient recruitment to this study. The register was established in 2002 and is currently funded and managed by the Western Norway Regional Health Authority. The register is based on information from all 31 Norwegian hospitals which initiate LTMV treatment (39). In 2012, the register was approved by the Ministry of Health and Care Services as a national medical quality register (39).

One of the main purposes of the register is to provide new knowledge on LTMV treatment through research. Additionally, it collects healthcare activity data to document the need for resources and measure changes in the specialist and municipal health service. Finally, the register provides information on geographical equalities and differences in the national healthcare of LTMV patients (39).

In 2013, the register received approval from the Data Inspectorate for linkage to the following national registers in Norway: the Norwegian Patient Register (NPR), the Cause of Death Register, the Prescription Register, the Medical Birth Register of Norway, the Cancer Register, and tax information from Statistics Norway (SSB). Further, patient-reported outcomes measurement (PROM) data were included from 2014 onwards in connection with the established electronic register version. All patients must sign a consent form before registration (39).

The LTMV Register includes patients with CHRF with a wide variety of causes who are permanently dependent on LTMV for more than four hours a day. Ventilation

modes include BiPAP with a back-up respiratory rate or pressure and/or volume-controlled ventilators. Ventilator connections between patient and ventilator are non-invasive, including masks, nozzles or mouthpieces, or invasive via a tracheostomy (39).

Exclusion criteria in the LTMV Register includes obstructive sleep apnoea syndrome (OSAS) and complex sleep disturbance among patients with CPAP, BiPAP or an adaptive servo ventilator (39) , but includes patients with OSAS as part of OHS treated with BiPaP. At the baseline period for this thesis, 1149 adults was enrolled on the register from all over the country, and 30 different diagnoses were reported as the underlying condition for LTMV (4, 36).

Recruitment and inclusion criteria

We contacted patients on the register from the counties of Rogaland, Hordaland and Sogn og Fjordane by post in March 2008 with study information and an invitation to participate, as well as indicating that data would be stored for 10 years for a possible follow-up study. Due to practical feasibility, we did not include patients from other parts of Norway. The study inclusion criteria were: patients with well-adapted LTMV treatment for at least three months, in a clinically stable state, above 18 years, and cognitively able to answer study questions themselves or with help from family members. Of the initial 211 patients on the LTMV Register in Rogaland, Hordaland and Sogn og Fjordane, 18 patients did not meet the inclusion criteria (Figure 1). Of the remaining 193 eligible patients, 127 (66%) attended the study by returning the completed questionnaire by mail.

Prior to the follow-up after six years in 2014, the Cause of Death Register was contacted to collect information on those who were diseased in the study sample from 2008. We contacted the surviving patients by post and requested them to participate in a new data collection round for the follow-up study. The patients provided written consent to participate in the follow-up study.

3.2 Health-related quality of life (Papers I to III)

We used specific HRQoL, both as exposure and as outcome, in this thesis (see Table 1). SRI measured specific HRQoL while SF-36 measured generic HRQoL by using self-administered questionnaires. The SF-36 questionnaire was included in Paper I for the validation of the Norwegian version of the SRI questionnaire. We sent questionnaires to participants by post in March 2008. Patients still alive were asked to fill in the same questionnaires once more in 2014 during their regular contact with the Outpatient Clinic at either Haukeland University Hospital or Stavanger University Hospital.
Papers I and II used the SRI data as the outcome, whereas Paper III used SRI data as the exposure.

SRI (Papers I to III)

The SRI questionnaire is a specific HRQoL instrument for people receiving LTMV (14). It includes 49 items and seven subscales. Each item belongs to only one of seven subscales; respiratory complaints (eight items), physical functioning (six items), attendant symptoms and sleep (seven items), social relationships (six items), social functioning (eight items), anxiety (five items) and psychological well-being (nine items)**.** The order of the items is not categorized in the seven divided subscales; but is in arbitrary order. The items refer to patients' HRQoL in the previous week. The answer options are graded using a five point Likert scale from "strongly agree" to "strongly disagree". The items are recoded and transformed, such that high values refer to high HRQL on the SRI subscales and in the sum score (14). The scale from 0 to 100 is similar to the scale of SF-36 and the mean values of each of the seven subscales are calculated if at least half of the items are answered. The order of the items is randomized, which also strengthens the internal validity. The SRI summary scale is the mean value of each subscale, which is not calculated if one of the subscales is missing

(159, 160). The SRI questionnaire has one summary scale in contrast to SF-36, which contains both physical and mental health component scales. One explanation for this is that all items on the SRI questionnaire have the same attribution concerning the cause of the limitation in social, psychological and physical health (14).

We contacted the author of the SRI questionnaire in order to obtain approval to use the questionnaire and to acquire access to procedures for recoding and calculating the SRI scores.

SF-36 (Paper I)

SF-36 is one of the most-used generic HRQoL questionnaire. It includes 36 items, measuring physical functioning (10 items), physical roles (four items), emotional role limitations (four items), bodily pain (two items), mental health (five items), social functioning (two items), general health (five items) and vitality (four items). The scores in each domain are transformed into a scale from 0 to 100 where higher scores indicate better HRQoL (161). SF-36 has been translated into many language including Norwegian (162). Without increasing the number of items, SF-36 version 2 has been evaluated, with the new version offering better reliability and validity (85). The new version also has identical items to those of the original SF-36, but the response scales have been extended with a wider range of response options which increase score precision and maintain comparability with the original version of SF-36 (161). SF-36 was used as a validation questionnaire for the criterion validity in the validation study of the SRI questionnaire in the German language (14). As part of the psychometric testing of the Norwegian version of the SRI questionnaire, SF-36 version 2 was included in this study. The use of SF-36 version 2 requires a licence, which this study obtained from Quality Metric.

Table 1 An overview of the studies

Paper	Design	Sample	Data collection	Analyses	Main outcome measures
I	Cross-sectional	LTMV treated individuals from Hordaland, Rogaland and Sogn og Fjordane (n=127)	Norwegian LTMV Register SRI questionnaire SF-36 questionnaire Other patient reported variables	T-test and chi-square test Cronbach's alpha Spearman's correlation coefficient ANOVA	Correlation between HRQoL measured by SRI and SF-36 SRI scores at baseline in 2008
II	Longitudinal	LTMV-treated individuals surviving and participating in the study in 2008 and 2014 (n=60)	Norwegian LTMV Register SRI questionnaire Other patient reported variables	Linear mixed-effects model Likelihood ratio test	Change in HRQoL, as measured by SRI, from 2008 to 2014 Factors of change in SRI scores
III	Prospective cohort	LTMV-treated individuals giving consent to link data to other registries (n=112)	Norwegian LTMV Register Norwegian Patient Register Norwegian Cause of Death Register SRI questionnaire Other patient reported variables	Two-sample t-test Kaplan-Meier survivor function with the log-rank test Cox regression analyses	Associations between SRI scores and mortality estimated by HR All-cause mortality from 2008 to August 31 2014

Abbreviations: LTMV, long-term mechanical ventilation; SRI, severe respiratory insufficiency; SF-36, Short Form-36; ANOVA, Analysis of variance; HR, hazard ratio.

3.3 Mortality (Paper III)

The Norwegian Cause of Death Register contains data on all deaths among Norwegian residents in Norway and abroad (163), and the purpose of the register is to monitor causes of death and elucidate changes in these causes over time, as well as provide a basis for preparation of statistics, research, planning and quality assurance (164). A

standardized death certificate for each individual death is required, provided by medical doctors (163). The structure of the death certificate is based on principles established by the WHO, and the Cause of Death Register has used the (International Classification of Diseases and Related Health Problems (ICD) (163) coding system since 1951. The register uses the IRIS software (165) with the Automated Classification of Medical Entities (ACME) module for coding (166), while input to this module is the ICD-10 for identifying the underlying cause of death (167). The Norwegian Cause of Death Register provided information on mortality in the cohort study. Information on mortality and cause of death was collected between 2008 until 31 August 2014 (up to 80 months).

3.4 Study design and sample selection criteria

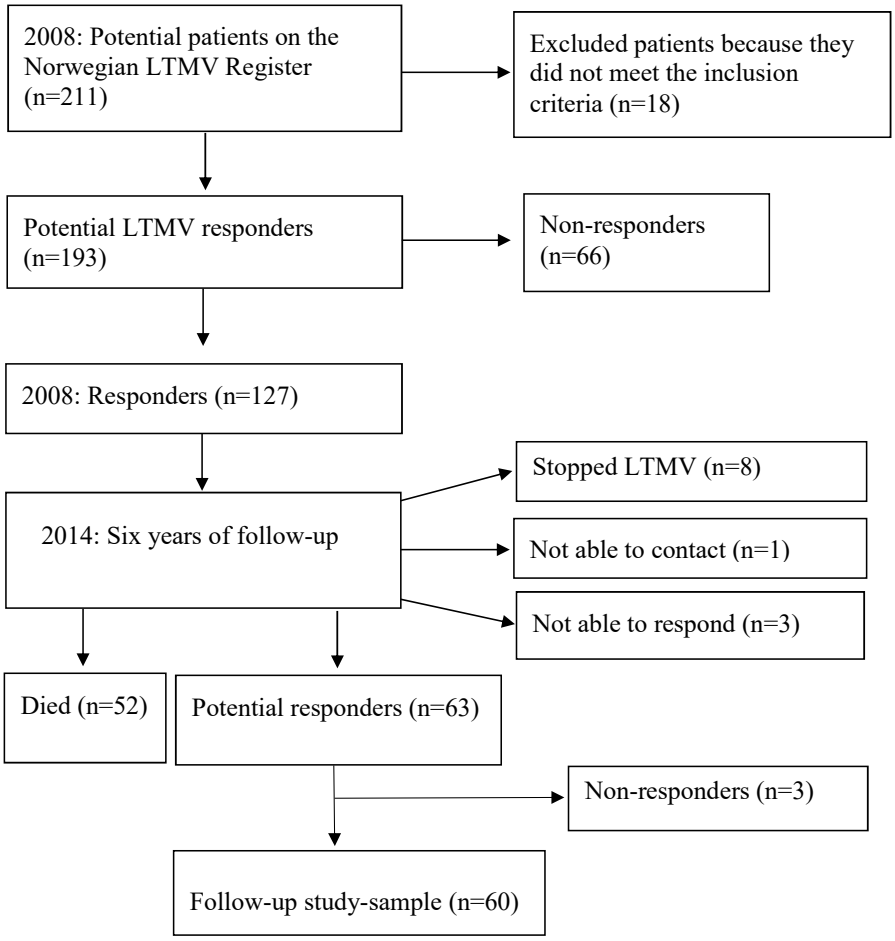
Paper I: This was a cross-sectional study including 127 patients, defined by the number of patients on the LTMV Register from three counties of Western Norway in 2008. As the diagnosis, obstructive sleep apnoea, was an exclusion criterion on the LTMV Register, four patients with this diagnosis should not have been included on it and were thus removed from the register after the invitation to participate in the study was sent (n=4). Nine people had stopped LTMV treatment (n=9). According to their family, two of the patients were unable to answer the questionnaires (n=2). Further two people moved from the region and we were not able to locate them (n=2). In addition, one patient died during the week that the postal invitation to participate was sent (n=1). Thus, the number of potential patients receiving LTMV who could respond was 193. Out of these, 127 patients (66%) consented to participate and returned the questionnaires.

Paper II: This was a longitudinal study including 60 of patients at baseline (2008) and who were still alive at end of follow-up (2014), still treated with LTMV and able to answer the questionnaire after six years of ongoing LTMV. Of the 127 patients treated with LTMV in 2008, 75 patients were alive in 2014. However, 15 patients were not

included because they stopped using LTMV (n=8); dementia or unable to answer the questionnaire according to relatives or nurses (n=3); unable to make contact (n=1) or they did not want to participate in the follow-up study (n=3). Among the reasons given to stop LTMV treatment were problems with adapting to LTMV, problems with falling asleep, side effects, and no need for LTMV due to weight reduction surgery. These excluded patients were related to the NMD (n=6), COPD (n=2), OHS (n=6) and CWD (n=1) disease groups, leaving a final study sample of 60 patients.

Paper III: This was a prospective cohort study including 112 patients. During the follow-up from 2008 to 2014 (80 months), 52 patients died. We obtained written consent from the patients to perform individual data linkage between the study sample and the NPR. The Regional Committee for Medical and Health Research Ethics gave exemptions from the consent requirement for patients who died during the follow-up period. The sample size reflects the number of patients who gave written consent to data linkage with the NPR. Initially, for this paper, we wanted to include the same 127 patients from Paper I. We, however, did not obtain written consent from 15 of the patients because they had stopped using LTMV (n=8); had dementia or unable to answer the question (n=3); unable to make contact (n=1); or did not want to respond (n=3).

Figure 1 Flow chart: study population (Papers I-III)



3.5 Other variables (Papers I to III)

We also collected data on marital status, education level, hours per day on LTMV, dependency on daily assistance with LTMV treatment, side effects of LTMV treatment, satisfaction with training in the use of ventilators and BIPAP, satisfaction with follow-up from healthcare professionals, and need for assistance to fill out the questionnaires. The variables were used in each paper for various purposes.

In Paper I, the above-mentioned variables were used for description purposes and to investigate whether the study population was similar to non-attendants. In Paper II, the variables were studied as risk factors for changes in SRI. In Paper III, we evaluated these variables as potential confounding factors in the relation between SRI and mortality. The variables were selected based on previous literature, as well as advice from experienced clinicians and members from the LTMV user organization Respira.

Data collected from the LMTV register concerned the following: age, sex, main diagnosis, date of starting LTMV, main ventilator mode and interface, additional treatment (LTOT and humidification), respiratory variables before treatment commencement and at baseline (FVC, FEV_1, PO_2, pCO_2), and BMI.

Comorbidity data were collected from the NPR (168). This register contains health information about all people who have received treatment or who are waiting for treatment in the specialist health service in Norway (168). We measured comorbidity by the total number of somatic ICD-10 diagnoses registered during hospital stays or outpatient visits for all patients during the recruitment period in 2008, when these patients answered the baseline specific HRQoL questionnaire.

3.6 Statistical analyses

In this section, I will provide a brief description of how we derived the SRI sum score and the corresponding subscale scores. I will also summarize the statistical methods used in each paper of the thesis. All statistical analyses were carried out using

Statistical Package for the Social Sciences version 18 and 20 (SPSS Inc., Chicago, IL, USA) or Stata SE version 14 (StataCorp LP, College Station, TX, USA) for Windows.

The items in the SRI questionnaire were analysed according to the guidelines(14, 160) including recoding of the following items: 1, 2, 4, 5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 19, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 34, 35, 38, 39, 40, 42, 43, 45, 46, 47 and 48.

The mean values of the SRI subscales were calculated if at least 50% of the items were answered. The process of transformation produces a score between 0 and 100 with higher values indicating a better HRQoL according to the content of the scale. The sum score was calculated by the mean of the values for the subscales (SRI-RC, SRI-PF, SRI-AS, SRI-SR, SRI-AX, SRI-WB, SRI-SF). The SRI sum score for an individual was not calculated if one of the subscales was missing.

SF-36 version 2 was scored according the User's Manual for the SF-36v2® Health Survey and Scoring Software 2.0 (161, 169). Missing item responses were handled according to the Half-scale Rule, which implies that the score of the scale is considered missing in cases where the respondent did not answer at least 50% of the items. Recoding item response values was performed for 10 items, with the transformation of subscale raw scores to a 0-100 metric with higher values indicating better HRQoL.

Paper I: Internal consistency for each subscale and the SRI sum score for the SRI questionnaire were calculated using Cronbach's alpha. Spearman's correlation coefficient was used to examine the associations between the subscales in the Norwegian version of the SRI and the SF-36 version 2 questionnaires. We used the chi squared test to test for difference in percentages and the two-sample *t*-test was used to test for difference in means. To examine the SRI questionnaire ability to discriminate between clinical differences among categories
of patients receiving LTMV, we used analysis of variance (ANOVA) to measure difference in SRI sub-scores between the four patient groups; NMD, COPD, OHS and CWD.

Paper II: We used linear mixed-effects models to investigate changes and risk factors associated with changes in SRI from 2008 to 2014. In the analysis of changes in SRI, the regression model included a random intercept term for the individual to account for correlated observations of the same individual and a fixed-effect term for the time to obtain estimates for SRI changes. To investigate risk factors associated with changes in SRI, we extended the first model to include the relevant factor and the product between the factor and time (i.e., factor-by-time interaction) as model terms. Estimated mean changes in the SRI subscales and sum score were reported using regression coefficients (β) with 95% confidence intervals (CIs). To obtain *p* values for factors associated with SRI changes, we used the likelihood ratio test, i.e., we compared the log-likelihood between models with and without the factor-by-time interaction term. We adjusted a priori for the following background variables: age, sex, education level, and marital status and disease groups.

Paper III: We used the Kaplan-Meier survivor function with the log-rank test to estimate and test the difference in the percentage of survivors across disease groups from study inclusion in 2008 to the end of follow-up 31 August 2014. To estimate the association between SRI and mortality, we used Cox regression models. We reported associations as hazard ratios (HRs) with 95% CIs. The association between SRI and mortality was estimated both by crude and by adjusted Cox regression models to control for factors that may potentially confound the true association between SRI and mortality. We adjusted a priori for the following background variables: age, education level, disease category, number of years treated with LTMV, hours per day on LTMV, and comorbidity. We also performed analyses for the specific disease groups NMD, COPD, and OHS, but not for CWD due to low numbers.

3.7 Ethical considerations and approval

The Western Norway Regional Committee for Medical and Health Research Ethics approved the project, reference 273.06-/4647 and reference 2012/1090-11. The

Norwegian Centre for Research Data (NSD) approved the project, number 16001. The Norwegian LTMV Register approved the project prior to the study. All studies were performed in accordance with the ethical principles stated in the Declaration of Helsinki

Common to all three studies was the mailed information letter about the study which was sent to potential eligible patients on the LTMV Register in Rogaland, Hordaland and Sogn og Fjordane, along with a request to participate in the study. This letter also informed that the data would be stored for 10 years for a possible follow-up study. An information letter about the follow-up study with a request to participate was sent by post to the surviving patients prior the longitudinal study.

The Regional Committee for Medical and Health Research Ethics required written consent from the participants to link data between the LTMV Register, the NPR and the Cause of Death Register. For cohort patients who had died, exemption from the written consent requirement for linking data between these registers was granted. This study also required approval from the Cause of Death Register and the NPR to collect and link data from these registers.

4. SUMMARY OF RESULTS

4.1 Study I

Norwegian version of the SRI questionnaire

Translation and validation of the SRI questionnaire from German into Norwegian were carried out according to generally accepted procedures. A pilot study including LTMV users and healthcare professionals evaluated the feasibility and face validity of the SRI questionnaire. Thereafter, the Norwegian version of the SRI questionnaire was psychometrically tested in the full survey. Of the 193 potential patients recruited from the Norwegian LTMV Register, 127 responded to the SRI questionnaire, giving a response rate of 66%. The patient groups included categories of NMD, COPD, OHS and CWD (Table 1, Paper I). Blood gases ($PaCO_2$ and PaO_2) taken before commencement of LTMV showed that all patients had CHRF with $PaCO_2$>6 kPa before starting up LTMV (Table 1, Paper I). There were no significant differences between responders and non-responders in age, gender, diseases, years treated with LTMV, BMI and $PaCO_2$. However, we found that no-responders had slightly lower FVC and FEV_1, compared with the LTMV patients who responded (Table 2, Paper I). Reliability and internal consistency, as measured by Cronbach's alpha, varied between 0.68 and 0.88 for the subscales and 0.94 for the SRI sum score (Table 3, Paper I). Correlations between the SRI subscales and the SF-36 subscales were found as one of the criteria for validating the Norwegian version of the SRI questionnaire. The highest correlations were found between SRI 'physical functioning' and SF-36 'physical function' ($r=0.73$; $p<0.001$) and between SRI 'psychological well-being' and SF-36 'vitality' ($r=0.72$; $p<0.001$), and between SRI 'psychological well-being' and SF-36 'mental health component' ($r=0.71$; $p<0.001$) (Table 4, Paper I).

The ability to detect some known differences between patient groups receiving LTMV was the criterion for the construct validity of the Norwegian version of the SRI questionnaire. This was confirmed by identifying that COPD patients had the lowest score on the SRI 'respiratory complaint' subscale at 40.3 (18.7), while CWD patients had the highest score at 65.0 (22.1) (Table 5, Paper I). Patients with COPD also had the poorest HRQoL indicator related to 'anxiety' at 41.2 (26.3), while patients with NMD had the highest score at 67.4 (24.6). In addition, COPD patients had a low SRI 'social functioning' score at 34.0 (22), compared to NMD patients who reported a score of 55.1 (22.6). Patients with NMD had the highest SRI sum score at 61.0 (14.7), while patients with COPD had the lowest SRI sum score at 43.3 (19.0) (Table 5, Paper I).

Ventilator hours per day were inversely correlated with the SRI sum score ($r=-0.20$; $p=0.03$), the SRI 'physical function' score ($r=-0.36$; $p<0.001$) and the SRI 'social function' score ($r=-0.20$; $p=0.03$), which also confirmed known a priori knowledge concerning LTMV treatment.

4.2 Study II

Factors associated with changes in HRQoL among individuals treated with LTMV: a six-year follow-up study

Non-invasive LTMV was still used by 58 of the 60 patients (97%) still alive after six years of follow-up. Two patients in the follow-up study were receiving LTMV via a tracheostomy. None of the patients surviving during the follow-up study had ALS. Baseline characteristics including background, treatment and respiratory variables are shown in Table 1, Paper II. Half of these individuals reported side effects (n=29) (50%), with air leakage between the face and the mask (n=21) (36%) and pressure soreness caused by mask pressure (n=10) (17%) being the most common.

We found that the SRI sum score increased by 4.74 (95% CI: 1.49-8.00) from 2008 to 2014 (Table 2, Paper II). Significant improvements in HRQoL were also found in four of the seven SRI subscales: 'social relationship' by 8.47 (95% CI: 3.48-13.5), 'anxiety' by 7.94 (95% CI: 2.42-13.5), 'psychological well-being' by 7.66 (95% CI: 3.28-12.0), and 'social functioning' by 5.89 (95% CI: 0.91-10.9) (Table 2, Paper II). There were no significant changes in the SRI subscales for 'respiratory complaints', 'physical functioning' or 'attendant symptoms and sleep' (Table 2, Paper II).

Among potential risk factors of changes in SRI, we selected the background variables of age, sex, educational level, marital status, disease group, and years treated with LTMV. The treatment variables chosen were LTMV hours a day, dependency of daily assistance related to LTMV treatment, side effects of LTMV, satisfaction with training, and satisfaction with follow-up from healthcare professionals. In addition, we chose the respiratory variables FVC and $PaCO_2$.

We identified age, FVC, patient-reported side effects of non-invasive LTMV, satisfaction with training on LTMV, and follow-up from healthcare professionals as important risk factors for changes in SRI scores from 2008 to 2014.

The treatment variable, side effects of masks or ventilator, was positively associated with changes in the SRI sum score (Table 3, Paper II) and the SRI 'physical function' subscale (Table S1, Paper II). People reporting side effects at baseline in 2008 increased their SRI sum score from 56.2 (16.1) in 2008 to 65.1 (15.4) in 2014 (p for change<0.001), while those not reporting side effects remained at the same high level of 63.9 (20.1) in 2008 and 64.7 (18.4) in 2014 (p for interaction=0.02) (Table 3, Paper II).

Patients reporting some satisfaction in training in the use of the ventilator or BIPAP equipment had the highest improvement in the SRI 'psychological well-being' score from 61.0 (16.0) at baseline to 74.4 (11.8) in 2014 (p for change=0.01) and from 58.5 (21.1) to 72.4 (16.2) (p for change<0.001). Those reporting very high satisfaction with training in 2008 also reported very high 'psychological well-being' both in 2008 and in 2014 (p for interaction=0.01)(Table 4, Paper II).

Patients reporting some satisfaction with follow-up by healthcare professionals at baseline in 2008 also reported the highest change in the SRI 'anxiety' subscale, from 49.5 (37.1) in 2008 to 75.0 (23.3) in 2014 (p for change<0.001) indicating less anxiety after six years of receiving LTMV. Patients reporting very high satisfaction with follow-up at baseline also reported the least anxiety in 2008 and in 2014 (p for interaction=0.009) (Table 5, Paper II).

Age was associated with changes in HRQoL, as younger patients (≤60 years) increased their SRI score from 46.1 (19.6) in 2008 to 52.4 (22.1) in 2014, while those older than 60 years had decreased their SRI 'physical functioning' score from 45.8 (25.7) in 2008 to 41.6 (23.6) in 2014 (p for interaction=0.04) (Table S1, Paper II).

The respiratory variable, FVC, appeared to be a significant risk factor for changes in the SRI 'social function' score, which increased by 7.87 per one unit in FVC (Table S2, Paper II).

4.3 Study III

HRQoL as a predictor of mortality in patients treated with LTMV

During the 80 months of follow-up from 1 January 2008 to 31 August 2014 as the final follow-up date, 52 (46%) patients died. One of the inclusion criteria for the study was that the treatment should have been established for at least three months; therefore, we counted 80 months of follow-up from 1 January 2008, and not from 1 March 2008.

Baseline sum score of the SRI questionnaire by background characteristics of the LTMV patients are shown in Table 1, Paper III. Patients with COPD had the highest overall mortality rate (75%), followed by patients with NMD (46%), OHS (31%) and CWD (25%) (Table 2, Paper III). The mortality rates differed between age groups, education levels, LTMV hours per day, years on LTMV, disease categories, and the burden of comorbidity (Table 2, Paper III). The mean SRI sum at baseline was substantially higher in survivors than in those who died during the 80-month follow-up (Table 3, Paper III). The score in six of the SRI subscales was also significant higher in the survivors compared with the deceased (Table 3, Paper III).

We repeated the analyses of SRI and mortality using Cox regression analyses to appropriately take into account the fact that people died at different time points and also to account for potential confounding factors regarding the associations.
Unadjusted Cox regression analysis showed a significant association between the SRI sum score and mortality (Table 4, Paper III). The association also remained significant after adjusting for age, education level, time since initiation of LTMV, hours per day on LTMV, comorbidity and disease category (HR 0.98; 95% CI: 0.96-0.99) (Table 4, Paper III). When analysing SRI subscales, adjusted associations with mortality were apparent in the case of the SRI 'psychological well-being' (HR 0.98; 95% CI: 0.97-0.99), 'physical functioning' (HR 0.98; 95% CI: 0.97-0.99) and 'social functioning' (HR 0.98; 95% CI: 0.96-0.99) subscales (Table 4, Paper III).
Among NMD patients, the SRI scores for 'psychological well-being' (HR 0.97; 95% CI: 0.95-0.99), 'physical functioning' (HR 0.97; 95% CI: 0.94-1.00) and 'social functioning' (HR 0.97; 95% CI: 0.94-0.99) remained significantly associated with mortality after adjustment for age, comorbidity and hours per day on LTMV (Table 5, Paper III).

5. DISCUSSION

The overall aim of this thesis was to provide new knowledge about quality of life in patients receiving LTMV. Patients treated with LTMV have been involved in this project in the translation and cultural adaptation of the SRI questionnaire from German into Norwegian, by providing advice concerning aspects important in their daily lives and by filling out questionnaires.

To the best of our knowledge, Paper II is first worldwide study to examine the long-term effect of LTMV using a specific and validated SRI questionnaire. Paper III is the first study to examine the ability of a specific SRI questionnaire to predict mortality in people receiving LTMV in a follow-up period of more than three years.

In the first part of this discussion, the main results will be discussed, while, in the second part, we will consider the strengths and limitations of the methodologies used in the studies.

5.1 Discussion of the results

Change in specific HRQoL

We translated and validated the SRI questionnaire in order to examine HRQoL in patients receiving LTMV. The improvements in the SRI sum score and four of the seven SRI subscales after six years of patients receiving LTMV (Paper II) represent important new knowledge in the discipline of LTMV. Previous research has shown consistent trends in the improvement of HRQoL as measured by SRI in patients with CHRF from before initiating LTMV to up to one year of receiving LTMV (10, 18, 19); however, no knowledge has been presented concerning how patients experienced HRQoL after one year. New knowledge is especially important because LTMV most commonly a lifelong treatment.

Anxiety related to severe respiratory insufficiency

A highly meaningful result for the patients receiving LTMV was that the SRI "anxiety" subscale improved after six years in all the four main disease groups. The findings imply that the patients after six years had fewer experiences of feeling anxious about suffering attacks of dyspnoea as well as breathlessness at night. The improvement in this subscale also reflects a lesser tendency among LTMV patients to avoid situations that are stressful due to breathing problems. Further, it indicates that patients receiving LTMV for a longer time period are less worried that their disease will get worse in the future. Another follow-up study found improvements in the SRI "anxiety" subscale in the same disease groups as our study, which covered the period from before initiating LTMV to one month and 12 months after starting LTMV (10).

Psychological well-being related to severe respiratory insufficiency

The improvement in the SRI "psychological well-being" subscale including nine items covering different aspects of life satisfaction and enjoyment of life is important for patients receiving LTMV. This indicates fewer feelings of sadness, nervousness and irritability because of reduced capacity and patients' better ability to cope with respiratory insufficiency and LTMV treatment. Psychological well-being also improved from before to one year after starting LTMV in the German study (10).

Social functioning related to severe respiratory insufficiency

The improvement in the SRI "social functioning" subscale implies that the majority of the patients receiving LTMV most probably experienced an improvement in how their disease impacts on their marriage or partnerships. The improvement indicates better contact with people and ability to attend social events. The study by Windisch (2008) also reported a significant improvement in the SRI "social functioning" subscale after one year.

Social relationship related to severe respiratory insufficiency

The highest improvement in this study was seen in the SRI "social relationship" subscale which was present in all the four patient groups. The results indicate that the LTMV patients have an improved experience of feeling comfortable in the company of other people as well as feeling less lonely and isolated. The results also indicate that the LTMV patients experienced less disease burden on family life. These results are different to the findings reported by Windisch (2008) who found no significant change in this subscale one month or one year after starting LTMV. The time perspective might be one reason for this difference. It might take some time to establish social relationships after the LTMV treatment has started.

The lack of improvement in the SRI subscales, respiratory complaints, physical functioning, and attendant symptoms and sleep during six years of ongoing LTMV can be explained by the fact that HRQoL at baseline was measured during ongoing LTMV and therefore the physiological efficacy of LTMV was already, at least largely, achieved at the baseline in 2008.

Factors predicting improvement in HRQoL

Although several studies have described patient-reported side effects of LTMV (3, 4, 9, 10, 17, 22), the association with HRQoL has, to the best of our knowledge, not been sufficiently studied. About half of the LTMV patients reported side effects at baseline in 2008. In addition, side effects were given as one of the reasons to terminate LTMV treatment.

A significant improvement in the SRI sum score among LTMV patients reporting side effects was seen during the six-year follow-up. One possible explanation is due to the reduction in patient-reported side effects from 51% in 2008 to 44% in 2014. Air leaks between the mask and the face were reduced from 36% in 2008 to 23% in 2014. Further, facial soreness and skin lesions were reduced from 18% to 15% and condensation inside the mask was reduced from 9% to 5%.

Our findings highlight the importance of addressing relevant interventions to prevent side effects. Importantly, some side effects such as air leaks, the most commonly reported side effect in this study, are unavoidable. However, significant air leaks should be addressed immediately to prevent patient-ventilator asynchrony and worsened gas exchange, which would reduce the effectiveness of treatment (27). Very high leakage might lead to less ventilator treatment pressure, lowered tidal volumes and a less effective reduction of CO_2. In addition, side effects might lead to less use of the ventilator and reduce the physiological effect of the treatment, in turn negatively influencing the prognosis. LTMV users from 11 European countries (Norway not included) reported that mask comfort was very important for 69% of the ventilator users (29). Interventions such as the choice of an appropriately sized mask, adjusting the straps, daily cleaning of the mask, and replacement masks every three to six months or sooner, if leakage or discomfort occurs, could help to prevent the major side effects.

In general, the gains of all treatments have to be weighed against possible negative side effects on quality of life, especially when patients are seriously ill with incurable disease (13). On the other hand, studies have shown that patients accept severe side effects if there is the prospect of some benefit in terms of improved survival (13). Further, if patients perceive their conditions as chronic or terminal (170), this might also influence their perception of the side effects.

The association between HRQoL and mortality

Poor HRQoL measured by SRI was associated with higher mortality in LTMV patients before and after adjustment for covariates. These results are in accordance with findings from the two previous studies measuring the relationship between SRI score and mortality (121, 148).

However, this study has a longer follow-up period and consequently a better foundation to examine the association between mortality and HRQoL as measured by

SRI. In addition, the analyses in the studies of Budweiser and colleagues (2007) and Oga and colleagues (2017) did not adjust for education level, LTMV hours per day, years on LTMV, main disease category, and comorbidity as in our study. However, Budweiser et al. (2007) included comorbidity in their univariate analyses; but, as they found no association with survival, they did not include comorbidity in their multivariate analyses. Meanwhile, two other studies (121, 148) adjusted for BMI, leukocytes, base excess, FEV_1 and inspiratory vital capacity (121), and BMI, PaCO2 and FVC (148). We also added baseline FEV_1 and FVC to the multiple Cox regression analyses, but this did not alter the results by much. In Paper III, we have elaborated on the reasons for choosing the adjustment variables and consider them as important contributors to the validity of the results in this study.

In the cumulative process of research, our study with longer follow-up time and other adjustment variables strengthened the main results from previous studies on the association between HRQoL as measured by SRI and mortality.

We found a highly significant numeric difference in SRI subscales and the sum score between survivors and deceased. The differences in SRI scores – 17 on the "social functioning" subscale, 19 on the "physical functioning" subscale, 10 on the "respiratory complaints" subscale, and 12 on the "anxiety" subscale – between survivors and those who died need to be addressed in clinical practice.
The SRI questionnaire is based on self-reported information on quality of life. Previous studies have examined how self-related measures were connected to mortality: in a review of 27 community studies, Idler (1997) found that self-rated health was an independent predictor of mortality. The same measure for self-rated health was applied in one previous study (171) and significant associations between this measure and risk factors for coronary diseases (such as smoking, serum cholesterol and blood pressure) were not found, indicating that low HRQoL relates directly to mortality, as opposed to through other known pathophysiological mechanisms of coronary diseases. Patients' self-report on quality of life could differ from physician-rated data, as seen in one recent study, where a measure of HRQoL was better than physician-rated clinical data (such as the Karnofsky Performance Scale

and absence of bone metastases) in predicting survival in patients with lung cancer (172). The authors suggest that a self-reported measure could contain important information which is not detected by traditional clinical data. Data from the Health Survey in Northern Trøndelag (HUNT 1) also showed that mortality increased significantly with decreasing self-perceived health (173). According to Jylha (2009), it is not quite clear which self-rated health measures are most closely related to death and why these data have such a strong association with mortality. She states that this difficulty may not stem from a lack of empirical information, but rather from the poor integration of knowledge. She presents this integration in a model with information from different disciplines, both social and biological (174). This process of self-reported health assessment contains contextual aspects based on cultural differences, in addition to the comparisons made of own health with reference groups such as age or gender (174). The individual aspects of this model contain a review of information such as medical diagnoses or symptoms, and an evaluation based on a comparison with different reference groups. This kind of information gathered on self-reported health may be transferred to self-reported data on quality of life.

Some of the risk factors for death cannot be influenced directly by healthcare professionals, such as age, education level, ventilator dependency, and main disease category. Other factors might be difficult to influence such as lung function and comorbidity. Importantly, it is always necessary to individualize care for LTMV patients in relation to these factors.

However, our findings showed that there is a significant potential for healthcare professionals to improve HRQoL by preventing the side effects of LTMV, and by effective training in the use of the ventilator and in the follow-up of patients receiving LTMV.

Whether or not the relationship between mortality and HRQoL is causal cannot be concluded from this study, based on the study design (Paper III). Improved survival without also maintaining or improving quality of life is not in accordance with ethics and the LTMV guidelines (4).

Importantly, improved HRQoL was found in the majority of patients receiving LTMV who were still alive after six years of treatment (Paper II).

5.2 Methodological considerations

Study design

In Paper I, we used a cross-sectional study design where data were collected at a fixed point in time (102). The cross-sectional design is appropriate for describing HRQoL and the relationship to other variables, such as socio-demographic and clinical measurements. However, the design cannot, in principle, demonstrate the direction or causation of associations. The lack of time perspective in this design can be reduced by obtaining information by asking questions about the past. However, recalling exposure data from the past may differ between comparison groups, a situation that could lead to a systematic error in estimates (175). On the other hand, data collection in cross-sectional design is simple, practical and cost-effective (102). This design is commonly used to test psychometric properties of HRQoL questionnaires, which was also the main purpose of Paper I.

In Paper II, we used a longitudinal design, in which data on HRQoL were measured twice, at baseline in 2008 and at follow-up in 2014. Longitudinal designs are appropriate for studying the dynamics of phenomena over time. A major advantage of longitudinal designs is that exposure is collected before the outcome under study. This might suggest both direction and causation of observed associations. One challenge with such designs is the loss of participants over time (102). In Paper II, 15 people still alive did not participate in the follow-up study. Of these, eight people had stopped LTMV treatment, three were unable to answer, three rejected participation, and one person did not respond. The loss of follow-up might have resulted in some bias because those who dropped out might differ systematically from those who continued to participate (102), a situation often referred to as selection bias (discussed below).

In Paper III, we used a prospective cohort study design based on data from the SRI questionnaire, the Norwegian LTMV Register, the NPR and the Norwegian Cause of Death Register. In a prospective cohort study, subjects are classified according to their exposure status and then followed over time to ascertain incidence of a disease (175). The exposure in Paper III was HRQoL as measured by SRI in 2008, while the outcome under study was mortality status assessed in 2014. Similar to the longitudinal designs where the exposure is collected before the outcome under study, prospective cohort studies can suggest both direction and causation of associations.

Psychometric properties of the SRI questionnaire

Testing the psychometric properties of a questionnaire includes testing for sufficient reliability, validity and responsiveness (101).

Reliability: The reliability examined by using Cronbach's alpha considers a value above 0.70 to be sufficient (176). Internal consistency of the Norwegian version of the SRI questionnaire, measured by Cronbach's alpha, was 0.94 for the SRI sum score and varied from 0.68 to 0.88 for the SRI subscales. This indicates an acceptable homogeneity for the Norwegian version of the SRI questionnaire, which is in line with other studies which tested the psychometric properties of the SRI questionnaire in different languages (14, 103-107).

Validity: In general, there are three main aspects of validity related to the psychometric properties of an instrument measuring HRQoL. First, content validity concerns whether the items are sensitive and reflects the intended construct of interest. Face validity, which refers to an inspection of the questions without any formal statistical analyses of the validity of the questionnaire, is often seen as a part of content validity (13). Members of Respira and healthcare professionals with experience in and knowledge of the LTMV field contributed to the face validity for the Norwegian version of the SRI questionnaire.

Secondly, criterion validity refers to whether the instrument has empirical associations with external criteria, for example, with other instruments measuring HRQoL (13). The SF-36 was used as a validation tool for the Norwegian version of the SRI questionnaire. The correlation between subscales measuring similar aspects was sufficiently high, similar to other validation studies of the SRI questionnaire (14, 104-107). The highest correlations were found between similar subscales such as SF-36 'physical function' and "SRI 'physical functioning' (r=0.73), and between SF-36 'vitality' and SRI 'psychological well-being' (r=0.72).

Thirdly, construct validity is the most important aspect of the validity of an instrument. It refers to what extent the instrument measures the construct it was developed to measure (13). Construct validity of the Norwegian version of the SRI questionnaire was examined by mostly the same criteria as used in the validation study by Windisch and colleagues (14), including its ability to differentiate between a priori known aspects in patients receiving LTMV. Construct validity was confirmed by identifying that COPD patients had the poorest score on the SRI 'respiratory complaint' subscale at 40.3 (18.7), compared with CWD patients who had the highest score at 65.0 (22.1). Furthermore, patients with COPD had the lowest HRQoL indicator related to 'anxiety' at 41.2 (26.3), compared to patients with NMD who had the highest score at 67.4 (24.6). We also confirmed a trend that hours per day on a ventilator were associated with lower HRQoL by the negative correlation between the SRI sum score and hours per day receiving LTMV (r=-0.20) and in SRI 'physical' and 'social function' subscales.

Responsiveness: The responsiveness of a questionnaire is of importance in longitudinal studies because it refers to the ability to detect improvement in or deterioration of HRQoL (13). In Paper II, we examined whether HRQoL changed from baseline in 2008 to follow-up in 2014, and found that HRQoL did change in four of the SRI subscales related to 'anxiety', 'social relations', 'social function' and 'psychological well-being'. Changes in HRQoL measured by SRI have previously been examined in a one-year longitudinal study among a mixed LTMV population. The SRI questionnaire was better than the generic questionnaire SF-36 in terms of

detecting changes in HRQoL after commencement of non-invasive LTMV (10). In addition, changes in HRQoL were detected in patients with COPD who were receiving non-invasive LTMV (18, 20).

Internal validity

Internal validity refers to the degree to which extent scientific inference can be drawn for the population under study (175). In order to obtain high internal validity in observational research, case and comparison groups should be selected and compared in a manner that reduces both systematic and random errors (175). Below, we discuss the challenges of random error and three main sources of systematic errors: selection bias, information bias and confounding.

Random error

Random error has been explained as variability which is reduced to 0 if the numbers of measurements become endlessly large (175). A small sample size also increases the risk of a type II error, which can cause the failure to detect statistically significant associations, even though there is an association between the variables from which the samples were drawn (102). Our study samples varied between 60 and 127 patients, numbers that might be considered as small, especially when performing subgroup analyses among disease groups. However, our limited sample sizes in part reflect the fact that LTMV patients are not in large in numbers in the population.

Systematic errors

Selection bias

Selection bias refers to the situation when the association between exposure and outcome among those included for analysis differs from the association among those who are eligible (177). Selection bias may occur due to the inappropriate selection of cases and controls in case-control studies, due to differential “loss to follow-up” of

comparison groups, or due to non-response to studies. Selection bias represents a major threat to internal validity in observational research.

All subjects in our study were recruited from the Norwegian LTMV Register. In order to achieve a high response rate, we used pre-stamped and pre-addressed return envelopes. We also mailed out one reminder letter where we had not received any return envelopes from patients. Of the 193 invited patients, 66% responded, a response rate that we considered acceptable given the grave conditions of many LTMV users.

In order to examine potential selection bias in our study, we compared the background characteristics of those who responded with those who did not respond. We found no significant differences in age, gender, diseases and treatment variables between responders and non-responders. However, LTMV patients who did not respond to the questionnaire had slightly lower FVC and FEV_1, compared with the LTMV patients who responded (Paper I). Given these small differences, we did not suspect that our three studies were subject to important selection bias.

In Paper II, 15 patients did not respond to the SRI questionnaire at follow-up in 2014. Consequently, there could be concern over selection bias because those who did not participate in the follow-up study could have had different associations with SRI than those participating. However, out of these 15 people, as many as eight had stopped LTMV treatment and therefore did not meet the inclusion criteria for the follow-up study. After excluding these, we do not believe that the loss to follow-up of the remaining seven patients represents a major threat to the estimates in Paper II.

In Paper III, data on SRI at baseline for all patients were linked to information on comorbidity from the NPR and to mortality from the Cause of Death Register for the period 2008-2014. Consequently, we had no loss to follow-up of patients. However, there could still be concern over selection bias because those who did not give consent to connect data to the NPR could have had different associations with SRI than those who did (Paper III).

Information bias

Information bias refers to a systematic error which results from incorrect measurement or classification of the exposure or outcome variable under study (175). Information bias is commonly grouped by differential and non-differential misclassification. Misclassification of exposure or outcome variables, which are not dependent on the value of the other, is called non-differential misclassification (175). If the exposure and outcome variables are dichotomous, non-differential misclassification often leads to attenuated association estimates (175).

Misclassification of exposure or outcome variables, which depend on the value of the other, is referred to as differential misclassification and can either overestimate or underestimate association measures. Recall bias is a specific case of differential misclassification and refers to the situation where patients with a condition better recall risk factors preceding the condition than those who do not have a condition. Compared to prospective studies, differential misclassification is more common in case-control studies and cross-sectional studies in which risk factors are collected after patients have become ill.

In Paper I, 27% of the LTMV patients reported that they had received assistance to complete the questionnaires. In Paper II, 22% of the patients reported that they had received this assistance at baseline, compared to 38% at the follow-up time in 2014. In Paper III, 26% of the patients reported that they had received assistance to complete the questionnaire. Patients needing assistance could represent individuals with advanced disease and severe respiratory failure. Requiring assistance to complete questionnaires may have affected responses to the SRI questionnaire, e.g., patients wanting to appear more positive in front of others than they really were. However, we considered such information bias as less problematic. The alternative, not including people needing assistance to fill out the questionnaire, could lead to a lower response rate and thus to a more serious selection bias.

We collected data at two time points. At follow-up in 2014, the patients completed the questionnaires when they had their regular outpatient contact in the hospital, while, at baseline in 2008, the questionnaires were filled in by the patients in their home and

returned by post. However, according to Lopez-Campos and colleagues (2007), the mode of administration does not influence the measures of the HRQoL level obtained from the SRI questionnaires (114).

Confounding

Confounding refers to the situation where a third variable (the confounding factor) explains all or part of the observed association between the exposure and the outcome under study (178). The confounding factors need to be controlled in case they are related to both the exposure and the outcome variables (102).

In Papers II and III, we accounted for confounding factors using multiple regression analyses. The potential confounding factors were identified from the previous literature, i.e., we selected those studies that were either associated with the exposure or outcome of interest, or with both. Variables considered as confounding factors in Paper II were; age, sex, educational level and marital status, with main disease category and length of LTMV treatment time as background variables. In Paper III, we adjusted for age, educational level, main disease category, length of LTMV treatment time since initiation of LTMV, hours per day on LTMV, and comorbidity. We also evaluated FVC and FEV_1 as confounding factors in the overall analyses.

We reported unadjusted estimates and confounder-adjusted estimates, together with a description of the confounding factors and why they were adjusted for. Despite adjusting for educational levels, other social inequalities might influence mortality in the LTMV population, such as household income. Norwegian society is among the most equal worldwide. Nevertheless, it has been highlighted as a paradox that social differences in mortality are just as high in the Nordic countries as elsewhere in Europe (179).

Importantly, the number of participants in this study limits the number of adjustment variables that can be adjusted for in regression analyses (rule of thumb: one variable per 10 events). To avoid potential overfitting, we therefore included only the most important adjustment variables in Papers II and III. Thus, our association measures might be subject to some unmeasured or residual confounding in these papers.

In Paper I, in which we did not adjust for variables, we performed psychometric testing of the Norwegian version of the SRI questionnaire without involving confounding factors.

External validity

External validity is the degree to which study results can be generalized to settings or samples other than the one studied (102). To achieve high external validity, our study needs to have high internal validity as well as to be representative of the larger population.

We recruited patients from the Norwegian LTMV Register. At the time of requirement in 2008, we did not have exact information on the cover rate of the LTMV Register on a county basis. However, despite large regional variations in LTMV treatment in Norway, the estimated cover ratio was as follows: that 90% of patients treated with LTMV from 2002 to 31 December 2007 were registered on the Norwegian LTMV Register (36). This indicates a similar cover ratio to that in 2018, where 91% measured from hospitals could provide the basis for calculation (four out of 29 hospitals could not provide the basis for calculating the cover ratio) (39). We concider this cover ratio to be very high, as a cover ratio above 80% is at the highest requirement for the Norwegian medical quality registers (180). Our study included patients from Rogaland, Hordaland and Sogn og Fjordane, representing approximately 21% of the Norwegian population. As we believe that LTMV patients' environment does not differ much between the Norwegian counties, we consider the three counties to be representative of Norwegian patients receiving LTMV. Given this, we propose that our results can be generalized to all patients receiving LTMV.

A representative sample is essential when the research goal is to provide a description of the total population (175). However, it may not be that important when the goal is to report associations and risk estimates rather than prevalence estimates (175), such as the association between HRQoL measured by SRI and mortality (Paper III). It has

been noted by several authors that a completely representative sample could even be more heterogeneous with respect to important confounders, in turn making it more difficult to control for confounding factors (175). One example is the cohort of associations between smoking habits and mortality among male British doctors. The study subjects were not representative of the general population; nevertheless, the results added important knowledge about the adverse effect of smoking habits on the general population (181).

5.3 Ethical considerations

The severity of patients' condition and ventilator dependency might lead to vulnerable situations; thus, special awareness of their integrity is required. The need for assistance and follow-up from healthcare professionals might put people treated with LTMV in a situation where they feel an obligation to participate in studies. On the other hand, the LTMV user organization, Respira, has encouraged research on LTMV (51). In addition, the follow-up and close contact over several years between each LTMV individual and healthcare professionals might lead to a common responsibility towards solving the problems and challenges related to LTMV, and such relationships might influence treatment-related patient reported outcomes. However, this patient-carer relationship includes the patient as an equal partner in decisions concerning her/his treatment and follow-up and has the potential to empower those receiving LTMV.

5.4 Implications and future research

For the first time, we have a specific, validated HRQoL questionnaire for Norwegian LTMV users. The Norwegian version of the SRI questionnaire opens up avenues for research collaboration within this patient group. For that purpose, this Norwegian version and other versions of the questionnaire in the most spoken languages

worldwide (14, 103-107) are available on the website of the German Respiratory Society free of charge for non-profit research (159).

We have shown that HRQoL has improved in the majority of patients receiving LTMV over a long period. Over time, patients receiving LTMV achieve enhanced overall satisfaction with life, reduced anxiety related to breathing and a better ability to cope with their condition. Their contact and relationship with other people also seem to be improved. The absence of deterioration in respiratory complaints, physical functioning, and attendant symptoms and sleep subscales during six years of ongoing LTMV also adds important knowledge both for healthcare professionals and for patients with CHRF concerning the preconditions for starting LTMV. Patient autonomy is fundamental in healthcare, and Norwegian health law emphasizes that patients have the right to receive information from competent healthcare personnel (182). However, there might be a risk that healthcare professionals and relatives judge patients' health to be worse than patient's own judgements (13). It has also been reported that healthcare professionals avoid informing patients about LTMV as a treatment option because they believe that the adverse effects of the treatment could outweigh the benefits (183). These concerns were related to invasive LTMV for diseases such as ALS. Importantly, none of the surviving patients in the six-year follow-up study had ALS. Nevertheless, our findings might add knowledge concerning long-term outcomes of HRQoL in patients receiving LTMV. This aspect is especially critical because LTMV is a life-supporting or a life-sustaining treatment (3, 4), with patients treated with LTMV having been described to be among the most vulnerable groups of patients (184).

There are many factors influencing HRQoL in patients receiving LTMV which are difficult for healthcare professionals to change, such as the main disease, lung function and comorbidities. Nevertheless, this study suggests that interventions by healthcare professionals might improve HRQoL in LTMV patients by reducing side effects and improving training and follow-up. However, further intervention studies are needed to confirm this hypothesis.

Recently, the minimal clinically important difference (MCID) of the SRI questionnaire was identified in patients with COPD who were treated with non-invasive LTMV (94), which supports the clinical implications of our finding. However, research is needed to identify the MCID value for other groups of LTMV patients.

We have shown that HRQoL measured by the SRI questionnaire is an independent predictor of survival and could therefore be used as an explanatory or outcome variable in further scientific studies, as well as a clinical follow-up instrument for this patient group. We cannot conclude with any causal relationship between improved HRQoL and survival in this study. However, the large differences in SRI subscales at the study baseline between LTMV patients surviving and dying during follow-up suggest that the early identification of subjects with a low SRI score and prompt interventions to improve HRQoL could be of great importance.

6. CONCLUSION

With quality of life as a framework, this thesis has provided new knowledge about HRQoL in patients receiving LTMV.

The Norwegian version of the SRI is a specific, valid and reliable questionnaire to measure HRQoL in people receiving LTMV both in research and in clinical practice.

A six-year longitudinal study of patients treated with LTMV found improved HRQoL when measured by the SRI questionnaire. Patients reported satisfaction with training and follow-up from healthcare professionals and side effects were associated with changes in HRQoL.

Finally, we found a strong independent association between HRQoL as measured by SRI and mortality in patients treated with LTMV.

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Errata

Title: Missing hyphen: 'Health related' corrected to 'Health-related'

Page 2, line18, 'the University of West Norway', corrected to 'the Western Norway University of Applied Sciences'

Page 25 line 8, reference (66) should be removed – corrected to: 'This scale has been used to measure life satisfaction in individuals with Duchene muscular dystrophy (DMD) who are treated with LTMV (78)'.

Paper 1: Markussen H, Lehmann S, Nilsen RM, Natvig GK (2015). The Norwegian version of the Severe Respiratory Insufficiency Questionnaire. Int J Nurs Pract. 21(3):229-38. Doi:10.1111/ijn.12256.

Page 233, under 'Reliability section', the sentence, 'Cronbach's α for each domain of the SRI varied from 0.76 to 0.88', - corrected to 'Cronbach's α for each domain of the SRI varied from 0.68 to 0.88'.

Papers I - III

Paper I

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RESEARCH PAPER

*The Norwegian version of the Severe Respiratory Insufficiency Questionnaire**

Heidi Markussen RN ICN MHSc

Assistant Director, Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

Research Fellow, Norwegian National Centre of Excellence in Home Mechanical Ventilation, Haukeland University Hospital, Bergen, Norway

Department of Global Public Health and Primary Care, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway

Sverre Lehmann MD PhD

Pulmonary Physician, Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

Norwegian National Centre of Excellence in Home Mechanical Ventilation, Haukeland University Hospital, Bergen, Norway

Associate Professor, Department of Clinical Science, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway

Roy M Nilsen Biostatistician PhD

Biostatistician, Centre for Clinical Research, Haukeland University Hospital, Norway

Postdoc Research Fellow, Department of Global Public Health and Primary Care, Faculty of Medicine and Dentistry, University of Bergen, Norway

Gerd K Natvig RN dr.polit

Professor, Department of Global Public Health and Primary Care, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway

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The Norwegian version of the Severe Respiratory Insufficiency (SRI) Questionnaire

The aims of this study were to translate and adapt the Severe Respiratory Insufficiency (SRI) questionnaire into Norwegians and to test its reliability and validity.Data were collected from a cross-sectional survey and were linked to the Norwegian Registry of patients receiving long-term mechanical ventilation (LTMV). Of 193 potential participants, 127 responded to the SRI questionnaire. Reliability as measured with Cronbach's α varied between 0.68 and 0.88 for the subscales and was 0.94 for SRI-sum score. Construct validity was obtained with high correlations between subscales in SF-36 and SRI. The SRI questionnaire discriminated well between universally accepted clinical differences among categories of patients receiving LTMV by significant dissimilarities in SRI-sum score and SRI subscales. The Norwegian version of SRI has well-documented psychometric properties regarding reliability and validity. It might be used in clinical practice and in international studies for assessing health-related quality of life in patients receiving LTMV.

Key words: chronic respiratory failure (CRF), health-related quality of life (HRQOL), long-term mechanical ventilation (LTMV), the Severe Respiratory Insufficiency (SRI) questionnaire, validation study.

Correspondence: Heidi Markussen, Department of Thoracic Medicine, Haukeland University Hospital, Jonas Liesvei 65, N-5053 Bergen,Norway. Email: heidi.markussen@helse-bergen.no

*Translation, adaptation and validation of the SRI questionnaire: A cross-sectional survey including patients receiving long-term mechanical ventilation in Norway

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INTRODUCTION

Long-term mechanical ventilation (LTMV) is a well-established treatment for patients with hypercapnic chronic respiratory failure (HCRF) caused by various underlying disorders, such as chest wall deformities, neuromuscular disorders and obesity hypoventilation syndrome (OHS).[1–4] The total number of patients treated with LTMV in Europe has increased and will rise further with medical advances and the ageing of the population.[5] The treatment prevalence in Norway at the end of 2010 was 26.5/100 000.[6]

Patient-reported health-related quality of life (HRQOL) is an important instrument to understand and improve overall quality of life in patients with chronic diseases such as HCRF. During the last two decades, several generic and disease-specific questionnaires have been developed to assess HRQOL.[7] Most generic questionnaires are not specific to any particular disease and allow comparisons of HRQOL to be made between patients with different diseases. One of the most commonly used and well validated is the 36-item Short Form Health Survey (SF-36).[8] Condition- or disease-specific questionnaires measure how a specific disease affects HRQOL. In the fields of respiratory care, the disease-specific questionnaires 'The Chronic Respiratory Questionnaire' (CRQ) and 'The St George's Respiratory Questionnaire' (SGRQ) are both well validated for use in patients with chronic obstructive pulmonary disease (COPD).[9,10] Patients with CRF caused by other diseases might report some of the same respiratory complaints as COPD patients. However, they might suffer from a heavier burden of symptoms and other kinds of disease-related problems, especially in the advanced stages of disease. About one in five LTMV users in the Norwegian population has a neuromuscular condition,[6] and their specific problems and symptoms are poorly covered in questionnaires such as the SGRQ and CRQ. As a consequence, two questionnaires were especially developed to measure HRQOL in patients with CRF on LTMV treatment: the Severe Respiratory Insufficiency (SRI) Questionnaire[11] and the Maugeri Foundation Respiratory Failure (MFR-28) Questionnaire.[12] The SRI, originally developed in German, has proven more reliable and valid than the MFR-28 in this specific patient population,[13] and the translation processes, validations and clinical applications have been published for the Dutch, English and Spanish versions.[14,15]

The SRI measures HRQOL in patients receiving LTMV. A questionnaire developed and tested in one country cannot merely be translated and used as a new version in another country. QOL questionnaires measure subjective and cultural relations, so it is necessary to test a new version of the questionnaire psychometrically to the specific country. The validation process consists of a number of stages, in which the researcher looks for evidence that the instrument produces useful measurements that reflect the respondents' QOL.[7] Particularly, 'construct validity' is the degree to which an instrument measures the construct it is supposed to measure. One of the most common approaches is to relate a construct to practical criteria, to examine the scores on the instrument of interest and then compare them with scores on a similar/comparable instrument.[16] In clinical research, the sensitivity of a scale and its ability to detect individual differences in clinical variables are also important.[17]

The aims of this study were to translate and transculturally adapt the SRI Questionnaire into Norwegian, and to test its reliability, internal consistency and construct validity. The specific research questions were threefold: (i) Is the SRI Questionnaire positively correlated with the SF-36?; (ii) Does the SRI Questionnaire discriminate between universally accepted clinical differences among categories of patients receiving LTMV?; (iii) Do the most ventilator-dependent patients have a lower HRQOL than patients requiring fewer hours on a ventilator? SRI data were collected from a cross-sectional survey, including patients from three counties in Norway in 2008.

MATERIALS AND METHODS

Design and patients

This cross-sectional study was performed in 2008 in the western region of Norway. Informed consent was obtained from each participant prior to the study, and the study has been approved by the Regional Committee for Medical Research Ethics and by the Norwegian Data Inspectorate.

All patients older than 18 years in the Norwegian National Registry of LTMV who were resident in three counties were invited to participate in the study. Patients treated with non-invasive and invasive LTMV who showed mental clarity and were well oriented were included. The LTMV had to be established for at least 3 months. The SRI and SF-36 Questionnaires, an information letter, and a stamped return envelope were sent by mail to the 211 LTMV users in the registry who met the eligibility criteria. Returning the questionnaire was

considered to constitute the patient's consent to participate in the study. After 1 month, a reminder letter and copies of the questionnaires were sent to the non-responders. The register was cross-checked with the National Inhabitant Registry before the questionnaires were mailed to avoid sending them to individuals who had recently passed away.

The SRI Questionnaire

The SRI Questionnaire was developed following an open interview in which patients receiving LTMV had given their important subjective impressions of their actual quality of life. It contains 49 items based on social, psychological and physical health domains, and is divided into seven subscales. The SRI was validated in a multicentre study that included 226 patients. All items are rated on a five-point scale, from 'strongly agree' to 'strongly disagree'. The summary scale (SS) is obtained as summary of the seven subscales. High SS values (range 0–100) indicate a better HRQOL.[11]

Validation instrument

For validation purposes, the SF-36 was used as the objective gold standard for criterion validity, as in the original validation study of the SRI.[11] The SF-36 was originally developed based on the Medical Outcome Study[8] and has been translated into and validated in several languages, including Norwegian.[18]

Procedures for the translation and cultural adaptation of the SRI into Norwegian were as follows. The author of the SRI consented to the Norwegian translation. The accepted procedures for the translation and adaptation of QOL instruments were followed.[19,20] A professional translator and a physician specialist in pulmonary medicine, whose first language was German, translated the SRI into Norwegian. The translators worked separately and did not cooperate in this phase. Two professional translators performed the back-translation to German. The translation process revealed discrepancies in the translation of some of the items, and modifications to the wording were made. In particular, translation of the word 'Luftnot' (English, shortness of breath) produced different Norwegian words. Finally, the translators agreed on a Norwegian version, ready for pretesting.

Measuring feasibility and face validity

A pilot test was performed to measure the face validity and feasibility of the translated instrument. Members of the Norwegian special interest organization for LTMV users, 'Respira', were invited to act as the pilot test group. All of the six individuals in question had been receiving LTMV for at least 3 months. They were requested to complete the questionnaire and were then asked if the questionnaire was clear, easy to understand and covered topics of interest, and whether any items had been difficult to answer. They were also asked whether the questionnaire was relevant to their lives as LTMV users.

A group of health-care workers, physicians and nurses experienced in LTMV were asked whether the items were relevant for use in the LTMV population. The back-translated version of the questionnaire was also sent to the author of the original SRI, who commented on it in terms of the equivalence between the original and the back-translated versions.

Finally, a consensus group compared the translated version and the original for equivalence, face validity and feasibility. After its translation and pretesting in both the consensus and user groups, the Norwegian version of SRI was ready for psychometric testing.

Statistical analyses

Statistical analyses were performed by SPSS for windows version 18.0 (SPSS Inc., Chicago, IL, USA).[21] All statistical tests were two sided, and *P*-values below 0.05 were considered statistically significant. Data were described as percentages or means ± standard deviation. The chi-squared test was used to test for difference in percentages, whereas the two-sample *t*-test was used to test for difference in means.

The items in the SRI were recoded according to the guidelines for the original SRI Questionnaire. The total SS of the SRI is calculated by summing the subscale scores (SRI-RC, SRI-PF, SRI-AS, SRI-SR, SRI-AX, SRI-WB and SRI-SF). Missing items in the SRI and SF-36 were treated according to the accepted guidelines for these questionnaires, that is, the calculations were not performed if results were missing for one of the scales.[11] Internal consistency for each domain, subdomain and the SS for the SRI questionnaire was calculated using Cronbach's α.

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) in per cent of the predicted value (FVC% pred and FEV1% pred) was calculated according to Langhammer *et al*.[22] Daytime arterial blood gas was taken prior to the initiation of mechanical ventilation and during spontaneous breathing in indoor air.

All scores in the SRI Questionnaire were correlated with all scores on the SF-36 using Spearman correlation coefficient. Analysis of variance (ANOVA) was further used to explore the differences in SRI scores between the four main diagnostic groups (i.e. neuromuscular disease (NMD), COPD, OHS, chest wall disease).

RESULTS

Initially, 211 subjects from the National Registry of LTMV patients met the inclusion criteria for the study. Four of the patients were excluded because of a primary diagnosis of obstructive sleep apnoea and therefore did not fulfil the inclusion criteria for the registry. Nine patients returned the questionnaire unanswered because they had stopped using the ventilator. One patient had died during the week that the questionnaire was sent. Two patients were unable to answer the questionnaire, as judged by their relatives, and two patients were impossible to locate. This reduced the number of potential responders to 193. After a reminder letter had been sent, 127 patients finally completed and returned the questionnaire, giving a response rate of 65.8%.

Clinical characteristics of the LTMV patients

The clinical and demographic characteristics of the LTMV patients are shown in Table 1. The group of patients with NMD was heterogeneous in terms of their diagnoses. It consisted of patients with acquired conditions (post-polio syndrome, $n = 16$; amyotrophic lateral sclerosis, $n = 5$; cervical spinal cord lesion, $n = 1$; multiple sclerosis, $n = 1$; brain damage, $n = 3$; central hypoventilation syndrome, $n = 2$; Cheyne-Stokes respiration, $n = 3$) and congenital conditions (spinal muscle atrophy, $n = 4$;

Table 1 Clinical and demographic characteristics of the LTMV patients

Variable	NMD	COPD†	OHS	Chest wall disease‡
Subjects (*n*, %)	54 (42.5)	26 (20.5)	37 (29.9)	9 (7.1)
Males (*n*, %)	23 (18.1)	16 (12.6)	23 (18.1)	6 (4.7)
Age, years	57.2 ± 17.8	67.7 ± 9.2	65.9 ± 12.2	51.6 ± 18.3
Years of LTMV	5.7 ± 4.5	2.6 ± 1.9	4.9 ± 3.0	7.1 ± 6.7
FVC % predicted	66.1 ± 29.3	58.3 ± 19.1	70.1 ± 17.3	42.2 ± 22.2
FVC, litre	2.3 ± 1.1	2.2 ± 0.9	2.8 ± 1.0	1.7 ± 1.3
FEV_1, litre	1.6 ± 0.9	1.1 ± 0.6	2.1 ± 1	1.2 ± 1.1
FEV_1 % predicted	58.9 ± 26.9	36.2 ± 18.9	63.0 ± 23.9	37.3 ± 18.5
FEV_1/FVC % predicted	93.7 ± 23.3	60.9 ± 18.8	88.7 ± 18.3	89.5 ± 23.6
PO_2, kPa daytime	9.8 ± 1.9	7.0 ± 2.1	8.0 ± 1.9	10.1 ± 2.9
PCO_2, kPa daytime	6.26 ± 1.4	7.73 ± 1.6	7.75 ± 3.0	7.80 ± 2.7
BMI, kg/m^2	27.9 ± 10.0	29.6 ± 8.9	40.5 ± 7.6	25 ± 7.0
Tracheotomy, *n*	10	0	0	0
LTMV h/day (*n*, %)				
5–8	29 (23.6)	8 (6.5)	17 (13.8)	4 (3.3)
8–12	15 (12.2)	13 (10.6)	14 (11.4)	4 (3.3)
12–24	8 (6.5)	5 (4)	5 (4)	1 (0.8)
Marital status (*n*, %)				
Married or cohabiting	27 (21.3)	18 (14.2)	20 (15.7)	5 (3.9)
Single	19 (15)	3 (2.4)	9 (7.1)	4 (3.1)
Divorced	3 (2.4)	2 (1.6)	4 (3.1)	
Widowed	6 (4.7)	3 (2.4)	4 (3.1)	

Data are presented as means ± SD, unless otherwise stated. † One of the patients in this group had severe bronchiectasis disease. ‡ Three of the patients in this group had other diseases. BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LTMV, long-term mechanical ventilation; NMD, neuromuscular disease; OHS, obesity hypoventilation syndrome; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen.

Table 2 Differences in the demographic and clinical characteristics of the LTMV patients who answered the questionnaire and those who did not return the questionnaire

	Participant	Non-participant	*P*-value
Subjects (*n*, %)	127 (100)	66 (100)	
Males (*n*, %)	68 (53.5)	37 (56)	0.763
NMD (*n*, %)	54 (42.5)	26 (39.4)	0.759
COPD (*n*, %)	26 (20.5)	10 (15.2)	0.439
OHS (*n*, %)	38 (29.9)	22 (33.3)	0.627
Chest wall (*n*, %)	9 (7.1)	8 (12.1)	0.287
Age, years	61.5 ± 15.6	58 ± 21.27	0.250
Years of LTMV	4.92 ± 4.05	4.67 ± 3.26	0.674
BMI kg/m^2	32.8 ± 10.5	32.2 ± 12.7	0.798
PO_2, kPa daytime	8.6 ± 2.24	8.3 ± 2.29	0.52
PCO_2, kPa daytime	7.16 ± 2.4	7.16 ± 2.0	0.993
FVC % predicted	64.6 ± 23.6	53.8 ± 23.2	0.052
FEV_1 % predicted	54.3 ± 25.9	47.8 ± 22.9	0.275
FVC, litre	2.4 ± 1.0	1.8 ± 0.9	0.005
FEV_1, litre	1.62 ± 0.96	1.32 ± 0.7	0.043

Data are presented as means ± SD unless otherwise stated. BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; LTMV, long-term mechanical ventilation; NMD, neuromuscular disease; OHS, obesity hypoventilation syndrome; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen.

Duchenne muscular dystrophy, $n = 2$; myotonic dystrophy, $n = 2$; other muscle atrophies, $n = 7$; limb-girdle dystrophy and neuropathies, $n = 2$; cerebral disease, $n = 2$; mitochondrial disease $n = 1$). The group of patients with COPD included one patient with severe bronchiectasis disease. The group of patients with chest wall diseases included three patients with miscellaneous diseases. All patients had severe hypercapnic CRF with $PCO_2 > 6$ kPa before the commencement of LTMV. The patients with chest wall diseases had spent the longest periods on LTMV (Table 1).

The demographic and clinical characteristics of the LTMV patients who answered the questionnaire are compared with those of the patients who did not return the questionnaire in Table 2. A statistically significant difference was only seen for FEV_1 and FVC.

Reliability

Cronbach's α for each domain of the SRI varied from 0.76 to 0.88 (Table 3). Because of the possible misinterpretation of item 15, Cronbach's α was measured also for the SRI-SF domain excluding item 15. This misinterpretation might be explained by a perceived difference in 'feeling bonded to' and 'feeling connected to' the patient's home. The Cronbach's α before and after exclusion of item 15 was 0.84 and 0.80, respectively.

Table 3 Internal consistency of the Norwegian version of SRI

Scale	Number of items	Cronbach's α
Respiratory complaints (RC)	8	0.81
Physical functioning (PF)	6	0.76
Attendant symptoms and sleep (AS)	7	0.68
Social relationships (SR)	6	0.82
Anxiety (AX)	5	0.81
Psychosocial well-being (WB)	9	0.88
Social functioning (SF)	8	0.79
Summary scale (SS)	49	0.94

SRI, Severe Respiratory Insufficiency.

Validity

The correlation matrix for SRI and SF-36 for our study population is shown in Table 4. Generally, the correlations were high when the subscales of the SRI and SF-36 referred to comparable aspects of HRQOL, and were lower when different topics were correlated. The highest correlations were found between SRI-PF and SF-36-PF ($r = 0.729$; $P < 0.001$) and between SRI-WB and SF-36 VT ($r = 0.72$; $P < 0.001$), and between SRI-WB and SF-36 MHC ($r = 0.714$; $P < 0.001$). The lowest correlation was between SRI-AS and SF-36-PF.

To examine whether SRI Questionnaire might discriminate between clinical differences among categories of patients receiving LTMV, we examined difference in SRI scores between NMD, COPD, OHS and chest wall diseases using ANOVA. A statistically significant overall difference was found for all SRI subscales, except for the domain of SRI-AS (Table 5).

DISCUSSION

The aim of this study was to translate a condition-specific questionnaire that measures HRQOL in patients receiving LTMV. The SRI Questionnaire was translated into Norwegian, and the scale was tested for its reliability and validity in a Norwegian patient population. In the process

Table 4 Correlation matrix for the SRI and the SF-36

SRI	SF-36									
	PF	RP	BP	GH	VT	SF	RE	MH	PHC	MHC
RC	**0.378**	**0.520**	**0.362**	**0.633**	**0.521**	**0.515**	**0.400**	**0.286**	**0.527**	**0.396**
PF	**0.729**	**0.661**	**0.246**	**0.524**	**0.345**	**0.398**	**0.430**	**0.270**	**0.608**	**0.290**
AS	0.172	**0.206**	**0.494**	**0.359**	**0.436**	**0.330**	**0.252**	**0.323**	**0.339**	**0.272**
SR	**0.272**	**0.430**	**0.481**	**0.475**	**0.579**	**0.664**	**0.418**	**0.523**	**0.465**	**0.582**
AX	**0.297**	**0.408**	**0.449**	**0.499**	**0.436**	**0.582**	**0.439**	**0.494**	**0.421**	**0.548**
WB	**0.281**	**0.480**	**0.543**	**0.629**	**0.720**	**0.695**	**0.580**	**0.637**	**0.430**	**0.714**
SF	**0.417**	**0.613**	**0.449**	**0.589**	**0.518**	**0.656**	**0.446**	**0.373**	**0.587**	**0.489**
SS	**0.452**	**0.617**	**0.578**	**0.702**	**0.645**	**0.736**	**0.560**	**0.537**	**0.622**	**0.614**

Significant correlations are shown in bold type; and summary scales for each questionnaire in grey. *Notes:* The SRI domains were respiratory complaints (RC), physical functioning (PF), attendant symptoms and sleep (AS), social relationships (SR), anxiety (AX), psychosocial well-being (WB), social functioning (SF), and summary scale (SS). The SF-36 domains were physical functioning (PF), role-physical (RP), body pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), mental health (MH), physical health component (PHC), and mental health component (MHC). SF-36, 36-item Short Form Health Survey; SRI, Severe Respiratory Insufficiency.

Table 5 HRQOL according to the four groups of patients receiving LTMV

	Total $n = 123$ Mean (SD)	NMD $n = 52$ Mean (SD)	COPD† $n = 25$ Mean (SD)	Obesity $n = 37$ Mean (SD)	Chest wall‡ $n = 9$ Mean (SD)	*P*
SRI						
SS	55.8 ± 18.4	61.0 ± 14.7	43.2 ± 19.0	58.4 ± 18.3	55.8 ± 18.4	0.001
PF	38.8 ± 24,7	35.5 ± 23.5	31.4 ± 23.2	47.6 ± 25.2	47.6 ± 25.2	0.048
RC	56.3 ± 22.1	60.3 ± 21.7	40.3 ± 18.7	61.4 ± 21.1	65.0 ± 22.1	0.001
AS	56.0 ± 20.2	60.5 ± 21.1	54.4 ± 21.1	52.8 ± 18.5	48.1 ± 16.7	0.169
SR	66.5 ± 24,0	72.7 ± 20.3	53.7 ± 27.2	67.8 ± 23.0	60.1 ± 26.7	0.009
AX	60.5 ± 27.5	67.4 ± 24.6	41.2 ± 26.3	66.4 ± 25.1	50.5 ± 31.7	0.001
WB	60.5 ± 23.3	68.1 ± 20.3	47.3 ± 24.5	59.1 ± 23.6	61.3 ± 20.9	0.003
SF	49.7 ± 23.4	55.1 ± 22.6	34.0 ± 22.0	53.6 ± 19.3	46.7 ± 23.4	0.001

† One of the patients in this group had severe bronchiectasis disease. ‡ Three of the patients in this group had other diseases. One-way ANOVA. Significance level 0.05. *Notes:* The Severe Respiratory Insufficiency (SRI) domains were respiratory complaints (RC), physical functioning (PF), attendant symptoms and sleep (AS), social relationships (SR), anxiety (AX), psychosocial well-being (WB), social functioning (SF), and summary scale (SS). HRQOL, health-related quality of life; LTMV, long-term mechanical ventilation.

of translating the SRI into Norwegian, general guidelines were followed[7,19] and no major problems were encountered. Consistent with previous studies, there were some items missing,[7] which might be explained by several factors, including the use of numerous items, the content of some items and the ambiguity in the answer alternatives.[23] For example, we found that some missing items were linked to a question about the influence on the patient's marriage, which lacked an alternative option for single patients.

Internal consistency measures the homogeneity of the items in a questionnaire. A Cronbach's α value above 0.70 is regarded as acceptable, a value above 0.80 as good and a value above 0.90 as excellent.[7] In the original

German version of the SRI, Cronbach's α ranged between 0.73 and 0.79 for three subscales, and between 0.80 and 0.89 for four subscales.[11] This indicates that the reliability of the present study was the same or even better than that of the German version of the SRI and similar to that in the English, Dutch and Spanish validation studies.[14,15] Cronbach's α increases as the number of items in the scale increases, which might explain the high Cronbach's α values for the sum scores.[7] For the remaining subscales of the SRI, Cronbach's α was good to excellent and consistent with those of previous studies,[14,15] indicating good item homogeneity in the SRI. However, a very high Cronbach's α might also indicate that several items in the questionnaire are approximately equivalent,[7] but this is not the occasion in this study.

Regarding our first research question, the correlation matrix of the SRI and SF-36 confirmed the same pattern as Windisch and colleagues,[11] who established strong associations between physical functions, well-being, vitality and social functioning. As expected, the strongest correlations were between subscales that focused on comparable aspects of HRQOL in patients receiving LTMV, and the weakest correlations were between the subscales that focused on different aspects of life as an example between respiratory complaints and mental health.

A correlation coefficient between 0.20 and 0.80 is regarded as acceptable, but correlation coefficients higher than 0.70 between the instruments might indicate that they are measuring the same construct.[7] In both the present and previous studies, the correlation coefficient was higher than 0.70 for the domain 'physical functions and vitality', indicating that they were measuring the same subdomain. Previous validation studies found the lowest correlation between the subdomain 'attendant symptoms and sleep' in the SRI and the domain 'role-emotional' in the SF-36.[11,14] This was expected because the SF-36 was not designed to measure sleep disturbances or respiratory complaints,[24] which are frequently reported in patients with CRF.

Construct validity is one of the most important characteristics of a questionnaire and refers to the degree to which it actually measures the construct it is meant to measure. Construct validity can be established by several methods. One approach is the 'known group technique', which tests the discriminatory ability of an instrument by administering the questionnaire to groups expected to differ in some known characteristics.[7] Concerning our second research question, the results of the present study confirm the findings of previous validation studies, indicating that the SRI can discriminate between different diagnostic groups of patients.[11,14,15] Consistent with the findings of previous studies, the COPD patients had the lowest SRI-SS. They have more respiratory constraints than the other groups of patients,[3,11,14,15] and the association between respiratory complaints and HRQOL was highest in COPD patients, as shown in another study,[25] on both the physiological component scale and the mental component scale. The higher levels of anxiety and depression in COPD patients compared with other patients are also consistent with the results of other validation studies,[11,14,15] and the SRI total score was strongly associated with anxiety and depression, as assessed with the Hospital Anxiety and Depression Scale.[13] A review of previous studies has shown contradictory results in patients after they commenced LTMV.[26] Some studies have found significant improvements in HRQOL after the initiation of LTMV.[27–30] In two of these studies, the improvement in HRQOL seemed more marked in patients with higher body mass indices (BMIs), those with no obstructive sleep apnoea syndrome or OHS and those traditionally known as 'blue bloaters'.[29,30] The COPD patients in the present study also had high BMIs which might represent a subgroup of COPD patients with concomitant OHS or obstructive sleep apnoea syndrome receiving LTMV. Until recently, randomized controlled trials have demonstrated no significant improvements in HRQOL in COPD after the commencement of LTMV.[4,31–36] However, these studies had two important limitations. First, they did not use questionnaires specific for patients receiving LTMV. Second, these studies used low-pressure ventilator settings.[4,31–36] A new high-intensity pressure strategy for non-invasive ventilation, aimed at maximal improvement of the blood gas values, has been evaluated in some studies, and assessments with the SRI have shown improvements in HRQOL.[3,37,38]

Concerning our third research question, we found that the most ventilator-dependent patients had lower HRQOLs than patients who spent fewer hours on ventilation. These results are consistent with the findings of previous studies of patients receiving LTMV.[11,14,15]

A low response rate is common in survey studies and might result in non-response bias.[7] The response rate in the present study was 65.8%, and the responders and non-responders were similar with regard to their age, sex, diagnosis and period of requiring LTMV, which might indicate that ours was a representative sample.[7,23]

However, those who did not return the questionnaire had lower scores on the lung function test than those who returned the questionnaire. A reasonable interpretation of this difference is that the non-responders suffered more severe disease than the responders did. Other studies have confirmed the tendency for patients with more advanced disease to fail to complete questionnaires.[39] Mailing questionnaires might be a less than optimal way to administer the questionnaires. However, the phenomenon of 'social desirability responding', or the tendency to idealize one's life, could be less pronounced when the questionnaires are mailed, thus circumventing meetings between the researcher and the study participants.[40]

Implications for nursing practice

Nurses have a central role in the care and monitoring for LTMV patients. The information in the SRI is crucial in planning the structure, performance and evaluation of patient care for LTMV patients. The use of SRI questionnaire will be an important tool in this effort and the subscales give an understanding of what HRQoL represents for this group, in a way which no other questionnaire does. The subscale, *Respiratory Complaints* (RC), includes; dyspnoea with or without physical activity, during speaking and meals. The RC subscale is crucial information for nursing care and intervention. The scale *Attendents Symptoms and Sleep* (AS), addresses the quality of sleep. This is measured by the patients reported waking up during the night, problems with falling asleep, general interruptions to the sleep cycle and also symptoms, such as daytime tiredness, dizziness and headaches.

The *Physical Function* (PF) subscale gives information which is important for the patient's self-care or need for support. Information regarding the patient's ability to execute daily activities such as getting clothed, doing housework, shopping and leisure time, is significant for the nursing care performance and follow-up.

The subscale *Anxiety* reflects the patient's concerns and fears of breathlessness. It also includes patient avoidance of situations which could escalate or induce breathlessness or embarrass the patient. Awareness of the patient's anxiety is required to perform the necessary interventions in care. The *Social function* scale gives information about the patient's ability to take part in social activities. The subscale includes factors such as patient capability of going out for the evening, having visitors, and impact of the disease on the patient's friends and family.

The *Well-Being* scale in SRI consists of several global questions of how the patients in general feel about life, their expectations for the future and their reactions to the limitations of their disease. Nurse staff has an impotent role in improving the patient's HRQoL, and the SRI questionnaire is an important instrument in the care of patients receiving LTMV.

Conclusion and suggestions for further research

Weighing the gains made in HRQoL by prolonging treatment against the potential disadvantages of the same treatment is challenging and complex. However, the Norwegian version of the SRI qualifies for use as a valuable research tool in assessing HRQOL in patients receiving LTMV. Longitudinal and follow-up studies are recommended to determine the responsiveness of the Norwegian version of the SRI and to identify the changes in HRQOL over time in different groups of patients with different diagnoses receiving LTMV. It should also be possible to examine how demographic and clinical variables act as predictors of HRQOL.

Our study demonstrates that the Norwegian versions of SRI shows good levels of internal consistency, and face-, criterion- and construct validities. The translation and cross-cultural adaptation of this instrument allow its application to clinical practice and research within Norway, and to comparative international studies that assess HRQOL in patients receiving LTMV.

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Paper II

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ORIGINAL RESEARCH:
EMPIRICAL RESEARCH – QUANTITATIVE

WILEY JAN

Factors associated with change in health-related quality of life among individuals treated with long-term mechanical ventilation, a 6-year follow-up study

Heidi Markussen[1,2] | Sverre Lehmann[1,3] | Roy M. Nilsen[4] | Gerd K. Natvig[2]

[1]Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

[2]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[3]Department of Clinical Science, University of Bergen, Bergen, Norway

[4]Department of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen, Norway

Correspondence
Heidi Markussen, Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway.
Email: heidi.markussen@helse-bergen.no

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Abstract

Aims: To examine changes and explanatory variables for changes in health-related quality of life in patients treated with long-term mechanical ventilation over a 6-year period.

Background: Long-term mechanical ventilation is a treatment for individuals with chronic hypercapnic respiratory failure, primarily caused by neuromuscular diseases, obesity hypoventilation syndrome, chronic obstructive pulmonary and restrictive thoracic diseases. Studies on long-term outcome on health-related quality of life and factors influencing it are lacking.

Design: Prospective cohort study.

Methods: Data were collected from the Norwegian Long-Term-Mechanical-Ventilation Registry and from patient-reported questionnaire in 2008 and 2014. Health-related quality of life was measured by the Severe Respiratory Insufficiency questionnaire, containing 49 items and seven subdomains. Linear mixed effects models were used to measure changes and identify factors for changes.

Results: After 6 years, 60 patients were still participating, out of 127 at baseline. Health-related quality of life improved significantly in the total score and in four subdomains of the questionnaire. Satisfaction with training in long-term mechanical ventilation was an explanatory variable for improved 'psychological well-being' and follow-up for improvement of 'anxiety'. Side effects of the treatment like facial soreness were associated with the total score. High age and high forced vital capacity were related to lower 'physical function' and improved 'social functioning', respectively.

Conclusion: Long-term mechanical ventilation over 6 years improved health-related quality of life in most patients. Patient training, follow-up and reduction of side effects, largely delivered by trained nurses, contribute to achieve the main goal of the treatment—improved health-related quality of life.

KEYWORDS
long-term care, patient perspectives, quality of care, quality of life, respiratory nursing

1 | INTRODUCTION

Long-term mechanical ventilation (LTMV) is a treatment used for individuals with chronic hypercapnic respiratory failure (CHRF) primarily caused by neuromuscular diseases (NMD), obesity hypoventilation syndrome (OHS), chronic obstructive pulmonary disease (COPD) and restrictive thoracic disorders (RTD) (Windisch, 2008). LTMV is defined as non-invasive ventilation using a mask or mouthpiece, or invasive ventilation using a tracheostomy for a period of at least 3 months on a daily basis and the treatment is carried out mainly in the user's home or at a long-term care facility (Lloyd-Owen et al., 2005). The estimated prevalence of LTMV in Norway and Europe is 37 and 6.6 per 100,000 respectively (Norwegian LTMV Registry 2016, Lloyd-Owen et al., 2005).

Most individuals treated with LTMV have incurable and often chronically progressive diseases (Huttmann & Windisch, 2015; p. 277). Without LTMV, individuals with CHRF have severely impaired health-related quality of life (HRQoL) (Dellborg et al., 2002), but LTMV might have an impact on daily life (Brooks et al., 2004; Lindahl, Sandmann, & Rasmussen, 2005) and lifelong follow-up from the healthcare service is needed (Leasa & Elson, 2016). Improving or maintaining HRQoL is one of the main goals both in invasively ventilated (AARC, 2007) and in non-invasively ventilated individuals (McKim et al., 2011).

1.1 | Background

The knowledge about how LTMV has an impact on HRQoL, has increased, but is still patchy (MacIntyre, Asadi, Mckim, & Bagshaw, 2016; Simonds, 2016). Certain aspects of HRQoL are well documented while others are poorly investigated. Knowledge from qualitative studies found that LTMV gave more energy to cope with daily life (Ballangrud, Bogsti, & Johansson, 2009) and young men with Duchenne muscular dystrophy (DMD) reported that acquiring a ventilator enabled them to make a new positive start to life (Dreyer, Steffensen, & Pedersen, 2010).

In a discussion paper on quality of life, Moons, Budts, and De Geest (2006) found that quality of life was an umbrella term, covering different other concepts such as HRQoL, health status, symptoms and happiness (Moons et al., 2006). As a result, research under the heading of quality of life may cover similar, but still different concepts. In clinical research, the term HRQoL is widely used, but as this term also is lacking in conceptual clarity, previous research is based on many different measures. According to Windisch (2008), the concept of HRQoL has many components and covers aspects of self-reported physical health, psychological well-being, social relations and functional capacities. Following a comprehensive methodological process, including patients treated with LTMV, the Severe Respiratory Insufficiency (SRI) questionnaire was developed, specific for measuring HRQoL in LTMV patients (Windisch et al., 2003). Condition-specific questionnaires are more tailored and responsive than generic questionnaires towards problems of particular importance to the target group of patients (Fayers & Machin, 2016, p. 118). The

Why is this research/review needed?

- The main goal with long-term mechanical ventilation is to increase or maintain health-related quality of life. People suffering from chronic hypercapnic respiratory failure not treated with long-term mechanical ventilation have severely impaired health-related quality of life.
- The knowledge of how long-term mechanical ventilation has an impact on health-related quality of life is poor and there are even fewer studies on which factors influence changes in it over several years.
- Previous studies measuring health-related quality of life in patient treated with long-term mechanical ventilation have most often used questionnaires not specific for this group. The validated Severe Respiratory Insufficiency questionnaire has been developed for and together with this group of patients, but not yet used in a long-term follow-up study.

What are the key findings?

- Six-year follow-up study of patients treated with long-term mechanical ventilation found improved health-related quality of life measured by the specific and validated Severe Respiratory Insufficiency questionnaire.
- The improvements were in the total score of the questionnaire and in the domains reflecting anxiety related to breathing, contact and relationships with other people and the ability to cope with their condition and overall satisfaction with life.
- Patient-reported satisfaction with training and follow-up from healthcare professionals were factors that contributed to improved health-related quality of life in this group. Side effects from non-invasive ventilation interacted with change in the total SRI score. High forced vital capacity from lung function measurements was a factor for improvements in the social functioning domain and high age was an explanatory factor for reduced score the physical function domain.

How should the findings be used to influence policy/practice/research/education?

- The findings add valuable new knowledge in the field of respiratory care and should be included in the current curriculum for healthcare professionals. The study outcomes are important to decision-making both at the individual level concerning treatment options and in terms of planning of healthcare services for patients treated with long-term mechanical ventilation.
- Nurses interact with long-term mechanical ventilation patients in the outpatient clinic, in hospital wards and through home care and are in a unique position to offer systematic patient training, prevent or reduce side effects of non-invasive ventilation and ensure that patients receive realistic information about possible side effects.
- We recommend further prospective international multicentre studies on the link between long-term mechanical ventilation and health-related quality of life aspects, including on intervention models for training and follow-up in this group of patients by including them as members of the multidisciplinary team and use of patient-reported and registry data to improve care and health-related quality of life.

scientific framework for the concept of HRQoL in the present study was therefore based on research that used the SRI questionnaire in patients treated with LTMV.

Applying the SRI questionnaire, a 1-year follow-up study found significant improvements amongst patients with CHRF in a mixed study population including NMD, OHS, RTD and COPD. HRQoL improved after 1 month of LTMV and the results remained stable at the elevated level during the following year (Windisch, 2008). Two randomized controlled trials (RCT) reported significant improvements in the SRI scores 1 year after initiating LTMV in patients with severe COPD (Köhnlein et al., 2014; Struik et al., 2014). Still, there is an ongoing discussion regarding the indication and benefit of LTMV in COPD patients (Simonds, 2016).

We have been unable to identify studies using a questionnaire specific to patients treated with LTMV in a follow-up study over more than 1 year, or studies focusing on the efficacy of ongoing LTMV over several years. However, some sociodemographic and clinical variables associated with HRQoL measured with the SRI questionnaire have been identified. Men had poorer HRQoL scores in the 'respiratory complaints' and 'anxiety' domains compared with women (López-Campos et al., 2008). The underlying disease was an explanatory variable for change in the single domains of the SRI, as significant improvements in 'physical function' were evident only in patients with COPD and RTD. The largest improvements were observed in NMD and OHS patients in the 'attendant symptoms and sleep' domain (Windisch, 2008). Co-morbidity was more prevalent in older patients with COPD, reducing their SRI score compared with younger patients with NMD (Huttmann, Windisch, & Storre, 2015). The physiological efficacy of the LTMV treatment is to decrease the work of breathing and support gas exchange (Georgopoulo, 2013). However, ventilation modes and additional long-term oxygen therapy were not associated with HRQoL (Budweiser et al., 2007) and ventilator settings in obese patients had no influence on change in HRQoL assessed by the SRI questionnaire (Murphy et al., 2012; Storre et al., 2006). Furthermore, the most common criteria generally used to examine the severity of CHRF are the physiological measurements, partial pressure of carbon dioxide ($pCO_{2)}$ and forced vital capacity (FVC) (Simonds, 2016).

These physiological measurements do not reflect the perceptions and subjective state of the patient, but correlations have been reported between these physical measurements and the physical aspects of HRQoL (Hahn et al., 2007). High ventilator pressure settings, aiming to reduce levels of pCO_2, were also proposed as the explanation for improved SRI scores in individuals with COPD (Köhnlein et al., 2014).

Some aspects of HRQoL in LTMV are well documented. However, there are certain areas especially relevant for nurses that have only been incompletely investigated. LTMV can be time-consuming and costly and may contribute to significant side effects. If LTMV increases the burden of disease without any positive effects on HRQoL, it would raise ethical concerns (Windisch, 2010 p. 582). Fex, Flensner, Ek, and Söderhamn (2012) recommended supplementary nursing support for people using advanced medical technology at home. Good HRQoL in individuals receiving LTMV depends on good care being provided by competent healthcare personnel (Brooks et al., 2004; Lindahl et al., 2005). However, shortcomings in the information and follow-up provided by healthcare staff have been reported. Access to better trained personnel has been requested by LTMV patients (Chang, Marsh, Smith, & Neill, 2010), who suffer from severe conditions requiring information, support and long-term care to enjoy the best quality of life available (Leasa & Elson, 2016). There is limited knowledge of how indicators like side effects of the treatment, satisfaction with LTMV training and follow-up might influence changes in HRQoL.

2 | THE STUDY

2.1 | Aims

The objectives of the present study were as follows:

- to examine changes in HRQoL in patients treated with LTMV from 2008-2014.
- To examine sociodemographic, clinical and patient-reported explanatory variables associated with changes in HRQoL in this group.

2.2 | Design

The research design was a prospective cohort study.

2.3 | Participants

In 2008, all patients aged ≥18 years in the Norwegian national LTMV registry in Western Norway were invited to participate in the study. The inclusion criteria were patients treated with non-invasive or invasive LTMV for at least 3 months who were mentally able to answer questions. Those who agreed to participate were followed until 2014.

2.4 | Data collection

Data collection included clinical variables from the LTMV registry as well as patient-reported clinical information from questionnaires at the start of the study in 2008 and at its end in 2014. At the start, an information letter, the baseline questionnaires and a stamped return envelope were sent by mail. The follow-up (2014) questionnaires were completed when the patients attended their regular consultation in the outpatient clinic at the two university hospitals in Western Norway.

2.4.1 | Norwegian registry for LTMV

The LTMV registry was established in 2002 and formally approved as a national medical quality registry 10 years later. The main purpose of the registry is monitoring LTMV to promote geographic equality, quality assurance, professional development, research and resource planning. Patients permanently dependent on non-invasive

or invasive LTMV during all or part of the day are included. There is a written consent to participate in the registry and it is possible for individuals to withdraw from the register. The national coverage ratio in the registry was 72% in 2016 (Norwegian LTMV Registry 2016). Data collected to the present study from the LTMV registry were sociodemographic data, the date and main diagnosis when starting LTMV, the type of connection to the ventilator, blood gas analyses and spirometry values.

2.4.2 | Explanatory variable for changes in HRQoL

Changes in HRQoL were examined according to baseline characteristics measured in 2008. The background variables used were: sex; age; education; marital status and disease. The potential explanatory variable for changes in HRQoL included: number of years treated with LTMV; pCO_2 and FVC. Patient-reported explanatory variable for changes in HRQoL included hours a day on LTMV, a yes/no question regarding whether they experienced any side effects, with further follow-up questions on which side effects, where they were given the following options: air leakage from the mask; soreness caused by mask pressure; condensation inside the mask; and an option to describe other side effects in their own words. Dependency on daily assistance with using the ventilator was measured by one yes/no question. Patient satisfaction with the follow-up from specialist healthcare professionals consisted of one statement ("Received adequate follow-up") as did patient satisfaction with training in the use of LTMV ("Received adequate training in LTMV"), both of which had five response categories ranging from "Strongly disagree"—"Strongly agree".

2.4.3 | Study setting: Clinical follow-up from healthcare professionals

Clinical follow-up for LTMV patients is organized through a national multi and interdisciplinary competence network. The network is coordinated by a physician and includes specially trained nurses and physiotherapists, specialists in neurology and general practitioners. It also includes a liaison nurse who plays an important role when the patient is transferred from hospital to their home with a ventilator, both in terms of educating the caregiver team and promoting contact with relatives and caregivers in the community. Follow-up visits take place 1 to 4 times a year depending on individual circumstances such as medical condition and psychosocial factors.

2.4.4 | Outcome variable of the study

The outcome variable in the present study was HRQoL, measured by the SRI questionnaire at baseline (2008) and follow-up (2014). This is a specific, multidimensional questionnaire covering physical, psychological and social functioning and was originally developed for and together with patients receiving LTMV to obtain subjective descriptions of issues that were important in their daily lives. The questionnaire contains 49 items and is divided into seven subdomains. High summary scale values (range 0–100) indicate a better HRQoL and the subscales are as follows:

SRI-Respiratory Complaints contains eight items relating to dyspnoea at rest and during physical activity. It covers how often breathlessness occurs and the degree of waking up with breathlessness at night. Breathlessness during speaking, eating and problems with coughing or mucus in the airways are included in this subdomain.

SRI-Physical Function consists of six items and includes the patient's ability to execute everyday physical activities, such as getting dressed, walking stairs and doing housework. Participation in physical leisure activities and how breathing problems have an impact on activities are covered by this subdomain.

SRI-Attendant Symptoms and Sleep contains seven items addressing the quality of sleep, measured by patient-reported waking up during the night, problems with falling asleep and general interruptions of sleep. Daytime tiredness, dizziness and headaches are also covered by this subdomain.

SRI-Anxiety consists of five items including experiences of feeling anxious about having attacks of dyspnoea and about suffering dyspnoea at night. Avoiding situations that are stressful due to breathing difficulties and being worried that the disease will get worse are also included in this subdomain.

SRI-Social Relationships contains six items including having friends and feeling comfortable in the company of other people or feeling lonely and isolated. The disease burden on family life is also covered in the subscore.

SRI-Social Functioning consists of eight items including the degree of broken contact with friends and acquaintances. Limited leisure opportunities, ability to attend social events and the impact of the disease on marriage or relationships are covered by this subdomain.

SRI-Psychological Well-Being includes nine items covering the patient's ability to cope with the disease. The degree of sadness and overall satisfaction with life are included. Each item belongs to only one subscale and all items are rated on a five-point Likert scale from "strongly agree" to "strongly disagree".

Questions refer to the patient's health status during the previous week. The summary scale was obtained by calculating the mean of the values of each scale (Windisch et al., 2003). However, the minimal clinically important difference of the SRI questionnaire has not been defined.

2.5 | Ethical considerations

The study was approved by the Norwegian Committee of Ethics in Medicine, Region III and by the Norwegian Centre for Research Data (project number 16001). In the Information letter, to the patients in 2008 it was informed that the data were stored for 10 years for a possible follow-up study and returning the questionnaires by mail were considered consent to participate in the study. One reminder letter was sent (Markussen, Lehmann, Nilsen, & Natvig, 2015). Prior to the follow-up study in 2014, the patients received a new information letter about the follow-up study. There was a written consent to participate in the follow-up study. It was possible for the patients

to decline from participation in the study, but still be a part in the register.

2.6 | Data analysis

All statistical analyses were carried out using SPSS version 20 (SPSS Inc., Chicago, IL, USA) and Stata *SE* 14 (StataCorp LP, College Station, TX, USA) for Windows. Descriptive statistics were used to quantify sample characteristics. The items in the SRI were recoded and summarized following the guidelines of the original SRI questionnaire (Windisch et al., 2003). All statistical tests were two-tailed and *p* values lower than.05 were considered as statistically significant.

To estimate changes in the seven SRI domains from the start of the study in 2008 to its end in 2014, we used linear mixed effects models. All models defined the time-period as a fixed effect, whereas a random intercept for the individual was specified to account for correlated observations of the same individual (an exchangeable correlation structure was assumed). Further, to identify explanatory variables associated with change in the seven SRI domains from 2008 - 2014, we extended the abovementioned models to include the relevant explanatory variables and the product between the explanatory variable and time-period (i.e. an explanatory variable-by-time interaction) as model terms.

Estimated mean changes in the SRI domains from 2008 to 2014 in categories of explanatory variables were reported using regression model coefficients (β) with 95% confidence intervals (CIs) and *p* values. To obtain *p* values for explanatory variables associated with SRI change, we used the likelihood ratio test, i.e. comparing the log-likelihood between models with and without the explanatory variables - by-time interaction term. Analyses were adjusted for the following background variables: sex; age; education; marital status; years on LTMV and disease.

2.7 | Validity, reliability and rigour

Validity and reliability in quality of life research has been discussed (Macduff, 2000; Moons et al., 2006). Good validity and international relevance of this study is provided by using the SRI questionnaire, that has shown very good psychometric qualities and has been professionally adapted and translated into several languages (Duiverman, Wempe, Bladder, Kerstjens, & Wijkstra, 2008; Ghosh, Rzehak, Elliott,

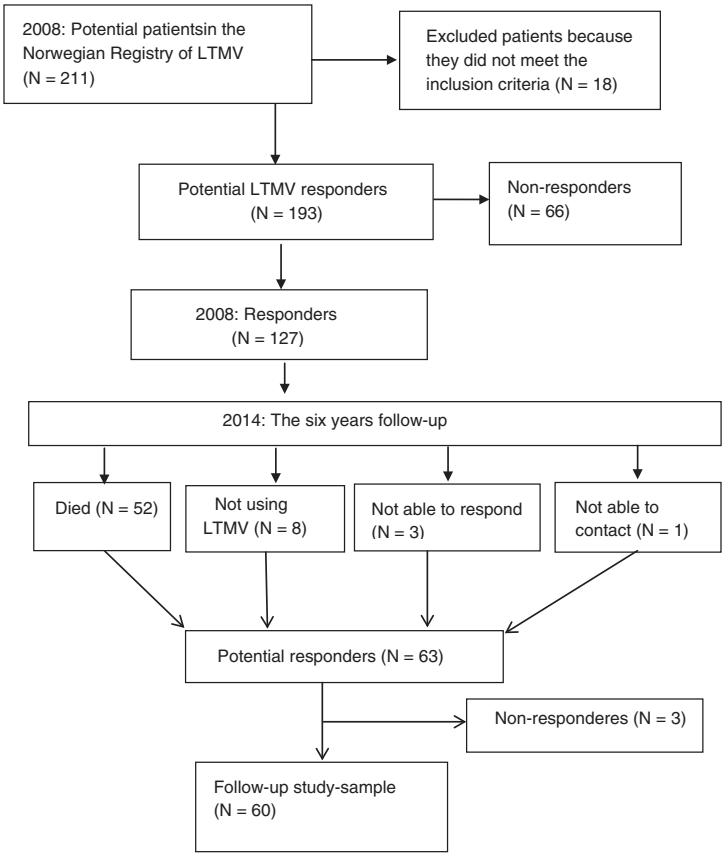

FIGURE 1 Flow diagram of the long-term mechanical ventilation (LTMV) patients from 2008 to 2014

& Windisch, 2012; Huttmann et al., 2015, p. 280; López-Campos et al., 2008; MacIntyre et al., 2016; Markussen et al., 2015; Oga et al., 2017; Ribeiro, Ferreira, Conde, Oliveira, & Windisch, 2017; Struik et al., 2013; Windisch, 2008; Windisch et al., 2003). Reliability and rigour are provided through high-quality clinical data from the LTMV registry.

3 | RESULTS

3.1 | Study population

Of 193 potential responders in the LTMV registry, 127 (65.8%) patients agreed to participate and completed the SRI questionnaire at baseline in 2008 (Figure 1). Of the 127 individuals eligible for follow-up in 2014, 52 had died during the 6-year period. Additionally, 15 patients were excluded for the following reasons: dementia or unable to answer the questionnaire ($N = 3$); stopped using LTMV ($N = 8$); unable to make contact ($N = 1$); and did not want to participate in follow-up study ($N = 3$). These exclusions related to the disease groups NMD ($N = 6$), COPD ($N = 2$), OHS ($N = 6$) and RTD ($N = 1$), leaving a final study sample of 60 (95%) patients (Figure 1), ranged in age from 18 to 85 years at inclusion in 2008. The majority of the patients lived in their own home, only five of the patients lived in nursing homes.

3.2 | Clinical characteristics

Before LTMV treatment (at least 3 months before the start of the study), the mean blood value of daytime carbon dioxide ($PaCO_2$ $kP_{a)}$ and oxygen (PaO_2 kP_a) was 6.7 (standard deviation [*SD*] 1.9) and 9.1 (*SD* 1.7), respectively. In 2008, the mean respirator inspiratory positive airway pressure (IPAP) was 15.5 cmH_2O (*SD* 2.8) and the expiratory pressure (EPAP) was 6.9 cmH_2O (*SD* 2.7) ($N = 45$). Non-invasive ventilation (NIV) was the main ventilation mode, only 2 of the surviving patients in 2014 had tracheostomy interface. No patients used a mouthpiece or helmet as an interface for LTMV. Side effects from the non-invasive LTMV were reported by 29 individuals (Table 1). The most common side effects were air leakage between the face and the mask ($N = 21$) and soreness caused by mask pressure ($N = 10$). Other patient-reported side effects were condensation inside the mask ($N = 5$), dry nose and mouth ($N = 2$), eye irritation, ventilator noise and patient-ventilator synchronization problem ($N = 1$). Three people reported three different kind of side effects, five individuals reported two different side effects, while most individuals reported one single side effect ($N = 21$).

3.3 | Change in HRQoL from 2008 to 2014

There were statistically significant improvements in the total SRI score at mean 4.74 ($p = .005$) and in four subdomains: SRI-Anxiety, SRI-Social Functioning, SRI-Social Relationships and SRI-Psychological Well-Being. The largest improvement was observed for the Social Relationships domain, with an improvement of 8.47 ($p = .001$) (Table 2) (Table S5). The improvements in the total score of SRI were seen in all disease groups, except in patients with COPD (Table 3), who also had a reduction in five of seven SRI subdomains (Table 4) (Table S1–S4).

TABLE 1 Baseline characteristic of the surviving individuals treated with LTMV in the longitudinal study

Characteristic	*N*	Baseline 2008
Background		
Sex, male (*n*, %)	60	32 (53.3)
Age, years (*M*, *SD*)	60	58.0 (15.5)
Education (*n*, %)		
Primary school	60	18 (30.0)
High school	60	23 (38.3)
College/University	60	19 (31.7)
Marital status (*n*, %)		
Married/cohabiting	60	34 (56.7)
Single/divorced/widowed	60	26 (43.3)
Years of LTMV (*M*, *SD*)	60	5.23 (4.0)
Disease (*n*, %)		
NMD[a]	60	26 (43.3)
COPD	60	6 (10.0)
OHS	60	22 (36.7)
RTD	60	6 (10.0)
Treatment		
LTMV h/day (*n*, %)[b]		
5–8	58	33 (56.9)
8–24	58	25 (43.1)
Dependency of daily assistance (*n*, %)	59	16 (27.1)
Side effects of non-invasive LTMV (*n*, %)	58	29 (50.9)
Satisfactions with LTMV training (*n*, %)[c]		
Some satisfaction	59	9 (15.5)
Quite satisfied	59	18 (30.5)
Very satisfied	59	32 (54.2)
Satisfactions with follow-up (*n*, %)[c]		
Some satisfaction	49	8 (16.3)
Quite satisfied	49	13 (26.5)
Very satisfied	49	28 (57.1)
Respiratory		
FVC (litre) (*M*, *SD*)	47	2.09 (1.07)
$PaCO_2$ kP_a daytime (*M*, *SD*)	47	5.66 (0.86)
PaO_2, kP_a daytime (*M*, *SD*)	44	10.3 (1.63)

SD, standard deviation; LTMV, long-term mechanical ventilation; NMD, neuro muscular disease; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; RTD, restrictive thoracic disorders; FVC, forced vital capacity; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen.

[a]None with amyotrophic lateral sclerosis (ALS).

[b]Because of low numbers, the 8–12 and 12–24 categories of this variable were grouped together.

[c]Because of low numbers, the three lowest categories of this variable were grouped together.

TABLE 2 Changes in HRQoL from 2008 to 2014 measured by The Severe Respiratory Insufficiency (SRI) questionnaire in the individuals treated with long-term mechanical ventilation

SRI	N	2008 M (SD)	N	2014 M (SD)	Change[a] mean	95% CI	p
Respiratory complaints	59	61.0 (22.4)	60	62.8 (20.8)	1.86	(−3.19, 6.91)	.46
Physical functioning	59	45.9 (23.0)	60	46.7 (23.4)	0.67	(−4.07, 5.42)	.78
Attendant symptoms and sleep	59	53.3 (20.1)	60	55.7 (21.6)	2.48	(−2.14, 7.11)	.29
Social relationships	59	70.7 (24.4)	60	79.1 (19.5)	8.47	(3.48, 13.5)	.001
Anxieties	59	64.2 (27.5)	60	72.1 (22.9)	7.94	(2.42, 13.5)	.006
Well-being	59	66.1 (22.0)	60	74.2 (17.0)	7.66	(3.28, 12.0)	.001
Social functioning	59	56.5 (24.9)	60	62.4 (25.7)	5.89	(0.91, 10.9)	.02
SUM score	59	60.0 (18.5)	60	64.8 (16.8)	4.74	(1.49, 8.00)	.005

HRQoL, health-related quality of life; *SD*, standard deviation; CI, confidence interval.
[a]Change in SRI is estimated by linear mixed effects model with random intercept.

TABLE 3 Change in the Severe Respiratory Insufficiency (SRI) sum score according to baseline characteristics

Characteristic	SRI-SS 2008 M (SD)	SRI-SS 2014 M (SD)	Estimated change in means[a]	95% CI	p for change	p for interaction
Background						
Sex						.88
Female	57.8 (16.1)	62.3 (15.0)	5.06	(0.30, 9.80)	.04	
Male	61.8 (20.0)	66.4 (18.0)	4.57	(0.21, 8.94)	.04	
Age						.79
≤60	61.7 (16.2)	66.9(15.1)	5.25	(0.40, 10.1)	.03	
>60	58.7 (20.0)	62.7 (17.6)	4.37	(0.08, 8.66)	.05	
Education						
Primary school	56.2 (20.8)	61.2 (19.1)	5.01	(−0.74, 10.8)	.09	.71
High school	56.0 (15.5)	61.7 (14.1)	6.16	(0.86, 11.4)	.02	
College/University	68.7 (16.8)	70.8 (15.9)	2.98	(−2.76, 8.72)	.30	
Marital status						.74
Married/cohabiting	59.9 (18.1)	64.9 (16.5)	5.25	(1.03, 9.48)	.01	
Single/divorced/widowed	60.2 (19.0)	64.0 (17.1)	4.17	(−0.76, 9.11)	.10	
Years on LTMV						.56
≤ 4	57.7(18.7)	63.0 (16.0)	5.65	(1.30, 9.99)	.01	
> 4	62.9 (17.8)	66.2 (17.5)	3.75	(−1.00, 8.49)	.12	
Disease						
NMD	62.8 (13.2)	65.2 (10.6)	3.2	(−1.61, 8.00)	.19	.14
COPD	51.1 (25.7)	48.5 (21.0)	−2.6	(−12.3, 7.06)	.60	
OHS	60.1 (20.2)	69.0 (18.5)	9.00	(3.85, 14.1)	.001	
RTD	57.8 (22.9)	61.6 (20.8)	3.83	(−5.83, 13.5)	.44	
Treatment						
LTMV h/day[b]						.88
5–8	61.0 (18.2	64.9(14.4)	4.51	(0.24, 8.77)	.04	
8–24	59.2 (19.6)	63.1(19.7)	4.02	(−0.82, 8.88)	.10	
Dependency of daily assistance						.76
No	60.9 (19.1)	65.4 (18.1)	4.56	(0.81, 8.31)	.02	
Yes	57.5 (16.2)	62.8 (12.4)	5.72	(−0.54, 11.9)	.07	
Side effects of non-invasive LTMV						.02

(Continues)

TABLE 3 (Continued)

Characteristic	SRI-SS 2008 *M* (*SD*)	SRI-SS 2014 *M* (*SD*)	Estimated change in means[a]	95% CI	*p* for change	*p* for interaction
No	63.9 (20.1)	64.7 (18.8)	1.07	(−3.38, 5.52)	.64	
Yes	56.2 (16.1)	65.1 (15.4)	8.89	(4.66, 13.1)	<.001	
Satisfactions with LTMV training[c]						.09
Some satisfaction[b]	51.1 (15.2)	60.7 (16.2)	9.56	(1.69, 17.4)	.02	
Quite satisfied	55.2 (18.2)	62.7 (17.4)	8.06	(2.35, 13.8)	.006	
Very satisfied	65.1 (18.0)	67.0 (16.6)	1.80	(−2.43, 6.03)	.40	
Satisfactions with follow-up[c]						
Some satisfaction	57.0 (27.4)	63.8 (16.9	9.87	(0.13,19.6)	.05	.24
Quite satisfied	53.1 (14.8)	60.0 (12.1)	6.90	(0.20, 13.6)	.04	
Very satisfied	66.4 (16.5)	68.5 (17.7)	2.01	(−2.63, 6.65)	.39	
Respiratory[d]						
FVC (litre)						
Per 1 unit increase			2.26			.17
$PaCO_2$ kP_a daytime						
Per 1 unit increase			−1.04			.62
PaO_2, kP_a daytime						
Per 1 unit increase			−1.67			.15

SRI-SS, severe respiratory insufficiency sum score; *SD*, standard deviation; CI, confidence interval; LTMV, long-term mechanical ventilation; NMD, neuro muscular disease; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; RTD, restrictive thoracic disorders; FVC, forced vital capacity; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen.

[a]Estimated by mixed effects models, adjusted for background variables: sex, age, education, marital status, years on LTMV and disease.

[b]Because of low numbers, the 8–12 and 12–24 categories of this variable were grouped together.

[c]Because of low numbers, the three lowest categories of this variable were grouped together.

[d]For continuous respiratory variables, data are presented as estimated change in SRI-SS for one unit increase (in the respiratory variables) and the corresponding *p* for interaction.

3.4 | Explanatory variables associated with change in HRQoL

Of 13 baseline characteristics evaluated as potential explanatory variables for change in HRQoL from 2008 to 2014, five variables were identified as significant factors for change in HRQoL. Side effects of the non-invasive LTMV were significantly associated with the total SRI score (Table 3) and SRI-Physical function (Table S1). Satisfaction with LTMV training was associated with an improved SRI-Psychological Well-Being score (Table 4). Satisfaction with follow-up from healthcare professionals in the specialist health care service was one explanatory variable for improvement in the SRI-Anxiety score (Table 5). High age was one explanatory variable for a lower SRI-Physical Function score (Table S1) and high FVC was correlated with improved HRQoL in the SRI- Social Functioning score (Table S2).

4 | DISCUSSION

This study adds valuable new knowledge by being the first study to examine the impact of 6 years of LTMV on HRQoL using the specific SRI questionnaire developed together with and for people treated with LTMV. HRQoL improved both as measured by the total score and by four of the seven SRI subdomains. The improvements occurred in the clinically important domains 'anxiety', 'social functioning', 'social relationships' and 'psychological well-being'.

This study is also unique in that it identified explanatory variables possible for nurses to intervene on, aiming to achieve the main goal of LTMV, which is to improve HRQoL. These results were based on self-reported measures and as in most research on HRQoL, the results may partly be explained by a better adaptation to living with a chronic illness. However, a meta-analysis examining the clinical significance of such an explanation, could not confirm this when examining studies based on measures of response shift (Schwartz et al., 2006).

4.1 | Patient evaluation of LTMV training and follow-up as factors associated with changes in HRQoL

The positive relationship between patient satisfaction with training in the use of LTMV and improvement in the SRI-Psychological Well-Being score is clinically important. It indicates that thorough basic training in use of the ventilator and interfaces are vital success factors for a better satisfaction with life after 6 years.

TABLE 4 Change severe respiratory insufficiency (SRI)-well-being (WB) score according to baseline characteristics

Characteristics	SRI-WB 2008 *M* (*SD*)	SRI-WB 2014 *M* (*SD*)	Estimated change in means[a]	95% CI	*p* for change	*p* for interaction
Background						
Sex						.92
Female	65.8 (22.7)	73.4 (18.2)	7.91	(1.52, 14.3)	.01	
Male	66.6 (21.8)	74.5 (16.0)	7.44	(1.57, 13.3)	.01	
Age						.96
≤60	66.8(21.7)	75.1(17.1)	7.73	(1.19, 14.2)	.02	
>60	65.8(22.6)	73.1 (17.0)	7.51	(1.74, 13.3)	.01	
Education						.87
Primary school	60.3 (24.4)	69.4 (18.2)	9.18	(1.41, 16.9)	.02	
High school	62.9 (19.2)	70.4 (17.1)	7.49	(0.36, 14.6)	.04	
College/University	76.2 (20.2)	82.3 (12.6)	6.32	(−1.42, 14.0)	.11	
Marital status						.24
Married/cohabiting	65.1 (19.3)	75.1 (15.4)	9.85	(4.23, 15.5)	.001	
Single/divorce widowed	67.7 (25.4)	72.4 (19.0)	4.66	(−1.90, 11.2)	.16	
Years on LTMV						.43
≤4	63.4 (23.3)	73.2 (17,7)	9.21	(3.38, 15.0)	.002	
>4	69.7 (20.1)	74.9 (16.2)	5.72	(−0.66, 12.1)	.08	
Disease						.18
NMD	71.2 (16.6)	76.0 (13.0)	5.33	(−1.18, 11.8)	.12	
COPD	62.0 (33.5)	60.6 (23.8)	−1.39	(−14.5, 11.7)	.83	
OHS	61.5 (23.7)	75.0 (18.8)	13.0	(6.07, 20.0)	<.001	
RTD	67.9 (23.0)	75.0 (16.1)	7.06	(−6.03, 20.1)	.29	
Treatment						
LTMV h/day[b]						.77
5–8	69.2 (21.8)	75.5 (15.9	6.65	(0.87, 12.4)	.02	
8–24	63.7 (22.7)	72.2 (18.8)	7.98	(1.39, 14.6)	.02	
Dependency of daily assistance						.94
No	65.9, 22.3)	74.0 (18.4)	7.40	(−1.02, 15.8)	.08	
Yes	67.2 (21.7)	73.6 (13.3)	7.76	(2.71, 12.8)	.003	
Side effects of non-invasive LTMV						.15
No	67.2 (23.2)	72.1 (20.6)	11.2	(5.35, 17.1)	<.001	
Yes	64.6 (21.5)	75.9 (13.7)	4.87	(−1.31, 11.0)	.12	
Satisfactions with LTMV training[c]						.01
Some satisfaction	61.0 (16.0)	74.4 (11.8)	13.4	(3.13, 23.6)	.01	
Quite satisfied	58.5 (21.1)	72.5 (16.2)	14.8	(7.45, 22.2)	<.001	
Very satisfied	71.8 (22.8)	74.5 (19.1)	2.14	(−3.35, 7.62)	.45	
Satisfactions with follow-up[c]						.06
Some satisfaction	62.0 (27.2)	67.7 (14.3)	6.25	(−6.23, 18.7)	.32	
Quite satisfied	60.0 (21.6)	74.6 (15.1)	14.5	(5.93, 23.1)	.001	
Very satisfied	74.2 (21.0)	76.7 (18.8)	1.78	(−4.17, 7.74)	.56	
Respiratory[d]						
FVC (litre)						
Per 1 unit increase			2.61			.27
$PaCO_2$ kP_a daytime						
Per 1 unit increase			1.93			.52

(Continues)

TABLE 4 (Continued)

Characteristics	SRI-WB 2008 *M* (*SD*)	SRI-WB 2014 *M* (*SD*)	Estimated change in means[a]	95% CI	*p* for change	*p* for interaction
PaO_2, kP_a daytime						
Per 1 unit increase			−2.93			.07

SRI-SS, severe respiratory insufficiency sum score; *SD*, standard deviation; CI, confidence interval; LTMV, long-term mechanical ventilation; NMD, neuro muscular disease; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; RTD, restrictive thoracic disorders; FVC, forced vital capacity; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen.
[a]Estimated by mixed effects models, adjusted for background variables: sex, age, education, marital status, years on LTMV and disease.
[b]Because of low numbers, the 8–12 and 12–24 categories of this variable were grouped together.
[c]Because of low numbers, the three lowest categories of this variable were grouped together.
[d]For continuous respiratory variables, data are presented as estimated change in SRI-SS for one unit increase (in the respiratory variables) and the corresponding *p* for interaction.

Patient satisfaction is related to the extent to which general healthcare needs and condition-specific needs are met (Guldvog, 1999). The importance of giving proper training to a ventilator-assisted individual is recognized as fundamental for good HRQoL. However, it has not previously been well documented (Norregaard & Escarrabill, 2010; p.172). According to Escarrabill (2015, p.282), the competencies of the LTMV patient are directly related to the clinical outcome. To our knowledge, no studies have focused on patient training or education in patients receiving LTMV with HRQoL as a primary outcome. A Cochrane review also concluded that there was a small improvement in quality of life in COPD patients without LTMV treatment who received a short patient training program compared with those receiving usual care (Howcroft, Walters, Wood-Baker, & Walters, 2016).

The SRI-Anxiety score was considerably improved both in the overall analysis and in subanalysis of the different disease categories, in line with the outcomes of other studies (Köhnlein et al., 2014; Struik et al., 2014; Windisch, 2008). The findings implicate that follow-up from healthcare professionals might contribute to improve the HRQoL of individuals receiving LTMV related to anxiety for breathlessness. Furthermore, it might indicate that they feel safer in situations where breathlessness may occur. According to Gibson, Brooks, DeMatteo, and King (2009), it is especially important for LTMV patients to have control over their day-to-day schedules, the assistance provided and how it is carried out.

One of the challenges in clinical practice is to identify and target the patients' genuine needs (Leasa & Elson, 2016). There are different approaches to follow-up. The setting for patient training and follow-up in this study was a 'real-world' setting, including a multi and interdisciplinary network model that shares and disseminates professional knowledge and skills in the field of LTMV. An evaluation of management of DMD emphasizes the importance of multidisciplinary care for these patients (Bushby et al., 2010). Escarbilrabill and Norregaard (2010, p.179), also highlight the benefits of network models, such as professional development and continuing education. An important element of patient education and follow-up in ongoing LTMV is the contact between patient and healthcare professionals over several years, where patients and professionals identify and discuss problems caused by, or related to, the LTMV. The patient is thus involved in the care process. This partnership might affect the evaluation of and satisfaction with, the healthcare service. However, the role of patient-reported outcomes measure (PROM) in facilitating communication between healthcare professionals in the multidisciplinary team and the patient as a team member is yet to be explored (Norekvaal, Faalun, & Fridlund, 2016).

4.2 | Patient-reported side effects as factors associated with changes in HRQoL

Patient-reported side effects of non-invasive LTMV were significantly associated with the total SRI score and the SRI-Physical function domain. To our knowledge, this study was the first to identify side effects, such as soreness caused by mask pressure or air leakage between the mask and face, were associated with a lower total SRI score at baseline compared with those reporting no side effects. According to Elliott (2004), some air leakage is an unavoidable consequence of non-invasive LTMV. However, frequent side effects can clearly worsen HRQoL or counteract the HRQoL benefits gained from LTMV (Windisch, 2010, p. 585).

4.3 | Clinical data from the LTMV registry as explanatory variables associated with changes in HRQoL

High FVC was one explanatory variable for improved HRQoL in terms of SRI-Social Functioning, a key domain because it indicates improved leisure opportunities, including the ability to go out in the evening and attend social events (Windisch et al., 2003). An explanation of high FVC as clinically important factor might be that the patients with higher FVC have more physical strength to carry out the social functioning. Interaction between high FVC and improved HRQoL are rarely reported. However, a weak but significant positive association between pulmonary variables and HRQoL was also found in patients with cystic fibrosis who were not treated with LTMV (Hahn et al., 2007).

High age was an explanatory variable for a lower score for SRI-Physical Function. This is in line with Huttmann et al. (2015), who found reduced HRQoL in individuals receiving LTMV of higher age and with chronic lung diseases, compared with younger patients with NMD. Tissot et al. (2015) also found that patients treated with non-

TABLE 5 Change in the severe respiratory insufficiency (SRI)-Anxiety (AX) score according to baseline characteristics

Characteristics	SRI-AX 2008 *M* (*SD*)	SRI-AX 2014 *M* (*SD*)	Estimated change in means[a]	95% CI	*p* for change	*p* for interaction
Background						
Sex						.53
Female	63.9 (25.4)	73.6 (23.0)	9.9	(1.87, 17.9)	.02	
Male	64.4 (29.5)	70.7 (23.0)	6.3	(−1.07, 13.7)	.09	
Age						.96
≤60	63.9 (27.2)	71.7 (23.2)	7.79	(−0.45, 16.0)	.06	
>60	64.4 (28.0)	72.3 (22.9)	8.05	(0.76, 15.3)	.03	
Education						.22
Primary school	58.3 (27.0)	72.8 (24.6)	14.4	(4.70, 24.2)	.004	
High school	59.8 (27.3)	66.9 (23.7)	7.17	(−1.61, 15.9)	.11	
College/University	74.9 (26.4)	77.6 (19.6)	2.76	(−6.71, 12.2)	.57	
Marital status						.53
Married/cohabiting	62.7 (29.1)	72.2 (21.9)	9.48	(2.31, 16.7)	.01	
Single/divorced/widowed	66.2 (25.5)	71.9 (24.5)	5.92	(−2.42, 14.3)	.16	
Years on LTMV						.59
≤4	60.7 (28.5)	70.0 (19.5)	9.28	(1.99, 16.6)	.01	
>4	68.6 (26.0)	74.6 (26.5)	6.26	(−1.93, 14.4)	.13	
Disease						.94
NMD	67.9 (24.0)	75.4 (16.0)	7.85	(−0.63, 16.3)	.07	
COPD	48.3 (32.3)	52.5 (24.6)	4.17	(−13.2, 21.5)	.64	
OHS	66.6 (27.4)	76.3 (25.8)	9.71	(0.63, 18.8)	.04	
RTD	55.8 (36.2)	61.7 (27.5)	5.83	(−11.5, 23.2)	.51	
Treatment						
LTMV h/day[b]						.40
5–8	64.5 (28.1)	73.5 (21.2)	9.28	(1.99, 16.6)	.01	
8–24	65.0 (27.8)	69.5 (25.5)	4.55	(−1.93, 14.4)	.27	
Dependency of daily assistance						.44
No	66.5 (26.7)	72.2 (24.2)	5.67	(−0.19, 11.5)	.06	
Yes	61.4 (26.6)	71.2 (20.0)	10.2	(02.3, 20.1)	.04	
Side effects of non-invasive LTMV						.15
No	69.8 28.1)	71.6 (25.1)	1.91	(−5.07, 8.90)	1.92	
Yes	62.3 (25.1)	71.4 (25.8)	9.09	(2.34, 15.8)	.008	
Satisfactions with LTMV training[c]						.29
Some satisfaction	53.3 (26.2)	68.8 (23.4)	15.5	(2.83, 28.3)	.02	
Quite satisfied	61.8 (24.9)	68.9 (23.4)	7.35	(−1.87, 16.6)	.12	
Very satisfied	70.3 (27.0)	74.5 (23.1)	4.18	(−2.57, 10.9)	.22	
Satisfactions with follow-up[c]						.009
Some satisfaction	49.5 (37.1)	75.0 (23.3)	26.9	(11.8, 41.9)	<.001	
Quite satisfied	53.1 (23.2)	66.5 (22.6)	13.5	(2.32, 24.6)	.02	
Very satisfied	73.6 (24.6)	75.3 (21.0)	1.69	(−5.90, 9.29)	.66	
Respiratory[d]						
FVC (litre)						
Per 1 unit increase			−1.54			.60
$PaCO_2$ kP_a daytime						
Per 1 unit increase			−1.19			.75

(Continues)

TABLE 5 (Continued)

Characteristics	SRI-AX 2008 *M* (*SD*)	SRI-AX 2014 *M* (*SD*)	Estimated change in means[a]	95% CI	*p* for change	*p* for interaction
PaO_2, kP_a daytime						
Per 1 unit increase			−2.18			.28

SRI-SS, severe respiratory insufficiency sum score; *SD*, standard deviation; CI, confidence interval; LTMV, long-term mechanical ventilation; NMD, neuro muscular disease; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; RTD, restrictive thoracic disorders; FVC, forced vital capacity; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen.
[a]Estimated by mixed effects models, adjusted for background variables: sex, age, education, marital status, years on LTMV and disease.
[b]Because of low numbers, the 8–12 and 12–24 categories of this variable were grouped together.
[c]Because of low numbers, the three lowest categories of this variable were grouped together.
[d]For continuous respiratory variables, data are presented as estimated change in SRI-SS for one unit increase (in the respiratory variables) and the corresponding *p* for interaction.

invasive LTMV >75 years had a significantly lower HRQoL measured with SF-36 than patients <75 years.

Previous research has found improvements in the SRI scores 1 year after initiating LTMV in patients with severe COPD (Köhnlein et al., 2014; Struik et al., 2014). One explanation of these differences might be the progressive nature of some of the disease categories might influence HRQoL more clearly in a 6-year study than in a 1-year follow-up. The severity of COPD (GOLD 2017) is also reflected in this study with a reduction in the total SRI score and in five of seven SRI subdomains in the few surviving COPD patients after 6 years in this study population. Huttmann et al. (2015), also found reduced HRQoL in individuals receiving LTMV with chronic lung diseases, compared with those with NMD. However, the ventilator pressure settings for these 60 patients were lower compared with some of the other studies (Windisch, 2008; Köhnlein et al. (2014). Nevertheless, in this study we observed significant reductions in carbon dioxide from before starting LTMV to baseline in 2008, indicating good physiologic effect of the LTMV treatment.

4.4 | Limitations of this study

The study has some limitations. Firstly, the study sample is relatively small and heterogeneous in terms of the diagnoses leading to LTMV, which means that the sample size is insufficient to perform subgroup analyses, such as interaction studies between explanatory variables and HRQoL for the specific subgroups, NMD, OHS, COPD or RTD. Secondly, non-responders in 2008 had lower FVC than those who attended, suggesting more severe disease and a lower HRQoL in the non-participating group, which might influence the representativeness of the sample and generalizability of the result. However, information about the physiological variables of non-participating LTMV patients is a strength for the study. Recruiting patients from the national registry also contributes to strengthen the representativeness of the sample and the generalizability of the result, even if the coverage ratio in the registry was not 100%. Thirdly, there was no control group in this study. Nonetheless, a RCT evaluation of HRQoL in patients receiving LTMV vs. a non-ventilated control group of patients would obviously be considered unethical. Despite the design was unable to examine causal relationships, the study revealed clinical important explanatory variables for improved HRQoL.

5 | CONCLUSION

This study adds important new knowledge by being the first study to examine the impact of 6 years of ongoing LTMV on HRQoL using the specific SRI questionnaire developed for and together with this patient group. The total SRI score and the scores in four of the seven subdomains improved in the majority of the patients treated with LTMV. This study pointed out that patient training, follow-up and reduction of side effects, a healthcare service largely delivered by trained nurses, contribute to achieve the main goal of LTMV treatment- improved HRQoL.

We recommend further prospective studies on HRQoL aspects in LTMV, including standardized intervention models to minimize side effects and to improve training, involvement and follow-up of the patients. LTMV is an expensive treatment for few patients in the community; to assure larger sample size we recommend international cooperation and multicentre studies using the SRI questionnaire.

AUTHOR CONTRIBUTIONS

All authors have agreed on the final version and meet at least one of the following criteria (recommended by the ICMJE [http://www.icmje.org/recommendations/]):

- substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
- drafting the article or revising it critically for important intellectual content.

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CONFLICT OF INTEREST

No conflict of interest has been declared by the authors.

ORCID

Heidi Markussen http://orcid.org/0000-0002-9754-3647

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SUPPORTING INFORMATION

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Paper III

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RESEARCH ARTICLE Open Access

Health-related quality of life as predictor for mortality in patients treated with long-term mechanical ventilation

Heidi Markussen[1,2*], Sverre Lehmann[1,3], Roy M. Nilsen[4] and Gerd K. Natvig[2]

Abstract

Background: The Severe Respiratory Insufficiency (SRI) questionnaire is a specific measure of health-related quality of life (HRQoL) in patients treated with long-term mechanical ventilation (LTMV). The aim of the present study was to examine whether SRI sum scores and related subscales are associated with mortality in LTMV patients.

Methods: The study included 112 LTMV patients (non-invasive and invasive) from the Norwegian LTMV registry in Western Norway from 2008 with follow-up in August 2014. SRI data were obtained through a postal questionnaire, whereas mortality data were obtained from the Norwegian Cause of Death Registry. The SRI questionnaire contains 49 items and seven subscales added into a summary score (range 0–100) with higher scores indicating a better HRQoL. The association between the SRI score and mortality was estimated as hazard ratios (HRs) with 95% confidence intervals (95% CI) using Cox regression models and HRs were estimated per one unit change in the SRI score.

Results: Of the 112 participating patients in 2008, 52 (46%) had died by August 2014. The mortality rate was the highest in patients with chronic obstructive pulmonary disease (75%), followed by patients with neuromuscular disease (46%), obesity hypoventilation syndrome (31%) and chest wall disease (25%) ($p < 0.001$). Higher SRI sum scores in 2008 were associated with a lower mortality risk after adjustment for age, education, hours a day on LTMV, time since initiation of LTMV, disease category and comorbidity (HR 0.98, 95% CI: 0.96–0.99). In addition, SRI-Physical Functioning (HR 0.98, 95% CI: 0.96–0.99), SRI-Psychological Well-Being (HR 0.98, 95% CI: 0.97–0.99), and SRI-Social Functioning (HR 0.98, 95% CI: 0.97–0.99) remained significant risk factors for mortality after covariate adjustment. In the subgroup analyses of patient with neuromuscular diseases we found significant inverse associations between some of the SRI subscales and mortality.

Conclusions: SRI score is associated with mortality in LTMV-treated patients. We propose the use of SRI in the daily clinic with repeated measurements as part of individual follow-up. Randomized clinical trials with interventions aimed to improve HRQoL in LTMV patients should consider the SRI questionnaire as the standard HRQoL measurement.

Keywords: Long-term mechanical ventilation, Health-related quality of life, Predictors, Mortality, Survival, The severe respiratory insufficiency (SRI) questionnaire

* Correspondence: heidi.markussen@helse-bergen.no
[1]The Norwegian National Advisory Unit on Longterm Mechanical Ventilation, Department of Thoracic Medicine, Haukeland University Hospital, Jonas Lies vei 65, N-5021 Bergen, Norway
[2]Department of Global Public Health and Primary Care, University in Bergen, Kalfarveien 31, 5018 Bergen, Norway
Full list of author information is available at the end of the article

Background

Chronic hypercapnic respiratory failure (CHRF) is a persistent state in which ventilation is insufficient to maintain a normal arterial pressure of carbon dioxide ($PaCO_2$) [1, 2]. Long-term mechanical ventilation (LTMV) is a treatment for patients with CHRF due to different aetiologies and includes both non-invasive and invasive mechanical ventilation [2–4]. In adults, CHRF is mainly caused by the following four disease categories: neuromuscular diseases (NMD), chest wall diseases (CWD), obesity hypoventilation syndrome (OHS), and chronic obstructive pulmonary disease (COPD) [2–4]. The number of individuals treated with LTMV is increasing, and the largest growth has been observed in the use of a non-invasive connection to the ventilator through a mask or a mouthpiece [2, 3]. One of the main goals of LTMV is to improve survival [2, 4]. Due to ethical reasons, few randomized controlled trials (RCTs) comparing LTMV versus no LTMV treatment have been carried out in these patients [2, 3]. One of the exceptions is RCTs involving COPD patients with CHRF, where the benefit of LTMV on survival has been and continues to be debated [3, 5, 6]. Two recent RCTs found improved one-year mortality in COPD patients treated with non-invasive LTMV [7, 8]. In NMD patients LTMV has been well-established for several decades [2–4]. One of the few RCTs in this heterogenic category found improved mortality in patients with amyotrophic lateral sclerosis (ALS) [9].

Additionally, several observational studies and uncontrolled trials indicated that LTMV has a positive effect on survival in patients with NMD [10–16], OHS [10, 13, 17–20] and CWD [10–13, 21–23] relative to historical controls.

Self-reported health or health-related quality of life (HRQoL) has been shown to provide prognostic information for different groups [11, 24–27]. The Severe Respiratory Insufficiency (SRI) questionnaire was developed to specifically measure patient-reported HRQoL in patients receiving LTMV [28]. The role of SRI in predicting mortality in patients with CHRF has been examined during two three-year follow-up studies [29, 30]. In the first study, the clinical variables body mass index (BMI), leukocytes, base excess, forced expiratory volume in one second (FEV_1), and inspiratory vital capacity were included in the multivariate analysis [29]. The SRI score was associated with mortality in all patients except for those with COPD [29]. The second study found significant relationships between the SRI score and three-year mortality in LTMV patients with COPD and pulmonary tuberculosis sequelae after adjustment for BMI, $PaCO_2$ and forced vital capacity (FVC), but without subgroup analyses for the different diagnosis group [30]. Other measures of HRQoL, such as St. George's Respiratory Questionnaire (SGRQ) and the Maugeri Respiratory Failure Questionnaire (MRF-28), were associated with mortality in LTMV-treated COPD patients from 21 study centres during 3 years of follow-up [26]. The SRI score's ability to predict mortality in patients treated with LTMV has been poorly investigated. Furthermore, findings are inconclusive [29, 30] and the associations have been investigated for only a limited time period (up to three years). Longer follow-up time might capture a more robust association due to higher mortality rates over time.

Methods

The main objective of the current study was to examine the association between HRQoL measured by the SRI questionnaire and all-cause mortality in LTMV patients over 80 months follow-up.

Study population

This study drew on resources from the Norwegian Registry for LTMV [31], the Norwegian Patient Registry [32], and the Norwegian Cause of Death Registry [33]. The registry data were linked by the personal identity number provided to all Norwegian citizens. The study was approved by the Regional Committee for Medical and Health Research Ethics number (273.06, 2012/1090–11) and the Norwegian Centre for Research Data (project number 16001). A written consent was a prerequisite from the Regional Committee for Medical and Health Research Ethics and the NPR to allow linking data between the registries. For cohort patients who died, exemption from the consent requirement for register connection to the Norwegian Patient Registry and Cause of Death Register was given.

The Norwegian Registry for LTMV was established in 2002 at Haukeland University Hospital, Bergen. The registry includes all patients in Norway who are treated with LTMV on a daily basis. The registry contains detailed information on patient characteristics, medical diagnosis, LTMV treatment and lung function. The registry has been described in detail previously [34, 35].

During the period of March to June 2008, patients in the Norwegian LTMV registry in Western Norway were invited to participate in the current study. The inclusion criteria were patients treated with non-invasive or invasive LTMV, over 18 years old and mentally able to answer additional study questions. Well-adapted LTMV treatment for at least 3 months was required for all participants. The invitation letter also included the SRI questionnaire, a form with questions on socioeconomic demographic conditions, and questions whether the patient had received help with completing the information.

Of 211 potential patients in the LTMV registry, 18 patients did not meet the inclusion criteria (Fig. 1). The remaining 193 eligible patients were invited to participate

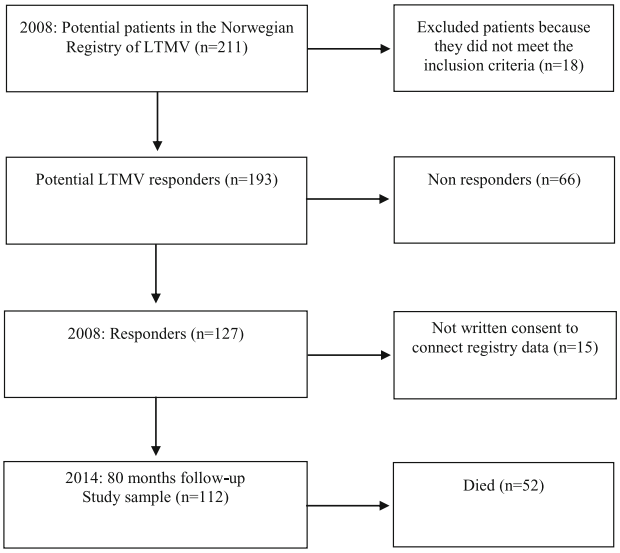

Fig. 1 Flow diagram of patients treated with long-term mechanical ventilation in the prospective cohort study from 2008 to 2014. Follow-up time was 80 months

in the study by postal mail, and 65% (n = 127) consented to participate [34]. Of the 127 patients eligible for follow-up, written consent to connect comorbidity data from the NPR were not available from 15 of the patients. The reason for this were dementia or unable to answer the question (n = 3), had stopped using LTMV (n = 8), unable to make contact (n = 1) or did not want to respond (n = 3). The disease category for these patients were NMD (n = 6), COPD (n = 2), OHS (n = 6) and CWD (n = 1), leaving a final study sample of 112 LTMV patients.

The severe respiratory insufficiency (SRI) questionnaire

Study participants were asked to complete the SRI questionnaire, which is a multidimensional questionnaire covering physical, psychological and social functioning. It was developed with a comprehensive methodology by physicians specialized in pulmonology and psychologists specialized in HRQoL and by open interviews with patients with CHRF treated with LTMV. The SRI questionnaire contains 49 items, and each item is categorized in one of the following seven subscales: SRI-Respiratory Complaints, SRI-Physical Functioning, SRI-Attendant Symptoms and sleep, SRI-Anxiety, SRI-Social Relationships, SRI-Social Functioning, or SRI-Psychological Well-Being. The subscales were added into a summary scale in which high values (range 0–100) indicate a better HRQoL [28]. The SRI questionnaire demonstrates very good psychometric qualities and has been validated and translated into several languages [2, 34–40]. The SRI and MRF-28 questionnaires were recommended for research on HRQoL in patients treated with LTMV [41]. However, the reliability and validity in were better in the SRI compared to MRF-28 Questionnaire, Clinical COPD Questionnaire and Chronic Respiratory Questionnaire in patients with severe COPD treated with non-invasive LTMV [42]. The responsiveness of the SRI to changes in HRQoL after initiating non-invasive LTMV was superior to the generic questionnaire Short form-36 [43] and the SRI had the best ability to predict mortality compared to other HRQoL questionnaires [30]. The English validation study of the SRI included both non-invasive and invasive (tracheostomy) ventilated LTMV patients [37].

All-cause mortality

Information on the date of death was obtained from the Norwegian Cause of Death Registry in October 2014. The Cause of Death Registry covers all deaths in Norway and the deaths of Norwegian citizens who die abroad [33]. All deaths (approximately 40,000 each year) are reported by doctors, who are required to complete a standardized death certificate for each death [33].

Other variables

Based on previous research we also obtained data on educational level [44] and marital status [45]. Educational level was categorized as primary school, high school or college/university, and marital status was classified as married/cohabiting or single/divorced/widowed. Ventilator

dependency was reported by the patients in hours a day they used the ventilator, the answer options were categorized as follow; less than 8 h, 8–12, 12–24 h a day.

From the LTMV registry, we collected data on patient age, sex, treatment time since initiation of LTMV, FVC, FEV_1, $PaCO_2$, partial pressure of arterial oxygen (PaO_2) and main medical diagnosis, which was further categorized into NMD, COPD, OHS, and CWD. Studies have shown that comorbidity is a major prognostic factor in LTMV patients with NMD [13], COPD [46], OHS [18] and CWD [22]. Data concerning comorbidity were not available in the LTMV registry and were therefore collected from the Norwegian Patient Registry (NPR) [33], In this study, comorbidity was assessed similar to another study [47], as the number of somatic ICD-10 diagnosis codes at hospital discharge or an outpatient control for each patient during the recruitment period from March to June 2008.

Statistical analysis

Patient characteristics were quantified using descriptive statistics. The description was performed according to mean SRI sum score and to mortality status. We used the Kaplan-Meier survivor function with the log-rank test to describe the percentage of survivors according to disease groups (NMD, COPD, OHS and CWD).

The association between SRI and mortality was estimated as hazard ratios (HRs) with 95% confidence intervals (95% CIs) using Cox regression models and HRs were estimated per one unit change in the SRI score. The time in months from study inclusion in 2008 (when baseline SRI was measured) until death was used as a measure of event-free time. All patients were followed up to 80 months until censoring, with August 30, 2014, as the final day of follow-up. We verified that the proportional hazards assumption was fulfilled for SRI, both in overall analyses and in subgroup analyses of NMD, COPD and OHS, by visual inspection of log-log plots. Subgroup analyses of CWD were not performed due to the small sample size.

The HRs with 95% CIs were estimated both by crude and adjusted Cox regression models to control for variables that may potentially confound the true association between SRI and mortality. The adjustment variables included age, education, hours a day on LTMV, treatment time since initiation of LTMV, main disease category and comorbidity. We also evaluated FEV_1 and FVC as confounding factors in the overall analyses of SRI. To avoid model overfitting in subgroup analysis of disease categories, only the most important covariates were included in the regression models (for NMD: age, hours a day on LTMV, and comorbidity; for COPD: age and comorbidity; for OHS: comorbidity only).

All statistical analyses were carried out using SPSS version 20 (SPSS Inc., Chicago, IL, USA) and Stata SE 14 (StataCorp LP, College Station, TX, USA) for Windows. All statistical tests were two-sided, and p values lower than 0.05 were considered to be statistically significant.

Results

Background characteristics

The study sample comprised 112 LTMV-treated patients. Of these patients, 48 (43%) were diagnosed with NMD, 24 (21%) with COPD, 32 (29%) with OHS, and 8 (7%) with CWD. At baseline, 103 (92%) patients received non-invasive LTMV, whereas 9 (8%) patients, with NMD, were ventilated invasively via tracheostomy. The mean BMI ($n = 71$) was 27.1 (9.5) in NMD patients, 29.2 (9.1) in COPD patients, 40.6 (7.7) in OHS patients, and 22.5 (5.1) kg/m^2 in CWD patients.

The baseline mean SRI sum score varied considerably by sex, age group, education level, LTMV hours a day, years on LTMV, disease category and comorbidity (Table 1). The SRI sum score in invasively ($n = 10$) and non-invasively ($n = 117$) ventilated patients was 57.0 (16.2) and 58.0 (18.8), respectively. Assistance to complete the SRI questionnaire was reported by 26% of the study participants.

Among the respiratory variables, baseline FEV_1 and FVC correlated significantly with all SRI subscales except for SRI-Attendant symptoms and sleep scale and SRI-Social Functioning (Additional file 1: Table S1). Baseline PaO_2 correlated significantly with SRI-Physical Functioning only. All participants were receiving ventilation treatment at study start, and $PaCO_2$ levels were therefore normalized at baseline. An inverse correlation between baseline $PaCO_2$ and SRI-Social Relationships was present, but no other associations were found for the SRI sum score or for any of the six remaining SRI subscales (Additional file 1: Table S1).

During the 80 months of follow-up, 52 (46%) patients died (Fig. 1). By Kaplan-Meier survival analyses (Fig. 2), we found that patients with COPD had the highest overall mortality rate (75%), followed by patients with NMD (46%), OHS (31%) and CWD (25%) ($p < 0.001$) (Fig. 2). The mortality rates differed between age groups, education levels, LTMV hours a day, years on LTMV, disease categories and burden of comorbidity (Table 2), but not between men and women ($p = 0.88$), and between married /cohabiting and single/divorced/widowed ($p = 0.91$). We found significant differences between survivors and deceased patients in baseline mean FEV_1 and FVC (both $p < 0.001$), and a minor difference in PaO_2 that was not statistically significant (Table 2). There was no significant difference in $PaCO_2$ between the survivors and deceased patients (Table 2).

Table 1 Baseline sum score of the Severe Respiratory Insufficiency questionnaire by background characteristics in 112 patients treated with long-term mechanical ventilation between 2008 and 2014

Characteristic	Participants, n[a] (*n* = 112)	SRI-SS Baseline (2008) mean (SD)
Sex		
Female	48	51.4 (16.7)
Male	57	57.7 (19.5)
Age		
≤ 60	37	59.0 (16.7)
> 60	68	52.5 (19.2)
Education		
Primary school	31	50.0 (20.5)
High school	41	52.2 (16.0)
College/university	33	62.5 (17.6)
Marital status		
Married /cohabiting	60	54.7 (19.1)
Single/divorced/widowed	45	54.9 (18.0)
LTMV h/day		
5–8	45	57.9 (18.3)
8–12	42	55.2 (18.8)
12–24	16	44.9 (17.1)
Years on LTMV		
≤ 4	60	51.9 (18.2)
> 4	45	58.6 (18.4)
Disease		
NMD	43	60.0 (14.8)
COPD	23	41.1 (18.3)
OHS	31	58.0 (18.5)
CWD	8	54.3 (21.1)
Co-morbidity		
No additionally diagnosis	41	60.2 (17.6)
1 additionally diagnosis	28	55.7 (17.9)
≥ 2 additionally diagnosis	36	48.0 (18.3)

Abbreviations: SRI-SS, Severe Respiratory Insufficiency sum score; SD, standard deviation; CI, confidence interval; LTMV, long-term mechanical ventilation; NMD, neuro muscular disease; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; CWD, chest wall diseasese
[a] Numbers do not add to 112 due to missing in the Severe Respiratory Insufficiency questionnaire, as well as missing in education level, marital status and daily hours on LTMV responses

SRI sum and subscales in relation to mortality

Crude analyses of baseline SRI showed significantly higher mean values among the survivors compared to the deceased for the SRI sum score and SRI subscales except in the SRI-Attendant symptoms and sleep scale (Table 3).

The association between the SRI sum score and mortality remained significant after adjustment for age, education level, hours a day on LTMV, treatment time since initiation of LTMV, disease category and comorbidity (HR 0.98, 95% CI: 0.96–0.99). In addition, SRI-Physical Functioning (HR 0.98, 95% CI: 0.96–0.99), SRI-Psychological Well-Being (HR 0.98, 95% CI: 0.97–0.99), and SRI-Social Functioning (HR 0.98, 95% CI: 0.97–0.99) remained significant risk factors for mortality after covariate adjustment (Table 4). Additional adjustment for baseline FVC and FEV_1 did not alter the results much for SRI sum score (adjustment for FVC: HR 0.97, 95% CI: 0.94, 0.99); adjustment for FEV_1: HR 0.97, 95% CI 0.94, 0.99).

Among NMD patients, SRI-Physical Functioning (HR 0.97, 95% CI: 0.94–1.00), SRI-Psychological Well-Being (HR 0.97, 95% CI: 0.95–0.99) and SRI-Social Functioning (HR 0.97, 95% CI: 0.94–0.99) remained significant factors for mortality after adjustment for age, hours a day on LTMV and comorbidity (Table 5).

In COPD patients, SRI-Attendant Symptoms and Sleep (HR 0.97, 95% CI: 0.94–1.00) and SRI-Psychological Well-Being (HR 0.98, 95% CI: 0.96–1.00) remained associated with mortality after adjustment for age and comorbidity (Table 6). The SRI sum score or subscales were not associated with mortality among patients with OHS (Additional file 1: Table S2).

Discussion

We found that HRQoL, as measured by the SRI questionnaire, was inversely associated with mortality in LTMV patients before and after adjustment for covariates. In the total group of LTMV patients, the adjusted analyses showed significant inverse associations between mortality and the SRI sum score and the SRI subscales, 'physical functioning', 'social functioning' and 'psychological well-being'. Furthermore, mortality varied considerably between the disease groups during the six-year period. The highest mortality was among COPD patients with established CHRF receiving LTMV. The majority of mortality in COPD is related to cardiac disease and the requirement of LTMV in COPD might be understood as a marker of overall frailty and multi-system disease severity. The lowest mortality was in the CWD group, reflecting the non-progressive nature of the disease in these patients.

As shown in previous studies [3, 10–13, 23], mortality in patients treated with LTMV is associated with underlying disease categories. Previous studies have shown large variations in the attending patient categories, severity of disease, and follow-up times. Thus, a direct comparison of mortality between studies on patients with LTMV is challenging and might lead to an oversimplification.

HRQoL as a prognostic factor

The association between poor HRQoL and increased mortality in the total group of LTMV patients is consistent with the main findings of other similar studies on

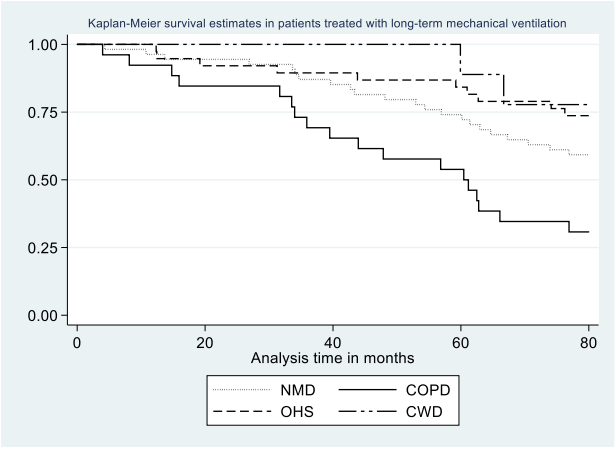

Fig. 2 Kaplan-Meier survival estimates in patients treated with long-term mechanical ventilation between 2008 and 2014. Follow-up time was 80 months. Abbreviations: NMD, neuro muscular disease; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; CWD, chest wall diseasese

LTMV patients [30, 31]. In line with Budweiser (2007a), crude analyses of SRI were significantly associated with mortality in all SRI subscales, with the exception of the 'attendant symptoms and sleep' scale.

The adjusted analyses among NMD patients showed that SRI 'physical functioning', 'psychological well-being' and 'social functioning' continued to be significant factors for mortality, which was consistent with the study by Budweiser [30], but with different adjustment variables than those in our study. We also found associations between SRI and mortality among COPD patients in the adjusted analyses in the 'attendant symptoms and sleep' and 'psychological well-being' SRI subscales.

The initial choice of the adjustment variables in the present study was based on previous work that evaluated age [10, 15, 26, 45], sex [18, 48], education level [44], marital status [45], disease categories (NMD, COPD, OHS and CWD) [2, 3, 10–13, 23] and comorbidity [13, 18, 22, 46]. The variables ventilator dependency and time since LTMV was initiated were chosen a priori. Marital status was not associated with neither mortality nor the SRI sum score and was therefore excluded as adjustment variable. There were no sex differences between survivors and those who deceased, thus sex also was excluded as an adjustment variable.

However, we have considered the possibility that HRQoL could be influenced by other confounding covariates that might also pose a risk of death, such as $PaCO_2$. Reduced $PaCO_2$ levels have been related to lower one-year mortality and improved SRI scores in COPD patients treated with LTMV [7, 8]. On the other hand, exploratory analyses did not identify any significant correlations between changes in hypercapnia status or baseline hypercapnia status and mortality in this group [5]. However, in the present study, $PaCO_2$ values were normalized at baseline as a result of ongoing LTMV and were therefore not included in the analyses. The results from studies on lung function and survival in LTMV patients are not conclusive. Some studies [19, 23, 30] reported associations between low FEV_1 and FVC and mortality, whereas another study [11] found no differences in baseline lung function between the survivors and deceased patients. When FVC and FEV_1 were added to the Cox regression analysis in the current study, the result was altered only slightly; however, this result might also be influenced by missing lung function data (FVC baseline numbers did not sum to 112 due to 23 missing data points, FEV_1 baseline numbers did not sum to 112 due to 22 missing data points), some of the missing data might be explained due to patients having difficulties performing the spirometry test.

We also considered to include ventilation mode as a covariate as longer survival were reported in patients with DMD using non-invasive LTMV compared to those receiving LTMV via a tracheostomy [14, 49]. However, another study concluded that the risk of death was not associated with use of invasive versus non-invasive LTMV in patients with DMD [16], No significant difference in one year mortality was found between patients receiving LTMV via a tracheostomy and those weaned after discharged from the Intensive Care Unit (ICU) and no significant difference in HRQoL measured by SRI at

Table 2 Background variables at baseline in the survivors and deceased individuals treated with LTMV between 2008 and 2014

Characteristic	All participants, n (*n* = 112)	Survivors, n (%) (*n* = 60)	Deceased, n (%) (*n* = 52)
Sex			
Female	53	28 (53)	25 (47)
Male	59	32 (54)	27 (46)
Age			
≤ 60	38	26 (68)	12 (32)
> 60	74	34 (46)	40 (54)
Education			
Primary school	33	18 (55)	15 (45)
High school	44	23 (52)	21 (48)
College/university	35	19 (54)	16 (46)
Marital status			
Married /cohabiting	64	34 (53)	30 (47)
Single/divorced/widowed	48	26 (54)	22 (46)
LTMV h/day[a]			
5–8	50	33 (66)	17 (34)
8–12	42	23 (55)	19 (45)
12–24	17	2 (12)	15 (88)
Years on LTMV			
≤ 4	65	33 (51)	32 (49)
> 4	47	27 (57)	20 (43)
Disease			
NMD	48	26 (54)	22 (46)
COPD	24	6 (25)	18 (75)
OHS	32	22 (69)	10 (31)
CWD	8	6 (75)	2 (25)
Co-morbidity			
No additionally diagnosis	44	32 (73)	12 (27)
1 additionally diagnosis	29	18 (62)	11 (38)
≥ 2 additionally diagnosis	39	10 (26)	29 (74)
Respiratory[a]			
FVC (litre) (mean, SD)	89	2.64 (1.15)	1.89 (0.93)
FEV1(litre) (mean, SD)	90	1.88 (1.04)	1.16 (0.70)
$PaCO_2$ kPa daytime (mean, SD)	84	5.61 (0.76)	6.01 (1.06)
PaO_2 kPa daytime (mean, SD)	69	10.1 (1.78)	9.14 (1.92)

Abbreviations: LTMV, long-term mechanical ventilation; NMD, neuro muscular disease; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; CWD, chest wall disorders; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen

[a] Numbers do not add to 112 due to missing in daily hours on LTMV and respiratory variables

discharge from ICU were found between the two groups [50]. However, HRQoL tended to be lower, in the SRI 'physical functioning', while scores for 'anxieties' tended to be better in patients receiving LTMV via tracheostomy compared to those treated with non-invasive LTMV [51].

Although the analyses in the present study were adjusted for education level, other economic confounding variables, such as income, might also have an impact on HRQoL and mortality. On the other hand, Norwegian society and health care services probably represent one of the most equitable systems worldwide, where all citizens have equal access to health care services. Nevertheless, the number of covariates that could be included in the analyses in this study was limited by the sample size at baseline, and we can never exhaustively cover all variables of minor importance among LTMV patients.

Table 3 Mean baseline scores (both sum score and subscales) of the Severe Respiratory Insufficiency questionnaire in patients treated with long-term mechanical ventilation between 2008 and 2014

SRI	Survivors ($n = 60$)			Deceased ($n = 52$)	*P* value[b]
	n[a]	mean (SD)	n[a]	mean (SD)	
SRI- Sum Score (SS)	58	60.0 (18.3)	47	48.4 (16.8)	0.001
SRI- Physical Functioning (PF)	59	45.9 (23.0)	50	26.9 (21.3)	< 0.001
SRI- Respiratory Complaints (RC)	59	61.0 (22.4)	50	51.1 (22.6)	0.02
SRI- Attendant Symptoms and Sleep (AS)	59	53.3 (20.1)	50	55.8 (20.2)	0.53
SRI- Social Relationships (SR)	59	70.7 (24.4)	49	59.0 (21.8)	0.01
SRI- Anxiety (AX)	59	64.2 (27.5)	49	52.9 (27.2)	0.03
SRI- Psychological Well-Being (WB)	58	66.2 (22.0)	47	52.3 (22.9)	0.002
SRI- Social Functioning (SF)	59	56.5 (24.6)	49	39.1 (18.7)	< 0.001

Abbreviations: SRI, Severe Respiratory Insufficiency; SD, standard deviation
[a] Numbers do not add to 60 and 52 due to missing in the Severe Respiratory Insufficiency questionnaire
[b] By two-sample t-test

Why and how SRI predicts mortality

Previous studies using patient-reported measures other than SRI have also reported an association between self-reported health and mortality in patients treated with LTMV [11, 26]. However, these studies did not adjust for the same covariates as the present study, and they lacked important variables, such as comorbidity and education level. There is a large body of evidence on the association between self-reported health measures and mortality in other settings and disorders, such as in communities [24], in patients with cancer [25] and idiopathic pulmonary fibrosis [27]. Explanations of these consistent findings are complex and imply that survey respondents' perceptions of health status are holistic; they include information on medical status but that information might be evaluated differently by men and women in different social positions, with different reference groups providing different social comparisons [24]. Further, the accuracy of self-reported health as a predictor of mortality depends on the comprehensiveness and accuracy of the information that the person incorporates into the self-rating [52]. This hypothesis corresponds with SRI as a multidimensional comprehensive questionnaire that captures the symptoms of CHRF and covers essential aspects of LTMV patients' daily life [28].

Clinical implication of the associations between SRI and mortality

Individuals suffering from CHRF treated with LTMV often have an incurable disease [2–4]. Health care professionals and relatives tend to behave differently depending on whether the disease is perceived as a chronic or terminal condition. However, the distinction between the patient's condition as chronic or terminal might become vague and can sometimes be ambiguous and difficult to interpret [53]. Prognostic information from the SRI questionnaire might provide valuable knowledge on how to cope with these situations, improving treatment plans and communication between involved professionals, family members, and the LTMV patient. Our study demonstrates that the

Table 4 Hazard ratios for mortality by baseline scores (both sum score and subscales) of the Severe Respiratory Insufficiency questionnaire in all patients ($n = 112$) treated with long-term mechanical ventilation between 2008 and 2014

SRI		Crude			Adjusted[a]		
	N[b]	HR	95% CI	*P* value	HR	95% CI	*P* value
SRI- Sum Score (SS)	103	0.97	(0.95, 0.98)	0.001	0.98	(0.96, 0.99)	0.04
SRI- Physical Functioning (PF)	107	0.97	(0.95, 0.98)	< 0.001	0.98	(0.96, 0.99)	0.007
SRI- Respiratory Complaints (RC)	107	0.98	(0.97, 0.99)	0.01	0.99	(0.98, 1.01)	0.28
SRI- Attendant Symptoms and Sleep (AS)	107	1.00	(0.99, 1.02)	0.50	0.99	(0.98, 1.01)	0.64
SRI- Social Relationships (SR)	106	0.98	(0.97, 0.99)	0.009	0.99	(0.98, 1.00)	0.14
SRI- Anxiety (AX)	106	0.99	(0.99, 1.00)	0.03	0.99	(0.98, 1.00)	0.25
SRI- Psychological Well-Being (WB)	103	0.98	(0.97, 0.99)	0.001	0.98	(0.97, 0.99)	0.009
SRI- Social Functioning (SF)	106	0.97	(0.96, 0.99)	< 0.001	0.98	(0.97, 0.99)	0.02

Abbreviations: *SRI* Severe Respiratory Insufficiency, *HR* hazard ratio, *CI* confidence interval
[a] Adjusted for age, education level, daily hours on LTMV, treatment time since initiation of LTMV, disease category and comorbidity
[b] Numbers do not add to 112 due to missing in the Severe Respiratory Insufficiency questionnaire

Table 5 Hazard ratios for mortality by baseline scores (both sum score and sub-scales) of the Severe Respiratory Insufficiency questionnaire in neuromuscular patients ($n = 48$) treated with long-term mechanical ventilation between 2008 and 2014

SRI		Crude			Adjusted[a]		
	N[b]	HR	95% CI	*P* value	HR	95% CI	*P* value
SRI- Sum Score (SS)	43	0.97	(0.94, 1.00)	0.09	0.97	(0.93, 1.01)	0.16
SRI- Physical Functioning (PF)	46	0.97	(0.94, 0.99)	0.008	0.97	(0.95, 1.00)	0.05
SRI- Respiratory Complaints (RC)	45	1.00	(0.98, 1.02)	0.88	0.99	(0.97, 1.02)	0.67
SRI- Attendant Symptoms and Sleep (AS)	45	1.01	(0.99, 1.03)	0.20	1.00	(0.98, 1.03)	0.43
SRI- Social Relationships (SR)	45	0.98	(0.96, 1.00)	0.14	0.99	(0.96, 1.01)	0.30
SRI- Anxiety (AX)	45	0.99	(0.98, 1.01)	0.46	0.99	(0.97, 1.01)	0.32
SRI- Psychological Well-Being (WB)	43	0.98	(0.96, 1.00)	0.08	0.97	(0.95, 0.99)	0.03
SRI- Social Functioning (SF)	44	0.96	(0.94, 0.99)	0.002	0.97	(0.94, 0.99)	0.02

Abbreviations: *SRI* Severe Respiratory Insufficiency, *HR* hazard ratio, *CI* confidence interval
[a] Adjusted for age, daily hours on LTMV and comorbidity
[b] Numbers do not add to 48 due to missing in the Severe Respiratory Insufficiency questionnaire

risk of death decreases by each unit increase in the SRI score. This result suggests that LTMV patients with low SRI should be identified, initiating thorough considerations on how to improve HRQoL. However, whether the relationship between mortality and quality of life is causal and changes in HRQoL status in some way influences mortality cannot be confirmed in this study design.

The minimal clinically important difference of the SRI questionnaire has not been defined [41]. However, the great numerical difference in SRI score at baseline between the surviving LTMV patients and those who died during the follow-up, support the clinical relevance of the study.

Strengths and limitations

As far as we are aware, this study is among the very first to examine SRI scores as a predictor for mortality in LTMV patients with a follow-up time as long as 80 months. The strengths of the study include the use of standardized data collection [32–34], including relevant confounders, such as comorbidity, which is often lacking in study of this type, and the prospective study design. Another strength is the use of the specific and validated SRI questionnaire, which can capture HRQoL related to symptoms and the experience of having CHRF and LTMV [2, 28–30, 34–43].

The study has some limitations. First, its small sample size may decrease the statistical power to detect clinically relevant associations in multivariate Cox analyses. Second, comorbidity modeled simply as the number of somatic diagnoses. Charlson Comorbidity Index [54] is a common index to measure comorbidity using ICD-10 codes. However, as complete ICD-10 codes were not available in our data, we chose to measure comorbidity as the number of somatic diagnoses. Thirdly, some of the LTMV patients answered that they received help to complete the questionnaire, which might introduce some information bias in SRI scores. However, it is of

Table 6 Hazard ratios for mortality by baseline scores (both sum score and sub-scales) of the Severe Respiratory Insufficiency questionnaire in chronic obstructive pulmonary disease patients ($n = 24$) treated with long-term mechanical ventilation between 2008 and 2014

SRI		Crude			Adjusted[a]		
	N[b]	HR	95% CI	*P* value	HR	95% CI	*P* value
SRI- Sum Score (SS)	23	0.98	(0.95, 1.01)	0.14	0.97	(0.95, 1.01)	0.19
SRI- Physical Functioning (PF)	23	0.98	(0.95, 1.01)	0.16	0.97	(0.93, 1.01)	0.13
SRI- Respiratory Complaints (RC)	23	0.98	(0.95, 1.01)	0.33	0.98	(0.95, 1.01)	0.26
SRI- Attendant Symptoms and Sleep (AS)	23	0.98	(0.96, 1.01)	0.15	0.97	(0.95, 1.00)	0.10
SRI- Social Relationships (SR)	23	0.99	(0.97, 1.01)	0.08	0.98	(0.99, 1.01)	0.37
SRI- Anxiety (AX)	23	0.99	(0.97, 1.01)	0.32	0.99	(0.97 1.01)	0.34
SRI- Psychological Well-Being (WB)	23	0.98	(0.96, 1.00)	0.07	0.98	(0.96, 1.00)	0.13
SRI- Social Functioning (SF)	23	0.99	(0.97, 1.01)	0.50	0.99	(0.97, 1.01)	0.64

Abbreviations: *SRI* Severe Respiratory Insufficiency, *HR* hazard ratio, *CI* confidence interval
[a] Adjusted for age and comorbidity
[b] Numbers do not add to 24 due to missing in the Severe Respiratory Insufficiency questionnaire

great importance to include the SRI scores from patients who needed help to fill out the questionnaire.

In addition, because of the observational study design, we cannot exclude the possibility of residual or unknown confounding. Whether HRQoL score reflects a perception by the LTMV patient of progression of her or his condition or whether change in HRQoL status in some way also influences the course of the condition is an interesting question. However, the research design cannot confirm causality between improvement in HRQoL and survival in this study. To address this question a randomized interventional study aiming to improve HRQoL with a control group receiving standard treatment would be more suitable.

Conclusion

This study suggests that SRI is an important factor in prognostic mortality models in LTMV-treated patients. The design and data do not allow us to imply any causal relationships between a change in HRQoL and a change in mortality. We propose an active use of the SRI questionnaire in the daily clinic with repeated measurements as part of individual follow-up. Future studies on this topic should be larger and preferably organized as multicentre long-term RCTs, including specific interventions aimed at improving HRQoL in LTMV patients, compared to standard care. Even if there is no comparison in this paper made between SRI and other quality of life measures, we suggest SRI to be used as the quality of life measure in the studies to come.

Additional file

Additional file 1: Table S1. Correlation between baseline scores (both sum score and subscales) of the Severe Respiratory Insufficiency questionnaire and respiratory variables in 112 patients treated with long-term mechanical ventilation between 2008 and 2014. **Table S2.** Hazard ratios for mortality by baseline scores (both sum score and subscales) of the Severe Respiratory Insufficiency questionnaire in obesity hypoventilation syndrome patients ($n = 32$) treated with long-term mechanical ventilation between 2008 and 2014. (DOCX 68 kb)

Abbreviations

BMI: Body mass index; CHRF: Chronic hypercapnic respiratory failure; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CWD: Chest wall disease; FEV_1: Forced expiratory volume in one second of expiration; FVC: Forced vital capacity; HR: Hazard ratio; HRQoL: Health-related quality of life; LTMV: Long-term mechanical ventilation; NMD: Neuromuscular disease; OHS: Obesity hypoventilation syndrome; $PaCO_2$: Arterial partial pressure of carbon dioxide; SD: Standard deviation; SRI questionnaire: Severe Respiratory Insufficiency questionnaire

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

HM, in cooperation with SL, RMN and GKN, designed and planned the study. HM drafted the manuscript. RMN supervised the analyses and results. SL interpreted the results and revised the manuscript for important critical content. RMN and GKN revised the manuscript for important critical content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study has been approved by the Norwegian Regional Committee for Medical and Health Research Ethics (number 273.06 and 2012/1090–11) and by the Norwegian Centre for Research Data (project number 16001). At baseline in 2008, the patients in the Norwegian LTMV registry in West Norway were contacted by post and asked to participate in the study. In an information letter it was informed that the data would be stored for a possible follow-up study. Consent to participate in the study was considered by returning of the filled out questionnaires. In the follow-up study there was a written consent to allow register connection between the registers. For cohort patients who died, exemption from the consent requirement for register connection to the Norwegian Patient Registry and Cause of Death Register was given from the Regional Committee for Medical and Health Research Ethics.
Data from the Norwegian Patient Register has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Register is intended nor should be inferred.

Consent for publication

Not applicable.

Competing interests

No conflicts of interest have been declared by the authors.

Publisher's Note

Author details

[1]The Norwegian National Advisory Unit on Longterm Mechanical Ventilation, Department of Thoracic Medicine, Haukeland University Hospital, Jonas Lies vei 65, N-5021 Bergen, Norway. [2]Department of Global Public Health and Primary Care, University in Bergen, Kalfarveien 31, 5018 Bergen, Norway. [3]Department of Clinical Science, University in Bergen, Bergen, Norway. [4]Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Inndalsveien 28, 5063 Bergen, Norway.

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APPENDIX I

UNIVERSITETET I BERGEN
Regional komité for medisinsk forskningsetikk, Vest-Norge (REK Vest)

Professor Astrid Wahl
Institutt for samfunnsmedisinske fag
Universitetet i Bergen

Deres ref	Vår ref	Dato
	273.06 – 06/4647/marne	04.12.2006.

Ad. prosjekt: Hvordan opplever voksne hjemmerespiratorbrukere i Norge sin livskvalitet og hvilke faktorer påvirker deres livskvalitet. (273.06).

Det vises til din søknad om etisk vurdering datert 14.11.06. REK Vest vurderte studien i møte den 30.11.06.

Komiteen mener dette er en velfundert studie, men har følgende merknader.

I informasjonsskrivet bør ordet *inviteres* utgå.
Det mangler informasjon om kodenøkkel blir oppbevart. Hvis så er tilfelle, er dataene ikke anonyme men avidentifiserte. Dette må i så fall endres i informasjonsskrivet.
I samtykkeerklæringen bør avsnitt 2 og 3 utgå.

Med disse merknadene er studien endelig klarert fra denne komité sin side.

Vi ønsker dere lykke til med gjennomføringen og minner om at komiteen setter pris på en sluttrapport, eventuelt en kopi av trykt publikasjon når dette foreligger.

Med vennlig hilsen

Jon Lekven
leder

Marit Nedreli
sekretær

Postadresse
Postboks 7804
5020 Bergen

rek-vest@uib.no
www.etikkom.no/REK
Org no. 874 789 542

Regional komité for medisinsk forskningsetikk, Vest-Norge
Telefon 55 97 84 97 / 98 / 99

Besøksadresse
Haukeland Universitetssykehus

HELSE BERGEN
Haukeland Universitetssykehus
Lungeavdelingen

Heidi Øksnes Markussen
Lungeavdelingen
Haukeland Universitetssykehus

Deres ref.: Vår ref.: 14. september 2008

Vedr. søknad datert 27.6.2008 om å benytte opplysninger fra Nasjonalt register for hjemmerespiratorbehandling

Vi har mottatt din søknad om tillatelse til å benytte opplysninger fra Nasjonalt register for hjemmerespiratorbehandling i masteroppgave ved Institutt for samfunnsmedisinske fag, Seksjon for sykepleievitenskap, Universitetet i Bergen.

Tema for oppgaven: Livskvalitet hos hjemmerespiratorpasienter.
Hovedveileder: professor dr. polit Brit Rokne Hanestad.
Biveiledere: leder NKH/overlege Ove Fondenes og overlege dr.med. Jon Hardie.
Medforfatter: statistiker Tore Wentzel-Larsen.

Prosjektet er godkjent av regional etisk komité (REK).

Opplysninger fra Nasjonalt register for hjemmerespiratorbehandling t.o.m. 31.12.2007 ble ferdig kvalitetssikret 1.9.2008 og opplysningene er nå klargjort for analyser.

Din søknad er innvilget.

Du vil få tildelt en anonymisert SPSS fil med opplysninger fra registeret t.o.m. 31.12. 2007 over hjemmerespiratorbrukere > 18 år i Hordaland, Rogaland og Sogn og Fjordane med følgende variabler:

Nr.	Variabel	Labell
1	HDIAG	Hoveddiagnose
28	DATOOPPS	Dato for start av behandlingen (dato, måned, år)
LUNGEFYSIOLOGISKE PARAMETER FØR BEHANDLINGSSTART		
30	FVK	FVK (liter)
31	FEV1	FEV1(liter)
34	PO2DAG	PO2 dagtid, arteriell (kPa)
35	PCO2DAG	PCO2 dagtid, arteriell (kPa)
36	PCO2NATT	PCO2 nattestid, arteriell (kPa)
37	HOYDE	Høyde (cm)
38	VEKT	Vekt (kg)

LUNGEFYSIOLOGISKE PARAMETRE 2007		
50	FVK 07	FVK (liter)
51	FEV107	FEV1(liter)
54	PO2DAG07	PO2 dagtid, arteriell (kPa)
55	PCO2DAG07	PCO2 dagtid, arteriell (kPa)
56	PCO2NATT 07	PCO2 nattestid, arteriell (kPa)
58	VEKT	Vekt (kg)
BEHANDLINGSTID PR DØGN		
59	BTID24	Behandlingstid per døgn
60	BTID24DPC	Oppfølging - Behandlingstid per døgn ? Nå
Annet tilleggsutstyr		
61	OKSYGEN	Oksygenbehandling ved oppstart Ja=1, Nei=2
62	TUTFUKT	Fukter ved oppstart Ja=1, Nei=0
RESPIRSTOR BEHANDLINGSMETODE OG TILSLUTNING		
73	HBE	Hovedbehandlingsmetode (markeres som 1)
75	TBEMETODE	Hovedtilslutning
83	HBE07	Hovedbehandlingsmetode (markeres som 1)
85	TBEMETODE07	Hovedtilslutning
BEREGNEDE VARIABLER		
118	C_KJØNN	Kjønn beregnet fra personnummer
119	C_FYLKE	Fylkeskode
121	C_ALDER	Alder pr.31.12.07 eller ved behandlingsslutt

Det er ikke førende, men ønskelig fra registerets side at opplysninger fra registeret publiseres i nasjonale eller internasjonale vitenskapelige tidsskrifter, framfor i en monolog.

Lykke til med en spennende masteroppgave!

Vennlig hilsen

Elin Tollefsen
Overlege dr.med.
Forskningsansvarlig Nasjonalt register for hjemmerespiratorbehandlig
Nasjonalt kompetansesenter for hjemmerespiratorbehandling og Lungeavdelingen
Haukeland Universitetssykehus

Vedlegg:
Dokument: Nasjonalt register for hjemmerespiratorbehandling; Retningslinjer for tildeling av analyserettigheter for data fra Nasjonalt register for hjemmerespiratorbehandling.

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Arne Salbu	55978498	06.09.2012	2012/1090/REK vest
			Deres dato:	**Deres referanse:**
			19.06.2012	

Vår referanse må oppgis ved alle henvendelser

Heidi Øksnes Markussen
Lungeavdelingen
Haukeland universitetssykehus

2012/1090 Når pusten svikter

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 20-AUG-12. Vurderingen er gjort med hjemmel i helseforskningsloven § 10, jf. forskningsetikklovens § 4.

Denne studien er en oppfølging prosjekt Hvordan opplever voksne hjemmerespiratorbrukere i Norge sin livskvalitet og hvilke faktorer påvirker deres livskvalitet (273.06) av prosjektleder Astrid Wahl.

Bakgrunnen for denne studien er et ønske om å forbedre livskvalitet og bidra til livsforlengelse for pasienter som behandles med Langtids mekanisk ventilasjon, LTMV. Det er nylig utviklet et spørreskjema, "The Severe Respiratory Inssuffiency (SRI), som er oversatt til norsk og validert og som benyttes for måling av livskvalitet for denne pasientgruppen. Foruten spørreskjema vil en også hente inn registerdata

Design og metode er adekvat.

Prosjektet er ment å være samtykkebasert. Imidlertid er de omsøkte registerkoblinger ikke beskrevet i forespørselen, noe en må gjøre for å tilfredsstille kravene til et samtykkebasert prosjekt. . For de pasienter fra kohorten som er døde, innvilges fritak fra samtykkekravet med hensyn til Norsk pasientregister og Dødsårsaksregisteret.

For øvrig gjør vi oppmerksom på at de regionale forskningsetiske komiteene nå er godkjenningsmyndighet og en må derfor skrive "godkjent" i forespørsel, ikke tilrådd.

Vilkår
Ønskede registerkoplinger må beskrives i forespørselen.

Vedtak
Prosjektet godkjennes på betingelse med at ovennevnte vilkår tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 01.12.2015. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de

opplysninger soim er gitt i søknaden, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Jon Lekven
leder, dr.med.

Arne Salbu
rådgiver

Kopi til: postmottak@helse-bergen.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Camilla Gjerstad	55978499	02.11.2018	2012/1090/REK vest
			Deres dato: 31.10.2018	

Vår referanse må oppgis ved alle henvendelser

Heidi Markussen
Lungeavdelingen

2012/1090 Når pusten svikter

Forskningsansvarlig: Helse Bergen HF - Haukeland universitetssykehus
Prosjektleder: Heidi Markussen

Vi viser til søknad om prosjektendring datert 31.10.2018 for ovennevnte forskningsprosjekt. Søknaden er behandlet av REK vest ved sekretariatet på fullmakt, med hjemmel i helseforskningsloven § 11.

Prosjektendring
Det søkes om endring av prosjektslutt der ny prosjektslutt vil være 31.12.2019.
Publisering har tatt lengre tid enn forventet. Artikkelen er nå revidert og sendt inn på nytt.

Vurdering
REK vest har vurdert endringssøknaden og har ingen merknader.

Vedtak
REK vest godkjenner prosjektendringen i samsvar med forelagt søknad.

Klageadgang
Du kan klage på komiteens vedtak, jf. helseforskningsloven § 10 og forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen
Camilla Gjerstad
rådgiver

Kopi til: *postmottak@helse-bergen.no*

Helsedirektoratet

Avtale om utlevering av opplysninger fra Norsk pasientregister

Avtale er inngått mellom

Helsedirektoratet avd. Norsk pasientregister (NPR)

og

Haukeland Universitetssykehus ved Heidi Øksnes Markussen,

heretter kalt *Virksomheten*, om utlevering av data fra NPR.

Definisjoner
Begrepene som beskriver ulike former for data som kan utleveres fra NPR er hentet fra Helseregisterloven og Norsk pasientregisterforskriften (NPR-forskriften).

Grunnlag
Virksomhetens søknad av 20.2.2014 med om utlevering av data fra Norsk pasientregister, jfr. saksnummer 14/3001.

Hjemmel for utleveringen
Utleveringen er hjemlet i NPR forskriftens <§ 3-6> i henhold til vedtak fattet av NPR av 2.2.2016.

Vilkår for utleveringen
Opplysningene kan bare benyttes til det angitte formålet i søknaden.

Kun medarbeidere i *virksomheten* som er spesifikt nevnt i søknaden til Datatilsynet og NPR skal ha tilgang til de utleverte data.

Dersom formålet utvides eller flere/andre personer enn de som er nevnt i denne avtalen skal håndtere de tilsendte data skal en formell henvendelse om dette sendes til NPR. Dersom den opprinnelige søknaden krever tillatelser fra andre instanser (for eksempel REK eller Datatilsynet) må også disse gi en utvidet tillatelse før formålet utvides eller andre personer kan gis tilgang til data.

Direkte tiltak eller vedtak overfor enkeltpersoner skal ikke gjennomføres med utgangspunkt i opplysninger fra NPR (jf. NPR-forskriften § 1-3).

Fødselsnummer utlevert til *virksomheten* kan bare benyttes for å supplere og/eller kvalitetssikre opplysningene fra NPR.

Virksomheten plikter å behandle opplysninger i tråd med personopplysningsloven, helseregisterloven, helsepersonelloven og helseforskningsloven, herunder gjennomføring av de informasjonssikringstiltak som følger av personopplysningslovens § 13.

NPR kan be om å få utlevert dokumentasjon på at *virksomheten* oppfyller vilkårene i denne avtalen.

Ansvar
Dersom NPR leverer feilaktige data i forhold til søknad eller avklaringer med søker har *virksomheten* rett til korrigert levering så raskt som mulig uten merkostnad. *Virksomheten* taper retten til kostnadsfri utlevering dersom feil ikke påpekes innen 3 uker etter at data er mottatt hos *virksomheten*.

Helsedirektoratet er ikke ansvarlig for konklusjoner som trekkes av *virksomheten* eller andre brukere på grunnlag av de leverte opplysninger. Publikasjoner hvor data fra NPR inngår skal inneholde den engelske eller norske teksten i boksen under:

Disclaimer
«Data from the Norwegian Patient Register has bee used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian patient register is intended nor should be inferred."

Fraskrivelse
«Publikasjonen har benyttet data fra Norsk pasientregister (NPR). Forfatterne er eneansvarlig for tolkning og presentasjon av de utleverte data. NPR har ikke ansvar for analyser eller tolkninger basert på de utleverte data.»

NPR har plikt til å vurdere både institusjoner og enkeltpersoners skikkethet til å motta personidentifiserbare opplysninger fra NPR. Dersom *virksomheten* eller enkeltpersoner bryter vilkårene i denne avtalen vil NPR vurdere fremtidige utleveringer til både *virksomheten* og enkeltpersoner i søknaden.

Sletting
Når prosjektet er avsluttet og **senest innen 31.12.2017** (jfr. brev REK, ref. 2012/1090/REK vest) forplikter *virksomheten* seg til å slette alle mottatte opplysninger, inkludert utskrifter og kopier av disse, samt umiddelbart varsle NPR på npr.felles@helsedir.no om at sletting er utført.

Tilgang til data
Følgende personer i *virksomheten* har tillatelse til å håndtere de mottatte data:

	Navn	Tittel	Enhet/kontaktperson
1.	Heidi Øksnes Markussen	Prosjektleder	Haukeland universitetssykehus
2.	Sverre Lehmann	Forskningsansvarlig	Haukeland universitetssykehus
3.	Roy Miodini Nilsen	Prosjektmedarbeider	Haukeland universitetssykehus

Dersom *virksomheten* ønsker at andre personer skal ha tilgang til data må det sendes revidert søknad med begrunnelse til NPR og eventuelt andre instanser i forkant, jamfør vilkårene ovenfor.

Spesielle vilkår
Ett eksemplar av alle publiserte arbeider hvor data omfattet av denne avtale er benyttet, skal vederlagsfritt sendes til Norsk pasientregister.

Norsk pasientregister skal oppgis som datakilde i alle publiserte arbeider.

Signering
Denne avtalen signeres av begge parter og partene tar vare på hvert sitt eksemplar.

For Norsk pasientregister:
Sted/dato: Trondheim 3.2.16
Seksjonssjef

For *virksomheten*:
Sted/dato: Bergen 4.2.16
Prosjektleder

APPENDIX II

HELSE BERGEN
Haukeland universitetssjukehus
Lungeavdelingen
Nasjonal kompetansetjeneste for hjemmerespiratorbehandling

Forespørsel om å delta i oppfølgingsundersøkelse om hvordan det er å leve med hjemmerespirator eller annet hjelpemiddel til pustestøtte

Tusen takk for at du i 2008 svarte på spørreskjema om hvordan det er å leve med hjemmerespirator eller annet hjelpemiddel til pustestøtte. Undersøkelsen bidro blant annet til testing og norsk godkjenning av et internasjonalt spørreskjema om livskvalitet til denne gruppe pasienter. Du kontaktes nå med spørsmål om å delta i en oppfølgingsundersøkelse. Vi håper at du vil fylle ut tilsvarende spørreskjema som du gjorde i 2008. Vi vil også spørre om din tillatelse til å sammenstille data fra denne undersøkelsen med opplysninger fra Norsk Pasient register.

Studiens hensikt:
Helsevesenet i Norge har mangelfulle opplysninger og kunnskap om hvordan det er å leve med hjemmerespirator eller annet hjelpemiddel til pustestøtte. Informasjon fra deg er viktig for å gi best mulig behandlingstilbud til personer som bruker eller er avhengig av denne type behandling.

Gjennomføring av undersøkelsen og hva dette innebærer for deg:
Neste gang du har time i Poliklinikken vil jeg kontakte deg for utfylling av spørreskjema. Det tar ca. 30 minutter å fylle ut spørreskjemaene.

Taushetsplikt
Alle medarbeidere i prosjektet har taushetsplikt og datamateriale behandles konfidensielt. Opplysningene avidentifiseres ved registrering. Datamateriale som inngår i undersøkelsen blir oppbevart og lagret etter gjeldende retningslinjer og vil bli oppbevart i 10 år for evt. en oppfølgingsundersøkelse. Data fra Nasjonalt register for langtids mekanisk ventilasjon vil bli innhentet for å få utvidet kunnskap om behandlingen. Prosjektet er tilrådd av Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste. Studien er godkjent av Regional komite for medisinsk forskningsetikk, Vest Norge.

Frivillig deltakelse:
Deltakelse er frivillig. Det vil ikke få noen betydning for ditt forhold til behandlere eller helsetjenesten dersom du ikke ønsker å svare på spørreskjemaene.

Prosjektgruppe:
Studien er et samarbeidsprosjekt mellom Lungeavdelingen, Nasjonal Kompetansetjeneste for hjemmerespiratorbehandling, Haukeland Universitetssykehus og Institutt for global helse og samfunnsmedisin ved Universitetet i Bergen. Professor Gerd Karin Natvig er hovedveileder i prosjektet, og seksjonsoverlege /førsteamanuensis, Sverre Lehmann er biveileder.

Har du spørsmål, ta gjerne kontakt. Jeg kan treffes på telefon 55 97 35 49/ mobil 97499915 eller e-post: heidi.markussen@helse-bergen.no

Vennlig hilsen
Heidi Øksnes Markussen
Master i helsefag/ Intensivsykepleier
Lungeavdelingen/ Nasjonal Kompetansetjeneste for hjemmerespiratorbehandling
Haukeland Universitetssjukehus
Jonas Lies vei 65
5021 Bergen

HELSE BERGEN
Haukeland universitetssjukehus
Lungeavdelingen
Nasjonal kompetansetjeneste for hjemmerespiratorbehandling

Erklæring om samtykke

Jeg er gjennom vedlagt informasjonsskriv gjort kjent med at det skal gjennomføres en oppfølgingsundersøkelse om hvordan det er å leve med hjemmerespirator eller annet hjelpemiddel til pustestøtte. Jeg er også gjort kjent med studiens formål og hvordan opplysninger skal innhentes og registreres.

Jeg samtykker herved på å delta i studien samt at data fra studien kan kobles sammen med data fra Norsk pasientregister.

Navn……
(Bruk blokkbokstaver)

Sted…..…… Dato……..…….

……
Underskrift

APPENDIX III

Spørreskjema for bruker av hjelpemiddel til pustestøtte

For hvert spørsmål, vennligst kryss av for det svaralternativet som passer best for din situasjon. Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan.

1. Sivilstand (sett ett kryss):

Gift / samboer ☐	Enslig ☐	Skilt ☐	Enke / enkemann ☐

2. Høyeste utdanning (sett ett kryss):

Grunnskole ☐	Videregående skole ☐	Høyskole ☐	Universitet ☐

3. Tilknytning til arbeidslivet (sett ett eller flere kryss):

Yrkesaktiv ☐ Helt ☐ Delvis ☐	Uføretrygdet ☐ Helt ☐ Delvis ☐	Pensjonist ☐

4. Hvor mange timer i gjennomsnitt pr. døgn bruker du din hjemmerespirator eller din BIPAP? (sett ett kryss)

5- 8 timer ☐	8-12 timer ☐	12-18 timer ☐	18-24 timer ☐

5. Hvordan er du tilkoblet din hjemmerespirator eller din BIPAP? (sett ett kryss)

Via en maske ☐	Via tracheostomi (åpning på halsen inn til luftrøret) ☐

Dersom du har tracheostomi kan du krysse av på følgende utsagn:

	Stemmer ikke i det hele tatt	Stemmer nesten ikke	Stemmer til en viss grad	Stemmer ganske bra	Stemmer helt
6. Jeg fikk tilstrekkelig informasjon før etablering av tracheostomien					
7. Jeg har fått tilstrekkelig opplæring vedr. min tracheostomi					
8. Jeg har mye ubehag av min tracheostomi					

9. Dersom du er tilkoblet pustestøtte via maske, hvilken maske bruker du? (sett ett eller flere kryss)

Nesemaske ☐	Maske som dekker både munn og nese ☐	Munnstykke ☐	Munnmaske ☐

10. Har du problemer med bruk av masken? (sett ett kryss)

Ja ☐	Nei ☐

11. Hvis JA, hvilke problemer har du? (sett ett eller flere kryss)

Lekkasje ☐	Trykksår ☐	Kondens ☐
Annet ☐ ……		

12. Hvor fikk du opplæring i bruk av din hjemmerespirator eller din BIPAP? (sett ett eller flere kryss*)*

Sykehus poliklinikk ☐	Sykehus sengepost ☐	Seksjon for behandlingshjelpemidler ☐
Andre steder ☐ ……		

Kan du krysse av på følgende utsagn:

	Stemmer ikke i det hele tatt	**Stemmer nesten ikke**	**Stemmer til en viss grad**	**Stemmer ganske bra**	**Stemmer helt**
13. Jeg fikk tilstrekkelig opplæring i bruk av min hjemmerespirator eller min BIPAP					

14. Trenger du hjelp til daglig til bruk av din hjemmerespirator eller din BIPAP? (sett ett kryss)

Ja ☐	Nei ☐

15. Hvis Ja, hvem er det som hjelper deg ? (sett ett eller flere kryss)

Personlig assistent ☐	Ektefelle/samboer ☐	Barn ☐	Hjemmesykepleien ☐
Andre ☐ ……			

Dersom du har behov for personlig assistent eller hjelp fra hjemmesykepleien kan du krysse av på følgende utsagn:

	Stemmer ikke i det hele tatt	Stemmer nesten ikke	Stemmer til en viss grad	Stemmer ganske bra	Stemmer helt
16. Mine hjelpere har fått tilstrekkelig opplæring					
17. Jeg får tilstrekkelig hjelp					

18. Har du hatt hjemmebesøk av helsepersonell fra spesialist helsetjenesten (personell fra sykehuset)? (sett ett kryss)

Ja ☐	Nei ☐

19. Dersom ja, hvor ofte?

Ca. 1 gang pr. halvår ☐	Ca.1 gang pr.år ☐	Sjeldnere enn 1 gang pr. år ☐
Annet ☐ ……...		

Vedr. oppfølging fra spesialisthelsetjenesten /sykehuset kan du krysse av på følgende utsagn:

	Stemmer ikke i det hele tatt	Stemmer nesten ikke	Stemmer til en viss grad	Stemmer ganske bra	Stemmer helt
20. Jeg opplever å få tilstrekkelig oppfølging					

Hvordan vil du beskrive din livssituasjon:

	Stemmer ikke i det hele tatt	Stemmer nesten ikke	Stemmer til en viss grad	Stemmer ganske bra	Stemmer helt
21. Jeg føler meg trygg i min hjemmesituasjon					

22. Har du hatt hjelp til å fylle ut spørreskjemaet? (sett et kryss)

Ja ☐	Nei ☐

Vennligst se etter at du har svart på alle spørsmål.

Takk for hjelpen!

ID

Spørreskjema til deg som bruker maskinell pustestøtte hele eller deler av døgnet

Følgende spørsmål berører den generelle helsetilstanden din.
Utsagnene nedenfor tar for seg forskjellige aspekter ved det daglige liv.
Hvordan har du hatt det i løpet av ***den siste uken***?
Vennligst sett et kryss ved svaret som passer best med HVERT enkelt utsagn.

	Stemmer ikke i det hele tatt	**Stemmer nesten ikke**	**Stemmer til en viss grad**	**Stemmer ganske bra**	**Stemmer helt**
1. Det er vanskelig å gå i trapper.					
2. Jeg har tung pust under måltider.					
3. Jeg kan gå ut om kvelden.					
4. Jeg føler meg ofte dårlig.					
5. Selv uten fysiske anstrengelser har jeg pustevansker.					
6. Jeg har ofte hodepine.					
7. Jeg har mange venner og bekjente.					
8. Jeg er bekymret for at sykdommen min skal bli verre.					
9. Jeg har ingen problemer med å sovne.					
10. Jeg kan godt omgås andre mennesker.					
11. Jeg er av og til svimmel.					
12. Jeg våkner med tung pust om natten.					
13. Jeg er redd for å få pustevansker om natten.					
14. Jeg har ofte vondt i nakken.					
15. Jeg er sterkt bundet til hjemmet mitt.					
16. Husarbeid er vanskelig for meg.					

The Severe Respiratory Insufficiency Questionnaire (SRI) ble utviklet i 2003 av W. Windisch, Universitätsklinik Freiburg.
Oversatt til norsk og validert av H. Markussen ved Nasjonal kompetansetjeneste for hjemmerespiratorbehandling,
Haukeland Universitetssjukehus

ID

Hvordan har du hatt det i løpet av ***den siste uken***?
Vennligst sett et kryss ved svaret som passer best med HVERT enkelt utsagn.

	Stemmer ikke i det hele tatt	**Stemmer nesten ikke**	**Stemmer til en viss grad**	**Stemmer ganske bra**	**Stemmer helt**
17. Jeg våkner ofte om natten.					
18. Jeg sover godt hele natten.					
19. Jeg er ofte kortpustet.					
20. Jeg ser positivt på framtiden.					
21. Jeg har følelsen av å være ensom.					
22. Jeg er tungpusten når jeg snakker.					
23. Det anstrenger meg veldig å få besøk.					
24. Jeg hoster mye.					
25. Jeg har ofte slim i luftveiene.					
26. Jeg unngår situasjoner der mine pustevansker kan gjøre det pinlig for meg.					
27. Jeg føler meg vel sammen med venner og bekjente.					
28. Jeg er redd for å få anfall med tungpust.					
29. Jeg er tungpusten ved fysisk anstrengelse.					
30. Jeg er irritert over innskrenkningene som min sykdom medfører.					
31. Mitt ekteskap /parforhold lider under sykdommen min.					
32. Jeg kan gå og handle.					
33. Jeg kan utøve alle fritidsaktiviteter som interesserer meg.					

The Severe Respiratory Insufficiency Questionnaire (SRI) ble utviklet i 2003 av W. Windisch, Universitätsklinik Freiburg.
Oversatt til norsk og validert av H. Markussen ved Nasjonal kompetansetjeneste for hjemmerespiratorbehandling,
Haukeland Universitetssjukehus

Hvordan har du hatt det i løpet av ***den siste uken***?
Vennligst sett et kryss ved svaret som passer best med HVERT enkelt utsagn.

	Stemmer ikke i det hele tatt	**Stemmer nesten ikke**	**Stemmer til en viss grad**	**Stemmer ganske bra**	**Stemmer helt**
34. Jeg føler meg ofte irritabel.					
35. På grunn av sykdommen min er kontakten med venner/bekjente innskrenket.					
36. Jeg gleder meg over livet mitt.					
37. Jeg kan delta på sosiale sammenkomster.					
38. Jeg er ofte trist.					
39. Pustevanskene mine plager meg når jeg er ute blant folk.					
40. Jeg er ofte nervøs.					
41. Jeg kan kle på meg selv.					
42. Jeg er trett på dagtid.					
43. Jeg føler meg isolert.					
44. Jeg klarer meg fint når det gjelder sykdommen min.					
45. Mine pusteplager hemmer meg i dagligdagse aktiviteter.					
46. Sykdommen belaster familielivet mitt.					
47. På grunn av mine pusteplager har jeg brutt kontakten med andre mennesker.					
48. Mine fritidsmuligheter er innskrenket.					
49. Generelt er jeg fornøyd med livet mitt.					

Tusen takk for utfylling av spørreskjemaet!

The Severe Respiratory Insufficiency Questionnaire (SRI) ble utviklet i 2003 av W. Windisch, Universitätsklinik Freiburg.
Oversatt til norsk og validert av H. Markussen ved Nasjonal kompetansetjeneste for hjemmerespiratorbehandling,
Haukeland Universitetssjukehus

Severe **R**espiratory **I**nsufficiency Questionnaire

SRI

Pasientspørreskjema om opplevelse av egen helse-tilstand ved respirasjonssvikt

Vurdering

For å gjøre verdiene sammenlignbare oppgis svaralternativene i tall fra 1 til 5:

Stemmer ikke	=>	1
Stemmer nesten ikke	=>	2
Stemmer delvis	=>	3
Stemmer ganske bra	=>	4
Stemmer helt	=>	5

Deretter blir sifrene rekodet slik at de høyere sifrene skal samsvare med sin:

Råverdi		Rekodet verdi
1	→	5
2	→	4
3	→	3
4	→	2
5	→	1

Punkter som skal rekodes :
1, 2, 4, 5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 19, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 34, 35, 38, 39, 40, 42, 43, 45, 46, 47, 48;

I neste omgang blir skalaene beregnet. Middelverdiene utregnes dersom minst halvparten av punktene er besvart. Ved hjelp av formlene nedenfor blir råverdiene omgjort til skalaverdier mellom 0 og 100.

Oversatt til norsk og validert, H. Markussen,
Nasjonal kompetansetjeneste for hjemmerespiratorbehandling
Haukeland Universitetssjukehus, Bergen

Respiratory Complaints

$$SRI - RC = \frac{Mean\ [2,5,12,19,22,24,25,29] - 1}{4} \bullet 100$$

Physical Functioning

$$SRI - PF = \frac{Mean\ [1,16,32,33,41,45] - 1}{4} \bullet 100$$

Attendant Symptoms and Sleep

$$SRI - AS = \frac{Mean\ [6,9,11,14,17,18,42] - 1}{4} \bullet 100$$

Social Relationships

$$SRI - SR = \frac{Mean\ [7,10,21,27,43,46] - 1}{4} \bullet 100$$

Anxiety

$$SRI - AX = \frac{Mean\ [8,13,26,28,39] - 1}{4} \bullet 100$$

Psychological Well-Being

$$SRI - WB = \frac{Mean\ [4,20,30,34,36,38,40,44,49] - 1}{4} \bullet 100$$

Social Functioning

$$SRI - SF = \frac{Mean\ [3,15,23,31,35,37,47,48] - 1}{4} \bullet 100$$

Totalsummen (**SRI-SS =** sumskala) regnes ut etter skalaverdienes middelverdi (SRI-RC, SRI-PF, SRI-AS, SRI-SR, SRI-AX, SRI-WB, SRI-SF). Dersom verdiene i en skala mangler, skal beregningen utelates. I vurderingen tilsvarer høye verdier høy livskvalitet , mens lave verdier står for lav livskvalitet.

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SF-36 SPØRRESKJEMA OM HELSE

INTRODUKSJON: Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.

Hvert spørsmål skal besvares ved å sette et kryss (X) i den boksen som passer best for deg. Hvis du er usikker på hva du vil svare, vennligst svar så godt du kan.

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1. Stort sett, vil du si at din helse er

Utmerket	Meget god	God	Nokså god	Dårlig
☐	☐	☐	☐	☐

2. Sammenlignet med for ett år siden, hvordan vil du si at din helse stort sett er nå ?

Mye bedre nå enn for ett år siden	Litt bedre nå enn for ett år siden	Omtrent den samme som for ett år siden	Litt dårligere nå enn for ett år siden	Mye dårligere nå enn for ett år siden
☐	☐	☐	☐	☐

3. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
a. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	☐	☐	☐
b. Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid	☐	☐	☐
c. Løfte eller bære en handlekurv	☐	☐	☐
d. Gå opp trappen flere etasjer	☐	☐	☐
e. Gå opp trappen en etasje	☐	☐	☐
f. Bøye deg eller sitte på huk	☐	☐	☐
g. Gå mer enn to kilometer	☐	☐	☐
h. Gå noen hundre meter	☐	☐	☐
i. Gå hundre meter	☐	☐	☐
j. Vaske eller kle på deg	☐	☐	☐

4. I løpet av de siste 4 ukene, hvor ofte har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

	Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. Du har måttet **redusere tiden** du har brukt på arbeid eller på andre gjøremål	☐	☐	☐	☐	☐
b. Du har **utrettet mindre** enn du hadde ønsket	☐	☐	☐	☐	☐
c. Du har vært hindret i å utføre **visse typer** arbeid eller gjøremål	☐	☐	☐	☐	☐
d. Du har hatt **problemer** med å gjennomføre arbeidet eller andre gjøremål (for eksempel fordi det krevde ekstra anstrengelser)	☐	☐	☐	☐	☐

5. I løpet av de 4 siste ukene, hvor ofte har du hatt noen av de følgende problemer i ditt arbeid eller andre av dine daglige gjøremål på grunn av følelsesmessige problemer (som for eksempel å være deprimert eller engstelig) l?

	Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. Du har måttet **redusere tiden** du har brukt på arbeid eller på andre gjøremål	☐	☐	☐	☐	☐
b. Du har **utrettet mindre** enn du hadde ønsket	☐	☐	☐	☐	☐
c. Du har utført arbeidet eller andre gjøremål mindre **grundig** enn vanlig	☐	☐	☐	☐	☐

6. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

Ikke i det hele tatt	Litt	En del	Mye	Svært mye
☐	☐	☐	☐	☐

7. Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 ukene?

Ingen	Meget svake	Svake	Moderate	Sterke	Meget sterke
☐	☐	☐	☐	☐	☐

8. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

Ikke i det hele tatt	Litt	En del	Mye	Svært mye
☐	☐	☐	☐	☐

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9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

	Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. Følt deg full av liv?	☐	☐	☐	☐	☐
b. Følt deg veldig nervøs?	☐	☐	☐	☐	☐
c. Vært så langt nede at ingenting har kunnet muntre deg opp?	☐	☐	☐	☐	☐
d. Følt deg rolig og harmonisk?	☐	☐	☐	☐	☐
e. Hatt mye overskudd?	☐	☐	☐	☐	☐
f. Følt deg nedfor og deprimert?	☐	☐	☐	☐	☐
g. Følt deg sliten?	☐	☐	☐	☐	☐
h. Følt deg glad?	☐	☐	☐	☐	☐
i. Følt deg trett?	☐	☐	☐	☐	☐

10. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følesesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.) ?

Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
☐	☐	☐	☐	☐

11. Hvor RIKTIG eller GAL er hver av de følgende påstander for deg ?

	Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
a. Det virker som om jeg blir syk litt lettere enn andre	☐	☐	☐	☐	☐
b. Jeg er like frisk som de fleste jeg kjenner	☐	☐	☐	☐	☐
c. Jeg tror at helsen min vil forverres	☐	☐	☐	☐	☐
d. Jeg har utmerket helse	☐	☐	☐	☐	☐

Vennligst kontroller at du har besvart alle spørsmålene

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