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MONITORING THE EFFICACY OF HOME MECHANICAL VENTILATION

PhD thesis

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List of abbreviations

Abbreviation	Definition
6MWD	6-minute walking distance
ALS	amyotrophic lateral sclerosis
ANOVA	analysis of variance
AVAPS	average volume assured pressure support
ARF	acute respiratory failure
BMI	body mass index
BOS	bronchiolitis obliterans syndrome
BPV-S/T	bilevel pressure ventilation -spontaneous/timed
CC	correlation coefficient
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
EPAP	expiratory positive airway pressure
FEV1	forced expiratory volume in 1 second
FVC:	forced vital capacity
HMV	home mechanical ventilation
HNHIF	Hungarian National Health Insurance Fund
HRQL	health-related quality of life
ICQ	item correlation coefficient with the rest of the questionnaire
ICS	item correlation coefficient with its own scale
IPAP	inspiratory positive airway pressure
NIV	noninvasive ventilation
NMD	neuromuscular disease

O_2	oxygen
OHS:	obesity hypoventilation syndrome
OSA	obstructive sleep apnea
p_aCO_2	arterial partial pressure of carbon dioxide
p_aO2	arterial partial pressure of oxygen
PCF	peak cough flow
PEEP	end expiratory pressure
PEF	peak expiratory flow
p_aO_2	partial pressure of oxygen
Pinsp	insiratory pressure
PTB	patient triggered breath
RCWD	restrictive chest wall disease
SD	standard deviation
SF-36	36 Item Short Form Survey
SF36-E/F	energy/fatigue scale
SF36-EP	role limitations due to emotional problems scale
SF36-EWB	emotional well-being scale
SF36-GH	general health scale
SF36-P	pain scale
SF36-PF	physical functioning scale
SF36-PH	role limitations due to physical health scale
SF36-SF	social functioning
SMA	spinal muscular atrophy
SRI	Severe Respiratory Insufficiency Questionnaire
SRI-AS	attendant symptoms and sleep scale
SRI-AX	anxiety scale

SRI-PF	physical functioning scale
SRI-RC	respiratory complaints scale
SRI-SF	social functioning
SRI-SR	social relationships scale
SRI-SS	summary score
SRI-WB	psychosocial well-being scale
Ti/Tt	inspiratory-total time ratio
VTE	expiratory tidal volume

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1. Introduction

1.1 History and current practice of home mechanical ventilation

The effort to establish home mechanical ventilation (HMV), providing long term ventilator support to patients with chronic respiratory failure in a domiciliary setting, dates back to the poliomyelitis epidemic of the 1940s and 50s, when about 10% of infected patients remained ventilator dependent (1). The state-of-the-art ventilation technique at the time, the external negative pressure device or the „iron lung", invented by Drinker and Shaw and further developed by Emerson (2), was both cumbersome and expensive, but served as a revolutionary device in the management of patients suffering from ventilatory-pump failure and gave a chance in some select cases for the patients to return to their home (3).

The earliest records of Hungarian patients being treated by such devices were also poliomyelitis survivors in the 1950s (4). These patients were using iron lungs up to the turn of the millennium (5).

Later advancements in the field of mechanical ventilation, such as supplying intermittent positive pressure ventilation through a tracheostomy (invasive ventilation – IV) and additionally, the development of noninvasive ventilation (NIV), supplying ventilatory support through a mouthpiece or mask, renewed interest in home mechanical ventilation and subsequently raised the number of clinical conditions treatable at home as well as the absolute number of patients receiving this long term treatment, especially in France, the United Kingdom and the United States (6-8).

Whereas initially, home mechanical ventilation was supplied by devices designed for health care use and adapted for domiciliary use, later technical advancements focused on the design of more compact, portable and financially feasible setups specifically for home use. Main developments to facilitate easier use were single limb circuits, demand systems using integral blowers rather than high pressure gas sources, external power source connections as well as rechargeable batteries, improved trigger, cycling and control of delivered breaths, well defined alarm functions and sophisticated monitoring tools, including downloadable storage of data generated during long term use (9). Emergence of reliable automated ventilation forms, such as volume assured pressure control modes,

automated back-up frequency modes and resistance-titrated expiratory pressure settings allow the delivery of more stable minute ventilation even for patients with variable respiratory mechanics and vulnerable airway patency, although clinical trials have failed to prove the superiority of these modes to classically used ones (10, 11).

Studies on patient-ventilator synchrony have verified that better synchrony is associated with improved comfort, which in turn can influence tolerance and success of ventilation (12, 13). Interestingly, time-cycled (or "controlled") modes, when adjusted optimally, can offer better synchrony and comfort for patients compared to flow-cycled pressure support modes, when a variable leak (probable in both NIV and cases of long-term tracheostomy) is present, which can lead to breath-to-breath variation in inspiratory time and consequently, autoPEEP and respiratory rate (14). New developments in automated control of cycling might further increase tolerability and dependability of pressure support modes, but convincing experimental data is not yet available on these new technologies.

Today HMV is an established mode of treatment for patients with chronic respiratory failure, resulting in increased survival in several different patient groups (15-17) as well as reduced costs, infection rates, optimized medical care utilization and improved health-related quality of life (18).

Noninvasive techniques have been gaining ground and are now used predominantly in most countries, even for individuals who require 24-hour ventilation (9). The Eurovent study in 2005 revealed that only 13% of HMV patients require invasive ventilation throughout Europe (19), Canadian noninvasive prevalence has been reported to be 72% (20), while more recently data from Australia and New Zealand showed that only 3.1% of patients have tracheostomies (21).

Use of HMV differs greatly in different parts of the world, with prevalence ranging from 2.9/100,000 in Hong Kong (22), 10.5 in Sweden (23), to 9.9-12.0 in Australia and New Zealand (21) and 12.9 in Canada (20). The most comprehensive survey of HMV practice to date has been the Eurovent survey, uncovering the characteristics of HMV provision for an estimated 21,000 patients, although the survey mainly focused on western- and central European centers and showed a markedly reduced rate of use in the one East-Central European country reviewed (0.1 versus 6.6 overall prevalence) (19).

Since the Eurovent survey, use of this technique has been more widespread, aided by better health care reimbursement systems, improving technological supply and other advancements such as telemonitoring (24). Many countries have created national registries, implemented national guidelines and established large HMV centers (23). New indications have been gaining ground, with obesity hypoventilation syndrome and chronic obstructive pulmonary disease supplying an increased demand for long term mechanical ventilation (21, 22, 25).

As a result of this, current prevalence of HMV is expected to be greater than those described in the Eurovent study, even in the countries where the practice was not widespread in the last decade and organization is still lacking compared to the aforementioned nations. Poland, the only country representing the East-Central European region in the Eurovent survey reported an astonishing 116-fold increase in the number of patients treated from 2000 to 2010, with diversifying indication groups and increased prevalence of the use of noninvasive interfaces (26).

Until recently, there has been no published data on HMV in Hungary, although the practice has been established since the 1990's and has been increasingly used in recent years with the emergence of noninvasive respiratory units and increased use of noninvasive ventilation (27). Extrapolation from the overall European prevalence of HMV from the Eurovent study would estimate about 650 patients in Hungary, not accounting for further possible increase by evolving indication guidelines, better diagnostics and improved patient recruitment.

National guidelines for HMV in the pediatric population have recently been published (28) and are underway for the adult population as well, likely improving diagnostics and care for these patients. The current Hungarian medical reimbursement system permits HMV for patients approved by the Committee of College of Health, but there are currently no assigned HMV centers. The Home Mechanical Ventilation Program of Semmelweis University was established in 2014, recruiting approximately 60 patients in its first five years of operation, with at least 80% of patients using noninvasive interfaces (29).

1.2 Indications and therapeutic goals of home mechanical ventilation

Chronic respiratory failure is a condition characterized by possible hypoxia, hypercapnia, secondary symptoms, diminished health-related quality of life (HRQL) and adverse outcomes. Etiology is versatile, but long term mechanical ventilation, which can be supplied through a noninvasive (mask) or invasive interface (tracheostomy) if noninvasive ventilation is contraindicated or not feasible (e.g. in the case of bulbar symptoms), has been proven to improve outcomes in most conditions (30-32).

Whereas the first indications for long term ventilatory support were restrictive diseases, such as muscular dystrophies, amyotrophic lateral sclerosis, tuberculosis sequelae and restrictive chest wall diseases, the conditions that are potentially suitable for long term ventilation in a domiciliary setting have now increased to hypoventilation syndromes, different neurological conditions, unsuccessful weaning and a select number of pulmonary diseases as well.

The most common HMV indications and the corresponding treatment goals according to current international guidelines (30-32) are as follows:

1.2.1 Obstructive diseases

Although acute noninvasive ventilation has been widely used for acute worsening or exacerbation of obstructive diseases, such as chronic obstructive pulmonary disease (COPD), bronchiolitis obliterans syndrome (BOS) and cystic fibrosis, the benefit of long term ventilation on clinical outcomes, such as increased survival, increased 6-minute walking distance, increased health-related quality of life, decreased frequency of exacerbations and hospitalizations, has only recently been proven for patients with documented daytime or nocturnal hypercapnia ($p_aCO_2 \geq 52.5$mmHg) in COPD (16, 33). Successful treatment entails effective reduction of p_aCO_2 levels, which might require high intensity ventilation (20-40 cmH_2O Pinsp and 14-16/min back-up frequency) (34).

1.2.2 Restrictive chest wall diseases

Restrictive chest wall diseases include scoliosis and other gross chest wall deformities, limiting effective ventilation. This is the disease group that most obviously benefits from

home mechanical ventilation, with three-fold increase in survival compared to long-term oxygen therapy during the course of ten years (35). Treatment goals include reduction of hypercapnia and prevention of secondary pulmonary hypertension, often present in late stages (36).

1.2.3 Central apnea-hypopnea syndromes

These conditions are either congenital or acquired and are characterized by diminished central ventilation drive and subsequent hypoventilation and hypercapnia. Congenital and secondary disorders are relatively rare but manifest in early childhood, often requiring invasive ventilation (37).

A special form of hypoventilation syndrome is obesity hypoventilation syndrome (OHS), a complex ventilatory disorder prevalent in patients with a BMI>30kg/m^2 which is characterized by global hypoventilation that is central in origin and leads to hypercapnia ($p_aCO_2 \geq 45$mmHg) and subsequent chronic respiratory failure (38). 90% of cases also include upper respiratory tract obstruction, making management more difficult (39). With 0.15-0.3% of the adult population affected, this syndrome is the fastest growing indication group in several countries failure (38). In Australia and New Zealand, 31% of all HMV cases are OHS related (20). Recent data shows that a trial of CPAP therapy rather than long term bilevel ventilation might be sufficient for some patients, while severe cases require noninvasive ventilation titrated during polysomnography (40). Treatment goal is reduction of daytime hypercapnia (even during non-ventilated hours), which in turn leads to reduction in secondary symptoms such as daytime sleepiness and headaches as well as increased survival (41).

1.2.4 Neuromuscular diseases

This is a versatile group of conditions with distinct time of manifestation and progression patterns. While some forms of metabolic disorders (Pompe disease) and spinal muscular atrophies (SMA) manifest in early childhood with rapid progression to severe respiratory failure requiring invasive ventilation, other conditions such as Duchenne dystrophy and myopathies are characterized with a slower progression of ventilatory insufficiency.

Initial symptoms often include fractured sleep, cachexia and inadequate cough. Effective airway clearance is achieved when a vital capacity of 2-4L and adequate glottic function is present, which normally produces a peak cough flow (PCF) of 360L/min. If PCF is reduced to 250-270L/min, the risk of ineffective secretion elimination and subsequent pneumonia is increased (42). Hence lung function monitoring is crucial in avoiding acute respiratory failure and emergency initiation of invasive ventilation, as long term survival is increased with adequate and timely initiation of noninvasive respiratory and cough assistance (43).

Adult onset but rapid progression is associated with amyotrophic lateral sclerosis, a condition with frequent early bulbar involvement. Long term ventilation is controversial for these patients, since bulbar involvement warrants invasive ventilation with the risk of the patient progressing to a fully locked-in state. Noninvasive ventilation can be effective in alleviating dyspnea, but is ineffective if bulbar symptoms make secretion elimination difficult. Noninvasive ventilation nevertheless is often supplied even in these cases as palliative therapy (44).

1.2.5 Trauma related diseases

As weaning failure and long term invasive ventilation need is quite common after severe spinal cord injury involving the cervical region as well as traumatic brain injury, home mechanical ventilation is a possibility in well-managed cases, although treatment goals need to be defined on an individual basis and ongoing ventilatory dependence is usually a marker of unfavorable outcome (45).

1.2.6 Failed weaning

Prolonged weaning because of persistent respiratory failure after an acute or acute-on-chronic disease is quite common in intensive care units as a result of muscle weakness or diaphragm dysfunction, but after transfer to specialized weaning centers, only about 21.4% of these cases actually qualify as weaning failure (after 3 months of unsuccessful weaning) and require ongoing invasive ventilation in a domiciliary setting (46). In some cases, step down to noninvasive ventilation is possible and is associated with better

outcomes (47). Overall, the need for ongoing invasive ventilation is often associated with several other comorbidities that might make home care impossible, hence this indication group is more likely to be treated in hospital long-term care settings with much worse overall outcome (48).

1.2.7 Other pulmonary diseases

A number of pulmonary diseases other than COPD might progress to chronic respiratory failure, such as interstitial lung diseases, pulmonary fibrosis, restrictive allograft syndrome after lung transplantation and pulmonary manifestation of autoimmune diseases. Overall outcome is poor in these disease groups, but long-term noninvasive ventilation can be applied as palliative treatment or as a bridge to lung transplantation (49).

Other rare indications of HMV include ventilation disorders and conditions with increased work of breathing and dyspnea, as well as complex sleep related breathing disorders. As there are no evidence based treatment algorithms for these patients, a case-by-case evaluation and management is warranted if long-term ventilation is started (50, 51).

1.3 Types of ventilation and levels of dependence

As a result of the many technical advancements of the last decades and the evolvement of sleep medicine aiming to treat patients with different forms of sleep disorders, ventilatory assistance can be supplied by vastly different devices and through various interfaces. Because there is an overlap between devices able to treat sleep disorders and ones able to provide ventilation to fully dependent patients, there is not always a clear, concise way in the literature to define what constitutes as mechanical ventilation and what constitutes as a sleeping aid.

Traditionally, patients treated with a bilevel pressure device through any kind of interface with a back-up frequency are considered to be home mechanical ventilation patients. Another important aspect is dependence from the ventilator. Although most patients who require home mechanical ventilation are able to survive for a shorter or longer period of

time without their device, if their daily ventilation hours don't meet the prescribed amount, health deterioration is imminent in most cases.

The level of dependence is defined by several aspects. Low dependency level patients use the ventilator during sleep and are ventilated through a noninvasive interface. Medium dependency patients require ventilation for 8-16 hours/day, which is supplied through noninvasive ventilation. High dependency patients are dependent on a ventilator for more than 16 hours a day or are receiving ventilation through an invasive interface (tracheostomy). Patients who require assistance in living or have severe central apnea periods also fall in the high dependency category (31, 32).

As can be seen, from the prior definitions and Figure 1, the amount of daily time spent on a ventilator does not always correlate with the level of dependence and additionally, the type of interface does not closely correlate with high daily ventilation need. While an invasive interface itself means a different level of care, patients who require it are often able to spend hours off the ventilator or even leave their home without it.

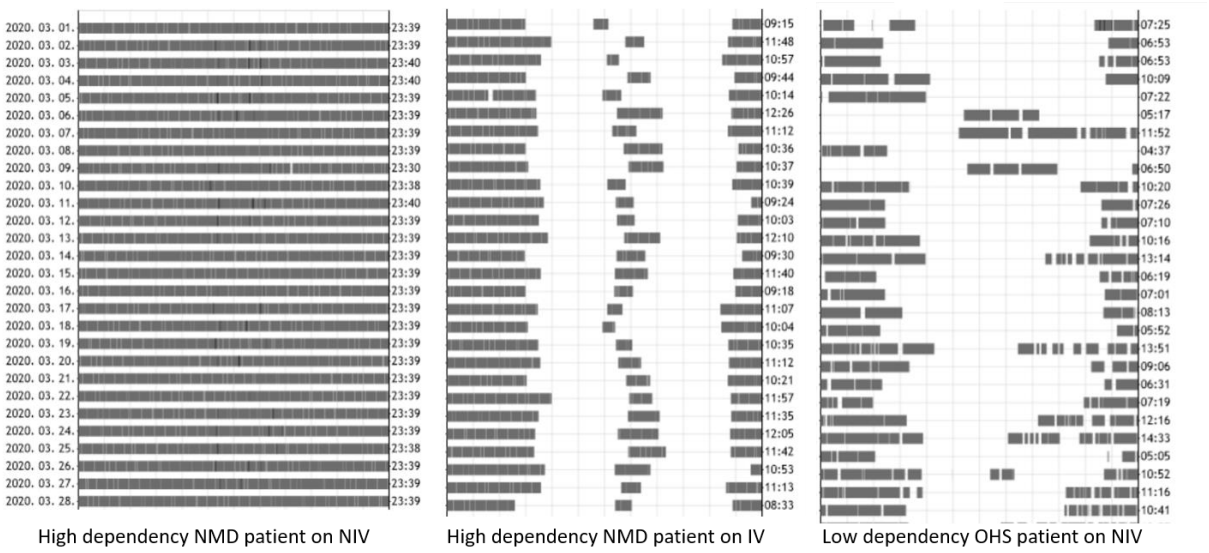

Figure 1. Different daily ventilation needs: *Ventilator recordings of daily ventilation use for a 28-day period for three different HMV patients. Shaded bars indicate use of device during a 24-hour period. Numbers indicate total hours of daily ventilation. Data taken from the Semmelweis University Home Mechanical Ventilation Program records.*

1.4 Long term management of home mechanical ventilation patients

Several national guidelines have been published with evidence based lists of indications and clearly defined, disease specific diagnostic algorithms (30-32), but treatment goals are less well established with loosely defined ventilation goals and settings, based on expert opinion rather than evidence based data. There is no current evidence on how adherence to treatment goals affects outcome or how often treatment goals should be evaluated.

Follow-up appointments or visits are important to pinpoint technical problems, suboptimal compliance or change in ventilation requirements, but too frequent checkups are not cost-effective for health care providers and as a recent systematic review concluded, extensive surveillance limits patients' sense of independency (52). As guidelines do not usually define minimal required frequency and method of follow-up for patients initiated on home mechanical ventilation, practice varies greatly in different regions but most centers offer annual or bi-annual inpatient appointments, which is not always feasible with highly dependent patients (53).

1.5 Monitoring efficacy in home mechanical ventilation

1.5.1 Morbidity and mortality

The conditions leading to chronic respiratory failure and HMV need have distinctively different progression patterns, moreover, the initiation of home mechanical ventilation has different effects on patients' overall state. The guideline indications are all currently supported by evidence of improved outcome, but exacerbation of the chronic condition remain a probability especially in COPD patients, where readmission rates are the highest after starting HMV. OHS patients however have distinctively low rehospitalization rates once starting HMV and since this population is usually younger in age, this has important socioeconomic consequences as well (54).

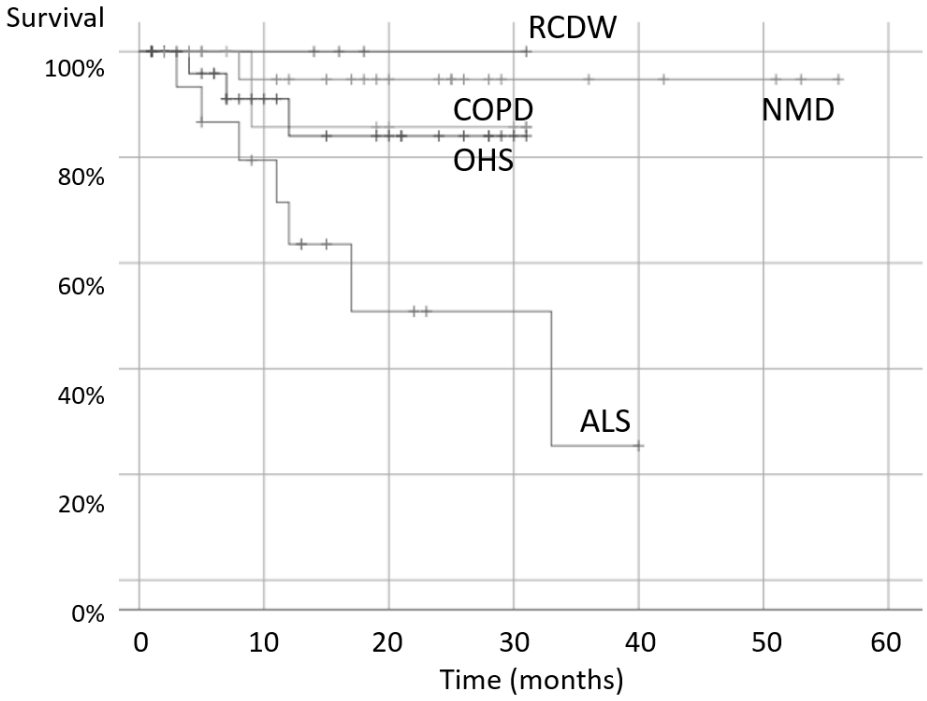

Figure 2. Survival of patients enrolled in the Home Mechanical Ventilation Program at Semmelweis University 2014-2019: *Kaplan Meier curves of patients with different indications. ALS - amyotrophic lateral sclerosis, COPD - chronic obstructive lung disease, NMD - neuromuscular disease, OHS - obesity hypoventilation syndrome, RCDW - restrictive chest wall disease. Data taken from the Semmelweis University Home Mechanical Ventilation Program records.*

Overall survival is different in the disease groups (see Figure 2). A recent prospective study in one of the largest weaning and home ventilation services in the UK showed a median time-to-death of 19.5 months, with RCWD and slowly progressive NMD patients fairing the best and COPD patients fairing the worst (55). Studies in COPD patients have shown a one-year survival of 80-88% (16, 56) on HMV, while OHS patients can expect a survival of 89% at three years of HMV, but comorbidities are common in this disorder and mortality is mostly associated with cardiovascular risk factors (57). Patients with restrictive chest wall disease and slowly progressing neuromuscular diseases have the greatest benefit when focusing on survival. RCDW has more than 90% survival at 1 and 76% at 8 years (versus just 32% without HMV) (35). Duchenne dystrophy, which was associated with a life expectancy of around 20 years, is now a disease that can be managed

well and several European centers report noninvasively ventilated patients surviving well into their forties (17, 58, 59). On the other hand, outcome in ALS remains poor. A study focusing on patients with respiratory symptoms has shown a median survival of 219 days on noninvasive ventilation after onset of symptoms and initiation of therapy compared to 171 days in the control group with no intervention, but this survival advantage is more typical for patients with preserved bulbar function (60).

1.5.2 Ventilation parameters and compliance with therapy

Most deaths during home mechanical ventilation occur because of disease progression, but the possibility of device malfunction or ventilation related emergencies is not negligible (61). Because of this, most national guidelines list minimum requirements such as extensive monitoring and alarm functions tailored to the individual patient's condition. It is also crucial for the ventilator to be able to collect and store a variety of data, which can be analyzed during follow-up by the physician in charge of therapy, including pressure, volume and flow tracings, leak values, inspiratory time measurements, spontaneous and assisted respiratory rates (see Figure 3), although there has been limited data and conflicting views on the overall relevance of monitoring these functions (62, 63). Apart from the ventilator, an alternative mode of monitoring is advised, especially for high dependency patients, although there is no clear data on what type of monitoring is optimal. Oxygen saturation monitoring does not always detect hypoventilation (35) and $etCO_2$ monitoring is difficult in noninvasive setups, although recent advances have been made with breath-analyzer modules (64). While transcutaneous carbon dioxide monitoring is ideal, it is currently only used during diagnostic studies (35). Although general compliance to therapy is an important determinant of survival (55) and basis for continued participation in most home mechanical ventilation centers, there is no data on how adherence to prescribed ventilatory parameters effects outcome.

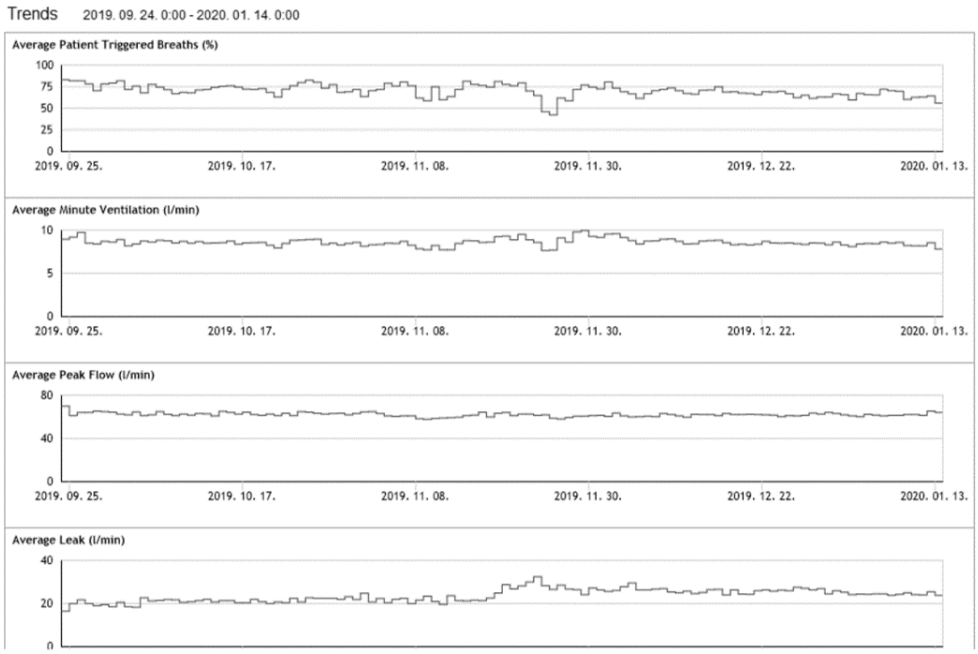

Figure 3. Monitoring trends of home mechanical ventilation: *Trend recording of noninvasive home ventilator with periods of higher leak and subsequent loss of patient trigger and diminishing minute ventilation. Data taken from the Semmelweis University Home Mechanical Ventilation Program records.*

1.5.3 Pulmonary function test

Pulmonary function test parameters such as forced vital capacity (FVC) and forced 1 second expiratory volume (FEV1), as well as their ratio are reliable markers of chronic respiratory failure and the basis for diagnosis in several disease groups (31, 32). Regular measurement is warranted in COPD and neuromuscular diseases, even in patients with tracheostomies, which can be performed with the adequate adjustment of the measuring device. Once mechanical ventilation is started, pulmonary function parameters are not indicative of outcome, although they remain important markers of cough function, which is especially important with noninvasive ventilation, when additional cough assist device is often needed for adequate airway secretion management (42).

1.5.4 Arterial blood gas

Arterial blood gas sampling is basis for establishing diagnostic criteria of mechanical ventilation need for patients with hypercapnic chronic respiratory failure as well as need for oxygen supplementation. Standard bicarbonate can be a surrogate for chronic hypercapnia and if it is above 27mmol/L, further diagnostic tests and long term ventilation is warranted in hypercapnic chronic respiratory failure patients (31). In other disease groups, random arterial sampling values are often not indicative of overall state. In neuromuscular patients especially, both p_aO_2 and p_aCO_2 can be within normal range despite severe restrictive pulmonary function parameters and abnormal polysomnography recordings. In fact, a 10 year analysis of the French ANTADIR database including more than 26,000 patients showed that p_aO_2 and p_aCO_2 values were independent mortality predictors only in COPD and pulmonary fibrosis patients (65).

1.5.5 6-minute walking distance

The 6-minute walking distance (6MWD) is an established marker of exercise tolerance and has been proven to correlate well with disease severity in several chronic respiratory failure conditions (66). 6MWD might improve in several conditions under HMV treatment (67). While individual monitoring of the 6MWD is useful, the confounding effect of comorbidities and baseline limited mobility in several patient groups limit its use as a general marker of efficacy, which is demonstrated by the results of the RESCUE trial focusing on long-term NIV in COPD patients after an exacerbation, where the 6MWD values were not reported since patients were so frequently unable to perform it (68).

1.5.6 Health-related quality of life

HRQL is usually measured through questionnaires and as general health quality surveys might be inaccurate in specific diseases groups, there have been attempts to establish a more focused questionnaire useful in chronic respiratory failure patients (69, 70). Perhaps the most efficient questionnaire for this purpose designed up until now is the SRI

Questionnaire, which is a multimodal tool with high psychometric properties, specifically designed to evaluate HRQL in patients battling chronic respiratory conditions (71). The SRI Questionnaire has been validated in several different conditions and has been proven to be a superior HRQL evaluation tool for patients receiving home mechanical ventilation (70, 72). The questionnaire has been used to evaluate HRQL in both IV and NIV patients and has been validated in several different languages (72-79).

The effect of starting HMV on patients' HRQL has been studied before, but these studies either used a general HRQL survey (80) or focused only on a well-defined, selected population often excluding patients with tracheostomas, or patients that were recruited after weaning failure or an acute worsening of their chronic condition (81). As a considerable proportion of home mechanical ventilation patients are started on long term therapy after such acute scenarios, these studies might not reflect real-life populations, as more severe patients are underrepresented (see Table 1). Studies have also shown that HRQL differs greatly in chronic respiratory failure patients with different diseases (see Table 1) and we can expect that the change in HRQL induced by home mechanical ventilation also varies (53, 75, 81, 82).

The factors that can possibly affect change in HRQL are baseline characteristics, initial diagnosis, initial HRQL, type of interface used for ventilation, duration of ventilation and lung function test parameters. Studies performed on specific patient groups might have different follow-up plans, and their HRQL changes might not be comparable. As is evidenced in Table 1, to our knowledge, no prospective study has examined one specific HMV protocol and its HRQL improving effects in a large, unselected case mix population.

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Table 1. Studies utilizing SRI to report detailed HRQL for HMV patients: *Data are presented as mean±SD. NIV - noninvasive ventilation, IV - invasive ventilation, HRQL – health-related quality of life, HMV - home mechanical ventilation, SRI-SS - Severe Respiratory Insufficiency Questionnaire Summary Score, COPD - chronic obstructive pulmonary disease, TB - tuberculosis sequelae, OHS - obesity hypoventilation syndrome, OL - overlap syndrome, NMD - neuromuscular disease, RCDW - restrictive chest wall disease, BPV-S/T - bilevel pressure ventilation -spontaneous/timed, AVAPS - average volume assured pressure support, ARF – acute respiratory failure.*SD not listed.*

Author	**Study aim**		**Patients**	**Main HRQL (SRI-SS) finding**
Windisch et al. (81)	Studies reporting change in HRQL	HRQL improvement during HMV	85 stable NIV patients	49±15 (baseline) 61±15 (1 month) 61±16 (1 year)
Struik et al. (68)		NIV vs. standard treatment	108 COPD patients after acute exacerbation	47.9±15.1 (baseline) 55.0±15.4 (12 months)
Murphy et al. (10)		O_2 therapy vs NIV+O_2 therapy	64 hypercapnic patients after acute exacerbation	45.8±15) (baseline) 50.6* (6 weeks)
Howard et al. (83)		CPAP vs Bi-level PAP	57 OHS patients (outpatient or hospital referral)	50.63±3.65 (baseline) 63.5±3.74 (3 months)
Storre et al. (11)		AVAPS in OHS	10 OHS patients starting NIV	63±15 (baseline) 78± 14 (6 weeks BPV-S/T) 76±16 (6 weeks BPV-S/T-AVAPS)
Murphy (84)	Studies reporting HRQL for a specific HMV patient group	High intensity vs high pressure NIV	7 COPD with established HMV	57±11 vs 69±16
Storre et al. (85)		High intensity vs target volume NIV	10 COPD patients with established HMV	59.3±14.8 vs 62.4±18.9
Arellano-Maric et al. (86)		NIV vs CPAP	42 OHS patients with established NIV	61.2±16 vs 65.3±14
Windisch (72)		SRI validation in COPD	162 COPD patients with established NIV	52±17
Walterspacher (87)		SRI for LOT COPD patients	42 COPD patients with established NIV	53.2±18.6
Oga et al. (69)		HRQL tool comparisons	56 COPD/TB patients with established NIV	56.0 ± 15.3

Chen et al. (73)		Chinese SRI validation	149 stable NIV patients	52.93±15.11
Budweiser (88)	Studies reporting HRQL for mixed HMV patient group	Prognostic value of HRQL	231 stable NIV and IV patients	61.2±17.7 (all patients) 52.2±15.6 (COPD) 66.2±17.2 (RCWD) 55.3±9.2 (NMD) 71.3±15.7 (OHS/OL)
Gosh et al. (74)		English SRI validation	152 stable NIV and IV patients	55.9±18.9 (all patients) 43.1±17.3 (COPD) 61.9±16.1 (RCWD) 58.8±20.3 (NMD) 53.4±18.8 (OHS) 53.5±19.7 (miscellaneous)
Oga et al. (78)		Japanese SRI validation	56 stable NIV patients	56.0±15.3 (all patients) 56.6±14.7 (COPD) 55.5±16.4 (Tb)
Ribeiro et al.(79)		Portuguese SRI validation	93 stable NIV and IV patients	56.6±15.7 (all patients) 57.0±16.5 (COPD) 55.6±15.1 (OHS) 62.0±12.6 (RCWD) 50.2±16.2 (COPD+OSA) 59.4±19.2 (NMD) 46.0±13.3 (miscellaneous)
Markussen et al. (77)		Norwegian SRI validation	127 stable NIV and IV patients	55.8±18.4 (all patients) 61.0±14.7 (NMD) 43.2±19.0 (COPD) 58.4±18.3 (OHS) 55.8±18.4 (RCWD)
Huttmann et al. (89)		HRQL after unsuccessful weaning	25 IV patients	49±16 (NMD) 47±20 (COPD)
Huttmann et al. (75)		HRQL of invasively ventilated HMV patients	32 IV patients	53±16 (all patients) 58±16 (NMD) 48±15 (lung diseases)
Raveling et al.(90)		Hypercapnia improvement as a survival predictor	240 COPD patients starting NIV	49.9±15.0 (all patients) 54.6±14.3 (stable patients) 47.9±14.9 (ARF patients)

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2. Objectives

There is a logical aim to develop more comprehensive practice guidelines that focus on evidence-based treatment goals as well as well-defined follow-up algorithms that are based on adequate monitoring of efficacy of therapy. There has been no information on how the level of adherence to current treatment goals influences outcome and no clear guidance on how often patients should be followed to ensure best possible quality of care. For this purpose, markers of efficacy of home mechanical ventilation have to be defined, but currently research in this field is still scarce.

As the indications and subsequent manifestations of chronic respiratory failure are quite diverse, monitoring classic markers of ventilation and respiration, such as blood gas parameters, pulmonary function parameters and respiratory parameters might be informative when following one particular patient, but have poor correlation with actual outcome and efficacy of therapy. On the other hand, health-related quality of life improvement has been studied in most conditions requiring long-term ventilation and has been proven to be associated with outcome (88), hence HRQL measurements could be an adequate marker of efficacy and important tools for quality control and optimization of therapy.

The aim of this thesis is to establish HRQL as a possible prospective marker for efficacy of home mechanical ventilation, by observing HRQL patterns after 6 months of optimal clinical care on a real-life HMV patient population. In order to adequately conduct such a prospective study and interpret the results for a more general HMV population, I first aimed to evaluate Hungarian home mechanical ventilation practice and validate the SRI Questionnaire for a Hungarian HMV population.

The objectives of my thesis are as follows:

2.1 Evaluating home mechanical ventilation in Hungary

The objective of the first study was to evaluate the prevalence of home mechanical ventilation in Hungary and describe its characteristics to better aid future development of home mechanical ventilation practice in the country as well as establish the feasible composition for the patient frame of the subsequent studies (91).

2.2 Validation of a quality of life tool for the Hungarian population

The aim of the second study was to create and validate the Hungarian version of the SRI Questionnaire as a quality of life tool suitable for further studies conducted in a Hungarian population of home mechanical ventilation patients (92).

2.3 Monitoring efficacy of home mechanical ventilation through quality of life change

The aim of the third study was to observe the effects of optimally conducted home mechanical ventilation on quality of life in different patient groups in order to provide a reference for best expected improvement in quality of life as a possible marker of efficacy. In order to achieve this, the third study was a prospective observational cohort of protocolized, optimally conducted home mechanical ventilation with standardized follow-up in a real-life, mixed case group of chronic respiratory patients using the validated Hungarian version of the SRI Questionnaire. The study objective was to evaluate HRQL change patterns for these patients (93). As described in the introduction, no prospective study has examined one specific HMV protocol and its HRQL improving effects in a large, unselected case mix population.

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3. Methods

3.1 Evaluating home mechanical ventilation in Hungary

3.1.1 Study design and participants

We conducted a nationwide study in Hungary using an online survey focusing on patients receiving ventilatory support through a bilevel pressure or volume device with or without internal batteries at home under the care of a prescribing physician. Representatives of intensive care units, pulmonology centers and pediatric centers were invited to participate in the survey. Questions of the survey included characterization of the site (type of unit, yearly patient number), experience with home mechanical ventilation, number of patients treated, indication for home mechanical ventilation (disease type), description of home mechanical ventilation (invasive/noninvasive, ventilation hours, duration of ventilation) and description of the care provided (type of follow-up visits, hospitalization need, reimbursement).

Participation was voluntary and consent was implied by response to the survey. Surveys were sent out via email to all identified sites, followed by an email reminder and a telephone reminder. Survey responses were collected from March 2018 to July 2018 via an online survey program (Google Forms, Google LLC, Mountain View, United States). Sites not submitting an answer by the end of the study period were recontacted through telephone and were asked to identify the reason for non-responder status as A ("missed deadline or did not wish to submit data) or B ("had no relevant information to share"). Returned surveys were analyzed anonymously. Data was summarized for all sites.

The study was approved by the research ethics board of Semmelweis University (TUKEB 253/2017).

3.1.2 Statistical analysis

Normality was tested by Shapiro-Wilks test. Data are presented as median (interquartile range) for continuous and as percentages for categorical values. Relationships between sites and therapy characteristics were analyzed by Chi-squared test. Analyses were

conducted using SigmaPlot 12 (Systat Software, San Jose, United States). 2018 Hungarian population data was obtained from the Hungarian Central Statistical Office (94).

3.2 Validation of the Hungarian version of the Severe Respiratory Questionnaire

3.2.1 SRI Questionnaire

The SRI Questionnaire is a self-administered quality of life verification tool which has been found to have high psychometric properties. It consists of 49 items and a corresponding 5 level Likert scale. The items are analyzed and grouped into 7 different subscales (respiratory complaints: SRI-RC – eight items, physical functioning: SRI-PF – six items, attendant symptoms and sleep: SRI-AS – seven items, social relationships: SRI-SR - six items, anxiety: SRI-AX - five items, psychosocial well-being: SRI-WB - nine items, and social functioning: SRI-SF - eight items), all of which result in a score ranging from 0 to 100. The summary score (SRI-SS) is calculated from the mean of all subscales, resulting in a range from 0 to 100, with higher scores signaling higher quality of life.

3.2.2 Translation-back translation method

The original German questionnaire was translated by two certified translators from German to Hungarian. A unified first version of the questionnaire was compiled by a group of experts in the field of pulmonology, critical care and mechanical ventilation, which was then backtranslated to German. The original author group verified the backtranslation based on equivalence for all questions and the Hungarian version was subsequently revised based on equivalence discrepancies. This revised second version was then tested in a pilot study and was amended, based on difficulties in understanding, into the third version. The third version of the Hungarian SRI Questionnaire was then tested for validity, viability and reliability in a large cohort.

3.2.3 Patients

Patients were recruited through the Semmelweis University Home Mechanical Ventilation Program, the Department of Pulmonolgy of Semmelweis University and the Department of Neurology of the Hungarian Army Medical Center. Adult, stable chronic respiratory failure patients receiving home mechanical ventilation with an aid of a bi-level ventilator through invasive or noninvasive interface were eligible for the validation study. Exclusion criteria were inability to cooperate with the survey, less than three months of treatment or acute worsening of chronic respiratory condition within the previous month. All patients were informed about the process of the validation study and signed written informed consent forms before enrollment.

During enrollment, demographic data [age, gender, body mass index (BMI), education level, employment status, smoking history, disease], clinical parameters (lung function test and arterial blood gas sample) and ventilation characteristics [duration of ventilation, daily ventilation use during the previous month, interface type, mean inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), frequency, inspiratory time/exspiratory time ratio (Ti/Tt), patient triggered breath ratio values during the previous month] were recorded. Arterial blood gas sampling was performed minimum 15 minutes after discontinuing ventilation and/or oxygen supplementation, unless patients were ventilator dependent and could not be disconnected for even short periods of time. Pulmonary function tests were performed with the Piston PinkFlow meter (Piston Ltd, Budapest, Hungary). Patients were asked to self-administer the Hungarian SRI and the 36 Item Short Form (SF-36) Questionnaires and were aided by the investigator if self-administration was not possible. Time to complete questionnaires was measured. Patients were asked to retake the survey in their home one week after enrollment to verify reproducibility. The repeated questionnaires were collected through mail, through electronic mail or at subsequent ambulatory visits.

The study was approved by the ethical committee of Semmelweis University (TUKEB 249/2017).

3.2.4 Psychometric properties

Psychometric properties were verified based on the protocol previously published during the Spanish validation of the SRI Questionnaire (76).
Viability was studied by recording the time spent to complete the questionnaire, ability to self-administer the questionnaire and the missing item rate for the questionnaire. Validity was determined by exploratory factor analysis of the 49 items in the Hungarian SRI, subsequent confirmatory factor analysis of subscales and by comparing the corresponding scales of the Hungarian SRI with the Hungarian SF-36 already in use (95). Reliability was determined by testing the internal consistency using the Cronbach alpha coefficient. A scale was deemed reliable if Cronbach alpha coefficient was greater than 0.7 and if its items correlated better with their own scale than items of the rest of the scales. Reproducibility was assessed by determining the correlation of the results of the two questionnaires submitted by the same patient at different time points.

3.2.5 Statistical analysis

Normality was tested by Shapiro-Wilks test. Data are represented as mean (±standard deviation) for quantitative variables and n (%) for qualitative variables. Groups were compared using the paired Student t-test. Intergroup differences were determined using the analysis of variance (ANOVA) test. Factor analysis was performed, after testing for sample adequacy, using the principal component method with a varimax rotation, using an eigenvalue >1 for extraction. Scale correlations were determined using Pearson correlation. Results were deemed statistically significant at $p<0.05$. Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) version 25.

3.3 Monitoring efficacy of home mechanical ventilation through quality of life change

3.3.1 Study design and participants

The purpose of this prospective observational follow-up study was to evaluate, using the Hungarian validated version of the Severe Respiratory Insufficiency Questionnaire, HRQL change six months after the initiation of home mechanical ventilation in patients suffering from chronic respiratory failure, and identify possible factors influencing said changes. We enrolled patients diagnosed with chronic respiratory failure in need for long term mechanical ventilation, who were treated through the Semmelweis University Home Mechanical Ventilation Program from January 2014 to December 2018. Patients were referred to the Program either through elective workup for a chronic condition (elective initiation) or after recovery from an acute exacerbation of a previously unknown chronic condition (acute initiation). All patients were enrolled based on work-up during stable conditions and diagnosed according to available international guidelines (30-32). Patients who were unable to complete the questionnaire were excluded. Patients who deceased before the study completion were noted as lost to follow-up. Written informed consent was obtained from all patients included in the study. The study was approved by the ethical committee of Semmelweis University (TUKEB 251/2017).

3.3.2 Home mechanical ventilation initiation and follow-up

Home mechanical ventilation was initiated according to the Semmelweis University Home Mechanical Ventilation Program Guideline either after discharge from an acute hospitalization or during an elective hospital admission. Given the current reimbursement system utilized in Hungary, patients have the benefit of receiving patient tailored ventilation plans and equipment supply, including cough assisting devices, if needed. Mechanical ventilation was supplied through A40 or Trilogy 100 home mechanical ventilators (Koninklijke Philips N.V., Amsterdam) and built in, AIRcon or HC150 humidifiers (WILAmed GmbH, Kammerstein; Fishel Paykel Healthcare, Auckland) in pressure controlled, volume targeted mode through a noninvasive interface if possible or invasive interface if noninvasive ventilation was contraindicated or not feasible. Inspiratory time was aimed at 25% for patients with obstructive lung function characteristics and 30% for all other patients, then further tuned for optimal patient comfort. Supplementary O_2 was applied if arterial blood gas values showed a p_aO_2 below 60 mmHg. Treatment goals for home mechanical ventilation were normalization of p_aCO_2

and p_aO_2 blood gas levels and adequate respiratory secretion management. Patients received individually tailored therapy with adequate interface (nasal, full, total face masks or cuffed tracheostomy tubes with reusable inner cannula), personalized daily ventilation plans and cough assisting device (CoughAssist T70, Koninklijke Philips N.V., Amsterdam) and/or tracheal suction devices if peak expiratory flows were below 250 L/min, suggesting insufficient coughing. Home mechanical ventilation was overseen by a voluntary family member or caregiver trained by our institution in skills specific to the patient's treatment plan. Patients did not receive other institutionalized assistance. Optimal care was achieved by frequent physician follow-up to achieve high compliance with therapy and continuously maintained treatment goals. Patients were followed up monthly or bimonthly by a physician of the program, trained in home mechanical ventilation. Data were not routinely collected for the purpose of this study during these physician visits.

3.3.3 Data collected

Demographic data (age, sex, initial diagnosis), treatment characteristics (initiation type, interface, daily ventilation need, O_2 supplementation need), arterial blood gas values and lung function tests were collected at baseline, ventilator settings and blood gas values (if feasible) were collected at 6 months. Arterial blood gas sampling was performed minimum 15 minutes after discontinuing ventilation and/or oxygen supplementation, unless patients were ventilator dependent and could not be disconnected for even short periods of time. Pulmonary function tests were performed with the Piston PinkFlow meter (Piston Ltd, Budapest, Hungary). Initial diagnosis leading to chronic respiratory failure and long-term mechanical ventilation need was identified as chronic obstructive pulmonary disease (COPD), restrictive chest wall disease (RCWD), obesity hypoventilation syndrome (OHS), slowly progressing neuromuscular disease (NMD) or progressive neuromuscular disease (amyotrophic lateral sclerosis) (ALS).

3.3.4 HRQL assessment

HRQL was assessed at baseline and 6 months after initiation of home mechanical ventilation using the Hungarian version of the SRI Questionnaire. The questionnaire consists of 49 statements and a five-point Likert scale. The results are interpreted in 7 different subscales (SRI-RC: Respiratory complaints, SRI-PF: Physical functioning, SRI-AS: Attendant symptoms and sleep, SRI-SR: Social relationships, SRI-AX: Anxiety, SRI-WB: Psychological well-being and SRI-SF: Social functioning) and the Summary Score (SRI-SS), with a value between 0 to 100, with 100 being the highest score. Patients were asked to fill out self-administered questionnaires and were assisted by caregivers if physical limitation or eyesight problems prohibited participation. The baseline questionnaire was filled out and collected during participating patients' hospital stay, while the follow-up questionnaires were collected by the visiting physician. Patients referred to our program after acute hospitalization were asked to base their baseline answers on the last month prior to their acute illness to reflect chronic health status.

3.3.5 Statistical analysis

Normality was tested by Shapiro-Wilks test. Continuous variables are described with means (±standard deviation) and categorical variables with frequencies and percentages [n (%)]. SRI scores were analyzed with Paired t-test or, in case of non-normally distributed data, Signed Rank Test. Characteristics were compared with t-test or, in case of non-normally distributed data, Mann-Whitney U Rank sum test. Diagnostic groups were compared with one-way ANOVA (Brown-Forsythe) or, in case of non-normally distributed data, ANOVA on Ranks. Pearson Product Moment Correlation was used for correlation analysis. A p-value of <0.05 was considered statistically significant. Clinically meaningful HRQL change was defined as >0.5 baseline SD (96). Analyses were conducted using SigmaPlot 12 (Systat Software, San Jose, United States) and SPSS Statistics for Windows 25 (IBM Corp., Armonk, NY). Bubble charts, commonly used to depict more complex, multidimensional correlations visually, were used to visualize quality of life change patterns in the following three dimensions: 1) size representing extent of change (larger bubbles mean larger changes), 2) texture representing direction of change (bubbles with – sign representing negative change, while bubbles with no

texture representing positive change), and 3) shading representing significance (non-significant bubbles are white, while significant bubbles are gray). Bubble charts were created in Microsoft Excel (Microsoft, Redmond, Washington, United States).

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4. Results

4.1 Home mechanical ventilation in Hungary

4.1.1 Survey response rate

Overall, 117 potential sites were contacted to participate in the survey. Initial response rate was 33.3% (39 sites). Telephone recontact of the sites after the initial study period showed that 91% (71) of the initially non-responder sites had no relevant information to share, while 9% (7 sites) missed the initial deadline or did not wish to participate in the survey. 47.2% (17) of sites that responded reported to actively oversee home mechanical patients, while 25% (9) provide care if needed, 13.9% (5) direct patients to other sites with more established practice. 11.1% (4) sites reported no need for HMV in any of their practice, while 11.1% (4) reported a need with inability to provide HMV. Out of the sites that responded, 72.2% (26) was aware of a HMV center, while 28.8% (10) was not. A HMV protocol was used in only 19.4% (7) sites.

4.1.2 Prevalence

Overall, the 17 sites reported 384 patients receiving home mechanical ventilation, corresponding to an overall prevalence of 3.9/100,000 for home mechanical ventilation in Hungary (see Table 2 and 3). When looking at number of patients treated by sites, we found that 93.2% of patients were treated by four sites that had a patient number of >50. When comparing sites with substantial case number (>50 patients) to sites with limited case number (<50 patients), we found that sites with a substantial case number had a significantly higher patient number (87.5 (58.5;122.5) vs. 1 (1;2.75); p=0.002) and were more likely to be pulmonology affiliated (75% versus 0%, p=0.003). Sites with a limited patient number were more likely to be intensive care unit affiliated (84.6% vs. 25%, p=0.003). Comprehensive results of the survey are provided in Table 2.

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Table 2. Results of the national survey. *NU - non-university, U - University, Nat - national institution, Ped - pediatric department, ICU - intensive care unit, Pulm - pulmonary department, NA - not available, Y - yes, N - no.*

site number	type	affiliation	number of patients	number of invasive patients	number of noninvasive patients	daily ventilation need			diagnosis					start of home mechanical ventilation					readmission needed				reimbursement type			follow-up type		secretion management	
						<8h	8-16h	>16h	chest wall	neuromuscular	central hypopnea syndrome	pulmonary	other	<6 months	6-12 months	1-5 years	5-10 years	>10 years	1-6 months	7-12 months	>12months	never admitted	daily government reimbursement	initial government aid	other	home visit	ambulatory visit	endotracheal suctioning	cough assist device
1	NU	Ped	7	6	1	0	2	4	0	5	2	0	0	0	2	5	0	0	2	2	3	0	7	0	0	Y	N	Y	N
2	NU	ICU	1	1	0	0	0	1	0	1	0	0	0	0	0	1	0	0	1	0	0	0	1	0	0	Y	N	Y	N
3	NU	ICU	1	1	0	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0	1	0	0	1	0	Y	N	Y	N
4	NU	ICU	1	1	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	Y	Y	Y	N
5	NU	ICU	1	0	1	0	1	0	0	1	0	0	0	0	0	0	1	0	0	0	1	0	1	0	0	Y	N	Y	N
6	NU	Ped	1	1	0	0	0	1	0	1	0	0	0	0	0	1	0	0	0	1	0	0	1	0	0	Y	N	Y	N
7	NU	ICU	2	2	0	0	0	2	0	2	0	0	0	0	0	1	1	0	NA	NA	NA	NA	2	0	0	Y	N	Y	N
8	NU	ICU	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NA	NA	NA	NA
9	NU	ICU	1	1	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	1	0	1	0	0	Y	N	Y	N
10	NU	ICU	1	1	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	1	0	Y	N	Y	N
11	Nat	ICU	6	6	0	0	0	6	0	0	0	0	0	0	0	0	2	4	NA	NA	NA	NA	6	0	0	Y	N	Y	N
12	NU	ICU	1	1	0	0	0	1	0	1	0	0	0	0	0	0	1	0	1	0	0	0	1	0	0	Y	N	Y	N
13	U	ICU	52	16	36	24	16	12	12	17	15	8	0	4	13	24	8	3	1	1	2	48	52	0	0	Y	Y	Y	Y
14	U	ICU	3	3	0	0	0	3	1	2	0	0	0	0	0	3	0	0	1	2	0	0	3	0	0	Y	N	Y	Y
15	U	Pulm	131	0	131	131	0	0	0	0	90	41	0	7	11	46	59	8	NA	NA	NA	NA	0	131	0	N	Y	N	Y
16	NU	Pulm	97	0	97	84	12	1	14	2	76	10	0	0	6	86	35	1	15	0	0	82	NA	NA	NA	N	Y	N	Y
17	Nat	Pulm	78	0	78	45	26	7	0	7	45	19	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	78	0	N	Y	N	NA
total			384	40	344	284	59	40	28	42	228	78	7	12	32	169	108	16	21	7	8	131	76	211	0				

Table 3. Distribution of responding sites involved in home mechanical ventilation (HMV)

	Intensive care unit affiliated	**Pulmonology affiliated**	**Pediatric affiliated**
Number of responding sites involved in HMV	12	3	2
Number of patients treated	70	306	8

4.1.3 Mode of ventilation

Out of the 384 patients, 10.4% (40) received invasive, while 89.6% (344) received noninvasive ventilation. Noninvasive ventilation was used more commonly by sites with substantial case number (95.6% vs. 7.7%, p=0.001), whereas invasive ventilation was the predominant mode in sites with limited case numbers (92.3% vs. 4.5%, p<0.001) (see Figure 4).

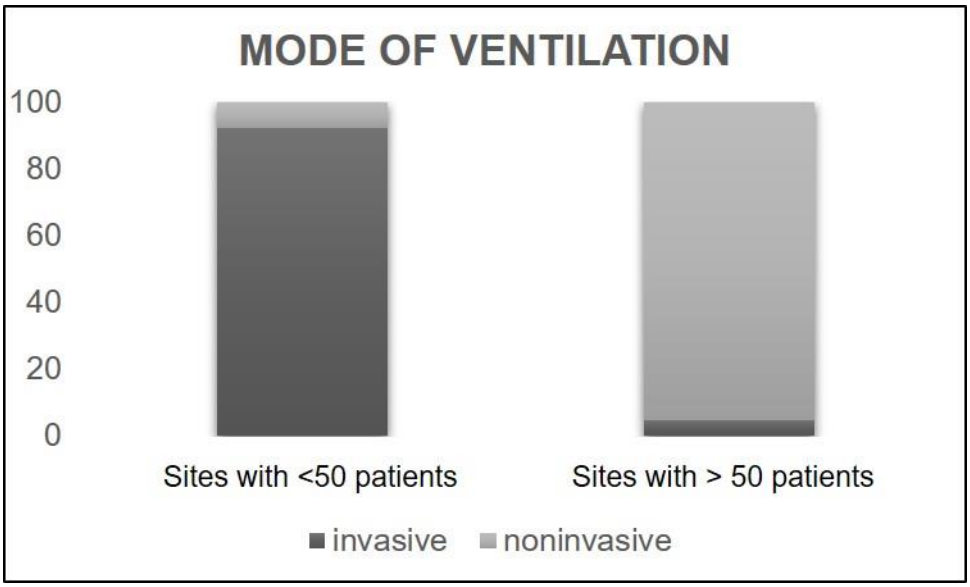

Figure 4. Distribution of mode of ventilation: *Y axis shows percentage of patients. First column shows data from sites that care for less than 50 patients, the second column shows data from units that care for more than 50 patients. Dark shading shows patients ventilated invasively, lighter shading shows patients ventilated noninvasively.*

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4.1.4 Indication for home mechanical ventilation

Possible indications for home mechanical ventilation need were identified as the following: central hypopnea syndromes (central alveolar hypoventilation syndrome, obesity hypoventilation syndrome); pulmonary diseases (chronic obstructive pulmonary disease, fibrosis); neuromuscular diseases (amyotrophic lateral sclerosis, systemic muscular atrophies, myasthenia, trauma related paralysis) and chest wall disorders (scoliosis, etc.). Prevalence for different indications is shown on Figure 5.

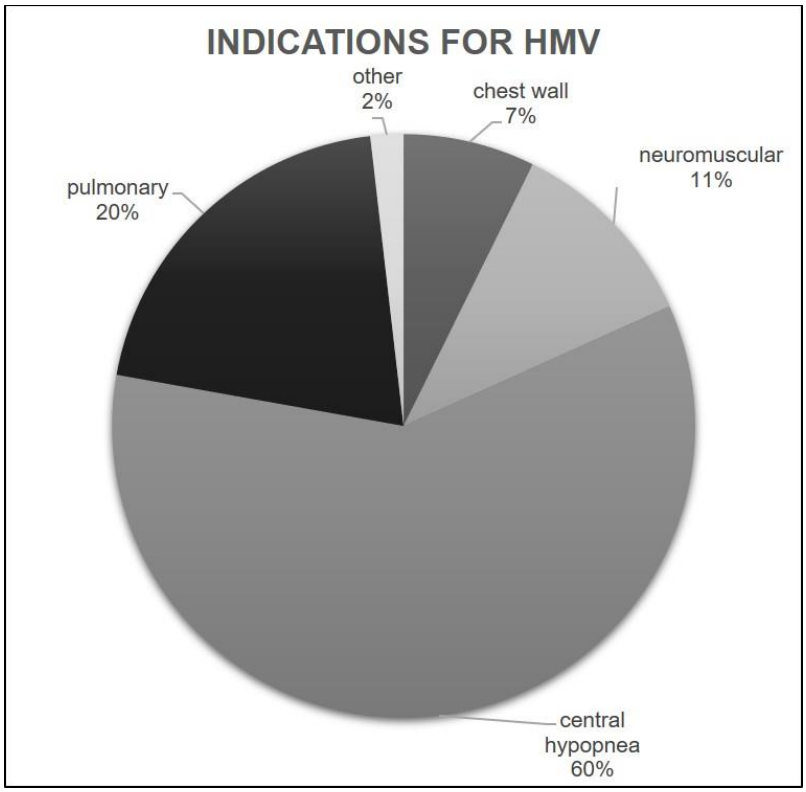

Figure 5. Pie chart of prevalence of indications for home mechanical ventilation

When observing the indications for sites with a substantial versus limited case number, we found that most common diagnosis was central hypopnea in sites with substantial case numbers (62.3%) whereas neurological disease was the most frequent indication in sites with a limited case number (80%) (p<0.001).

4.1.5 Characteristics of home mechanical ventilation

Daily ventilation need was less than 8 hours in 74.2%, between 8 and 16 hours in 15.4% and more than 16 hours in 10.4% of patients reported to be receiving HMV. We found that increased hours of ventilation (>16 hours/day) was more common in patients treated by a site with limited case numbers (80% vs. 5.6%, $p<0.001$).

Duration of home mechanical ventilation was less than 6 months in 3.6%, 6-12 months in 9.5%, 1-5 years in 50.1%, 5-10 years in 32% and more than 10 years in 4,7% of patients reported. Distribution of duration of ventilation did not differ significantly in sites with larger versus sites with limited case numbers ($p=0.111$), although there was a trend that showed a longer duration with patients treated in sites with limited experience.

4.1.6 Characteristics of care provided

Follow-up of patients treated with home mechanical ventilation was provided during home visits in 13.4% of cases reported, while ambulatory follow-up was provided in 86.6% of cases. Home visits were more frequent at sites with limited case number compared to sites with a substantial case numbers (96.2% vs. 7.2%, $p<0.001$).

Readmission rates were low overall in reported cases, with readmission needed more than twice a year in 12.6%, once a year in 4.2% and less rarely than once a year in 4.8% of reported cases. 78.4% of reported cases had no reported readmissions. When comparing sites with limited and substantial case numbers, readmission was more frequent in the former (82.9% vs. 15%, $p<0.001$).

88.2% of sites treating home mechanical ventilation patients reported using additional devices to aid secretion elimination. Since most sites were ones treating a limited number of invasively ventilated patients, the most common reported secretion elimination method was endotracheal suction provided by 76.5% of sites, while a cough assisting device or both methods were reported to be provided by less sites (11.8% and 11.8% respectively). Notedly, cough assisting devices were only used by sites with substantial experience.

Reimbursement for HMV was either daily government reimbursement (26.4%) or initial government aid (73.5%) provided in most reported cases. Daily government

reimbursement was used more frequently by sites with limited case number versus those with substantial case number (92.3% vs. 32.3%, $p<0.001$).

4.2 Validation of the Hungarian version of the Severe Respiratory Questionnaire

4.2.1 Backtranslated questionnaire

The backtranslated first version of the original questionnaire was rated as “totally equivalent” for 9 items and “similar” for 36 items by the original author group. 4 items rated “doubtful” in the backtranslated version were subsequently discussed and revised if needed by the expert panel. The changes effected 1 of the items, the doubtfulness of the other 3 items were thought to be a consequence of backtranslation issues and were unchanged as per the decision of the expert panel. The pilot study of the second version resulted in no apparent difficulties of understanding by test subjects and was accepted as the third version (see Figure 6).

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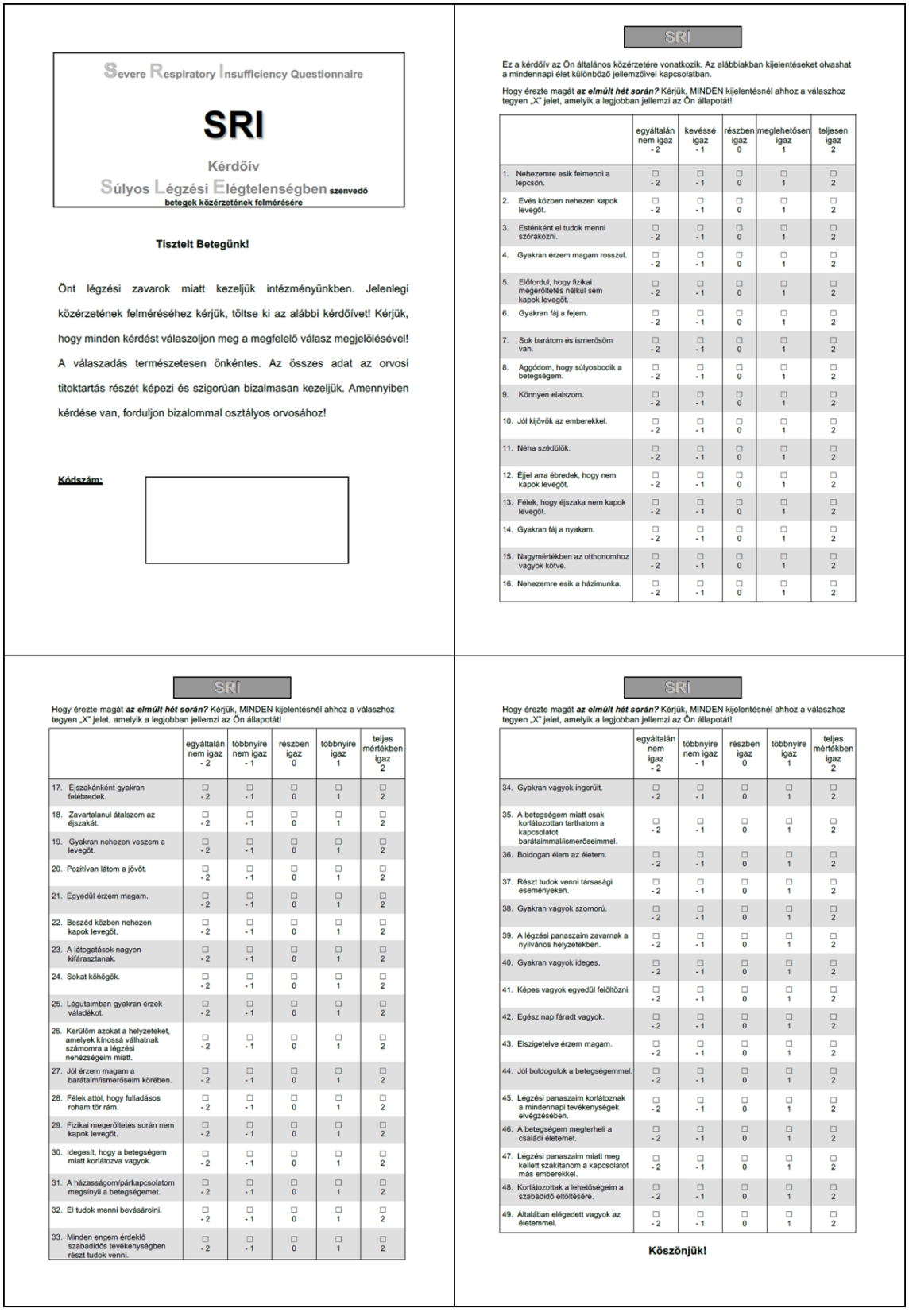

Severe Respiratory Insufficiency Questionnaire

SRI

Kérdőív

Súlyos Légzési Elégtelenségben szenvedő betegek közérzetének felmérésére

Tisztelt Betegünk!

Önt légzési zavarok miatt kezeljük intézményünkben. Jelenlegi közérzetének felméréséhez kérjük, töltse ki az alábbi kérdőívet! Kérjük, hogy minden kérdést válaszoljon meg a megfelelő válasz megjelölésével! A válaszadás természetesen önkéntes. Az összes adat az orvosi titoktartás részét képezi és szigorúan bizalmasan kezeljük. Amennyiben kérdése van, forduljon bizalommal osztályos orvosához!

Kódszám:

SRI

Ez a kérdőív az Ön általános közérzetére vonatkozik. Az alábbiakban kijelentéseket olvashat a mindennapi élet különböző jellemzőivel kapcsolatban.

Hogy érezte magát ***az elmúlt hét során?*** Kérjük, MINDEN kijelentésnél ahhoz a válaszhoz tegyen „X" jelet, amelyik a legjobban jellemzi az Ön állapotát!

	egyáltalán nem igaz - 2	kevéssé igaz - 1	részben igaz 0	meglehetősen igaz 1	teljesen igaz 2
1. Nehezemre esik felmenni a lépcsőn.	□ - 2	□ - 1	□ 0	□ 1	□ 2
2. Evés közben nehezen kapok levegőt.	□ - 2	□ - 1	□ 0	□ 1	□ 2
3. Esténként el tudok menni szórakozni.	□ - 2	□ - 1	□ 0	□ 1	□ 2
4. Gyakran érzem magam rosszul.	□ - 2	□ - 1	□ 0	□ 1	□ 2
5. Előfordul, hogy fizikai megerőltetés nélkül sem kapok levegőt.	□ - 2	□ - 1	□ 0	□ 1	□ 2
6. Gyakran fáj a fejem.	□ - 2	□ - 1	□ 0	□ 1	□ 2
7. Sok barátom és ismerősöm van.	□ - 2	□ - 1	□ 0	□ 1	□ 2
8. Aggódom, hogy súlyosbodik a betegségem.	□ - 2	□ - 1	□ 0	□ 1	□ 2
9. Könnyen elalszom.	□ - 2	□ - 1	□ 0	□ 1	□ 2
10. Jól kijövök az emberekkel.	□ - 2	□ - 1	□ 0	□ 1	□ 2
11. Néha szédülök.	□ - 2	□ - 1	□ 0	□ 1	□ 2
12. Éjjel arra ébredek, hogy nem kapok levegőt.	□ - 2	□ - 1	□ 0	□ 1	□ 2
13. Félek, hogy éjszaka nem kapok levegőt.	□ - 2	□ - 1	□ 0	□ 1	□ 2
14. Gyakran fáj a nyakam.	□ - 2	□ - 1	□ 0	□ 1	□ 2
15. Nagymértékben az otthonomhoz vagyok kötve.	□ - 2	□ - 1	□ 0	□ 1	□ 2
16. Nehezemre esik a házimunka.	□ - 2	□ - 1	□ 0	□ 1	□ 2

SRI

Hogy érezte magát ***az elmúlt hét során?*** Kérjük, MINDEN kijelentésnél ahhoz a válaszhoz tegyen „X" jelet, amelyik a legjobban jellemzi az Ön állapotát!

	egyáltalán nem igaz - 2	többnyire nem igaz - 1	részben igaz 0	többnyire igaz 1	teljes mértékben igaz 2
17. Éjszakánként gyakran felébredek.	□ - 2	□ - 1	□ 0	□ 1	□ 2
18. Zavartalanul átalszom az éjszakát.	□ - 2	□ - 1	□ 0	□ 1	□ 2
19. Gyakran nehezen veszem a levegőt.	□ - 2	□ - 1	□ 0	□ 1	□ 2
20. Pozitívan látom a jövőt.	□ - 2	□ - 1	□ 0	□ 1	□ 2
21. Egyedül érzem magam.	□ - 2	□ - 1	□ 0	□ 1	□ 2
22. Beszéd közben nehezen kapok levegőt.	□ - 2	□ - 1	□ 0	□ 1	□ 2
23. A látogatások nagyon kifárasztanak.	□ - 2	□ - 1	□ 0	□ 1	□ 2
24. Sokat köhögök.	□ - 2	□ - 1	□ 0	□ 1	□ 2
25. Légutaimban gyakran érzek váladékot.	□ - 2	□ - 1	□ 0	□ 1	□ 2
26. Kerülöm azokat a helyzeteket, amelyek kínossá válhatnak számomra a légzési nehézségeim miatt.	□ - 2	□ - 1	□ 0	□ 1	□ 2
27. Jól érzem magam a barátaim/ismerőseim körében.	□ - 2	□ - 1	□ 0	□ 1	□ 2
28. Félek attól, hogy fulladásos roham tör rám.	□ - 2	□ - 1	□ 0	□ 1	□ 2
29. Fizikai megerőltetés során nem kapok levegőt.	□ - 2	□ - 1	□ 0	□ 1	□ 2
30. Idegesít, hogy a betegségem miatt korlátozva vagyok.	□ - 2	□ - 1	□ 0	□ 1	□ 2
31. A házasságom/párkapcsolatom megsínylí a betegségemet.	□ - 2	□ - 1	□ 0	□ 1	□ 2
32. El tudok menni bevásárolni.	□ - 2	□ - 1	□ 0	□ 1	□ 2
33. Minden engem érdeklő szabadidős tevékenységben részt tudok venni.	□ - 2	□ - 1	□ 0	□ 1	□ 2

SRI

Hogy érezte magát ***az elmúlt hét során?*** Kérjük, MINDEN kijelentésnél ahhoz a válaszhoz tegyen „X" jelet, amelyik a legjobban jellemzi az Ön állapotát!

	egyáltalán nem igaz - 2	többnyire nem igaz - 1	részben igaz 0	többnyire igaz 1	teljes mértékben igaz 2
34. Gyakran vagyok ingerült.	□ - 2	□ - 1	□ 0	□ 1	□ 2
35. A betegségem miatt csak korlátozottan tarthatom a kapcsolatot barátaimmal/ismerőseimmel.	□ - 2	□ - 1	□ 0	□ 1	□ 2
36. Boldogan élem az életem.	□ - 2	□ - 1	□ 0	□ 1	□ 2
37. Részt tudok venni társasági eseményeken.	□ - 2	□ - 1	□ 0	□ 1	□ 2
38. Gyakran vagyok szomorú.	□ - 2	□ - 1	□ 0	□ 1	□ 2
39. A légzési panaszaim zavarnak a nyilvános helyzetekben.	□ - 2	□ - 1	□ 0	□ 1	□ 2
40. Gyakran vagyok ideges.	□ - 2	□ - 1	□ 0	□ 1	□ 2
41. Képes vagyok egyedül felöltözni.	□ - 2	□ - 1	□ 0	□ 1	□ 2
42. Egész nap fáradt vagyok.	□ - 2	□ - 1	□ 0	□ 1	□ 2
43. Elszigetelve érzem magam.	□ - 2	□ - 1	□ 0	□ 1	□ 2
44. Jól boldogulok a betegségemmel.	□ - 2	□ - 1	□ 0	□ 1	□ 2
45. Légzési panaszaim korlátoznak a mindennapi tevékenységek elvégzésében.	□ - 2	□ - 1	□ 0	□ 1	□ 2
46. A betegségem megterheli a családi életemet.	□ - 2	□ - 1	□ 0	□ 1	□ 2
47. Légzési panaszaim miatt meg kellett szakítanom a kapcsolatot más emberekkel.	□ - 2	□ - 1	□ 0	□ 1	□ 2
48. Korlátozottak a lehetőségeim a szabadidő eltöltésére.	□ - 2	□ - 1	□ 0	□ 1	□ 2
49. Általában elégedett vagyok az életemmel.	□ - 2	□ - 1	□ 0	□ 1	□ 2

Köszönjük!

Figure 6. The Hungarian SRI Questionnaire

4.2.2 Descriptive statistics

The total number of patients recruited for the study was 104, all patients completed the study. Mean age was 54.5 (±16.2) years, 77 (74.0%) patients were male. Highest level of education was primary school for 22 (21.1%), secondary school for 53 (51.0%), university for 29 (27.9%) patients. Current state of employment was employed for 27 (26.0%), never worked for 9 (8.6%), disabled/unable to work for 31 (29.8%) and pensioner for 37 (35.6%) patients. None of the patients were smoking at the time of enrollment, 47 (45.2%) never smoked, while 57 (54.8%) were prior smokers. Cumulative smoking was found to be 14.7 (±23.1) packyears/person. Cause for chronic respiratory failure and mechanical ventilation need was found to be chronic obstructive pulmonary disease (COPD) in 20 (19.2%), restrictive chest wall disease (RCWD) in 6 (5.8%), obstructive sleep apnea or obesity hypoventilation syndrome (OSA/OHS) in 45 (43.3%) and neuromuscular disease (NMD) in 31 (29.8%) patients, while two patients (1.9%) suffered from other causes (pulmonary fibrosis and scleroderma). The most frequently used interface was a full-face mask in 59 (56.7%) patients, while 23 (22.1%) used a total face mask, 8 (7.7%) used a nasal mask and 14 (13.5%) were ventilated through a tracheostomy. Patients received HMV for a mean of 9 (±4.8) hours per day, and they had been using HMV for 26.2 (±32.7) months. O_2 supplementation was used in 46 (44.2%) patients, overall oxygen use was 1.2 (±1.8) L/min/patient.

The clinical characteristics of the patient sample are summarized in Table 4.

Table 4. Clinical characteristics of the study population: *COPD – chronic obstructive pulmonary disease, RCWD – restrictive chest wall disease, OHS/OSA – obesity hypoventilation syndrome/obstructive sleep apnea, NMD – neuromuscular disease, BMI – body mass index, HMV – home mechanical ventilation, FVC – forced vital capacity, FEV1 – forced expiratory volume within 1 second, O_2 – oxygen, PEF – peak expiratory flow, p_aCO_2 – partial arterial carbon dioxide pressure, p_aO_2 – partial arterial oxygen pressure, IPAP – inspiratory positive airway pressure, EPAP – expiratory positive airway pressure, PTB – patient triggered breath, VTE – expiratory tidal volume, Ti/Tt – inspiratory – total time ratio*

	COPD	**RCWD**	**OHS/OSA**	**NMD**	**Total**
n (%)	20 (19.2%)	6 (5.8%)	45 (43.3%)	31 (29.8%)	104 (100%)
Age (yr)	66.0 (±6.8)	36.5 (±13.0)	57.3 (±13.3)	46.7 (±18.8)	54.5 (±16.2)
Male (%)	15 (75%)	1 (8.3%)	35 (77.8%)	7 (88.4%)	77 (74.0%)
BMI (kg/m^2)	33.9 (±7.4)	19.4 (±3.4)	41.2 (±10.8)	24.1 (±4.4)	33.1 (±11.6)
Smoking (packyear)	26.7 (±29.6)	7.5 (±17.9)	16.8 (±22.3)	6.3 (±16.9)	14.7 (±23.1)
HMV (hr/d)	8.0 (±2.0)	10.7 (±6.4)	6.4 (±1.7)	12.4 (±5.7)	9.0 (±4.8)
HMV (mo)	28.1 (±29.6)	27.5 (±39.6)	30.6 (±37.2)	19.7 (±26.8)	26.2 (±32.7)
O_2 need	14 (70%)	4 (6%)	19 (42.2%)	7 (22.6%)	46 (44.2%)
FVC%	71.2 (±23.6)	23.8 (±12.5)	80.9 (±19.6)	36.1 (±19.5)	68.3 (±28.9)
FEV_1%	44.7 (23.6)	23.8 (±12.5)	72.5 (±20.6)	36.4 (±22.1)	53.3 (±27.5)
FEV_1/FVC%	63.0 (±20.6)	86.3 (±17.8)	92.2 (±13.7)	100.5 (±17.8)	88.0 (±21.4)
PEF%	44.7 (±23.7)	28.8 (±16.3)	71.2 (±24.4)	31.6 (±21.0)	51.6 (±28.9)
pH	7.40 (±0.05)	7.38 (±0.03)	7.41 (±0.04)	7.40 (±0.04)	7.40 (±0.04)
p_aCO_2 (mmHg)	44.8 (±10.4)	43.8 (±9.4)	42.3 (±9.6)	41.4 (±8.8)	42.6 (±9.5)
p_aO_2 (mmHg)	70.2 (±15.6)	84.0 (±10.3)	73.3 (±10.4)	87.0 (±10.6)	77.5 (±13.3)
IPAP (cmH_2O)	17.9 (±3.3)	22.0 (±3.2)	19.3 (±4.7)	18.5 (±3.9)	18.9 (±4.1)
EPAP (cmH_2O)	7.8 (±2.9)	6.7 (±2.9)	9.6 (±3.1)	7.6 (±3.4)	8.4 (±3.3)
PTB (%)	62.7 (±34.2)	25.5 (±25.4)	65.5 (±32.0)	45.9 (±28.3)	57.0 (±32.5)
VTE (mL)	669.1 (±155.9)	367.9 (±62.5)	648.3 (±245.2)	483.6 (±94.4)	585.5 (±205.1)
T_i/T_t	31.7 (±5.6)	32.0 (±7.4)	36.4 (±5.4)	32.1 (±5.5)	33.8 (±5.9)

Quality of life scores were not homogenously distributed within patient groups (see Figure 7).

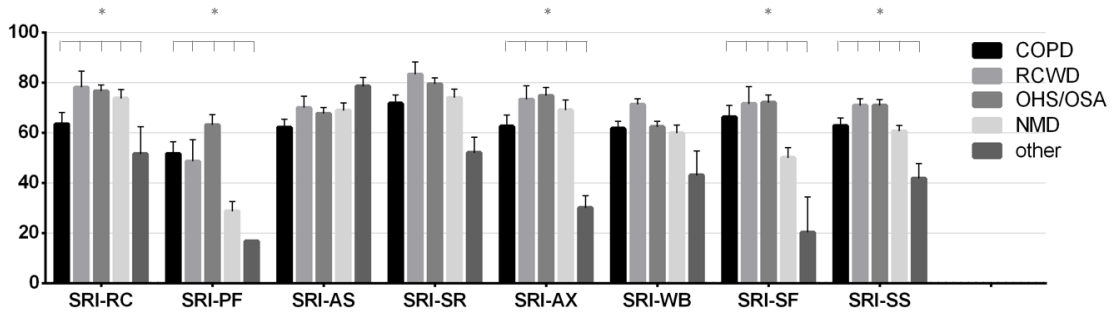

Figure 7. Box plot of SRI subscales in different diagnostic groups: *Boxes represent means, whiskers represent standard error. Significant differences are marked with asterisk. COPD – chronic obstructive pulmonary disease, RCWD – restrictive chest wall disease, OHS/OSA – obesity hypoventilation syndrome/obstructive sleep apnea, NMD – neuromuscular disease, SRI-RC - respiratory complaints, SRI-PF - physical functioning, SRI-AS - attendant symptoms and sleep, SRI-SR - social relationships, SRI-AX - anxiety, SRI-WB - psychosocial well-being, SRI-SF - social functioning, SRI-SS - summary scale*

SRI-RC, -PF, -AX, -SF and -SS scales showed notable differences in patient groups (p=0.048, p<0.001, p=0.022, p<0.001 and p=0.003 respectively).

SRI-PF was diminished in NMD patients compared to COPD and OHS/OSA patients (28.7±21.9 compared to 51.6±21.6 and 63.1±27.4; p=0.004 and p<0.001 respectively). SRI-SF was less in RCDW and NMD patients than in OHS/OSA patients (48.6±21.0 and 50.0±22.7 compared to 72.0±20.4, p=0.039 and p<0.001 respectively). SRI-SS was less in NMD patients compared to OSA/OHS patients (60.6±13.2 compared to 70.8±15.7, p=0.033).

When comparing patients ventilated through noninvasive and invasive interface, we found that SRI-RC, -PF, SF and -SS subscale scores were higher in the noninvasive group (SRI-RC: 74.3 (±18.5) vs. 63.4 (±22.2), p =0.049; SRI-PF: 52.5 (±27.7) vs. 25.7 (±20.5), p=0.001; SRI-SF: 65.3 (±23.0) vs. 50.2 (±23.6), p=0.025, SRI-SS: 66.8 (±15.1) vs. 58.2 (±13.6), p=0.046), while other subscales showed no significant difference (see Figure 8).

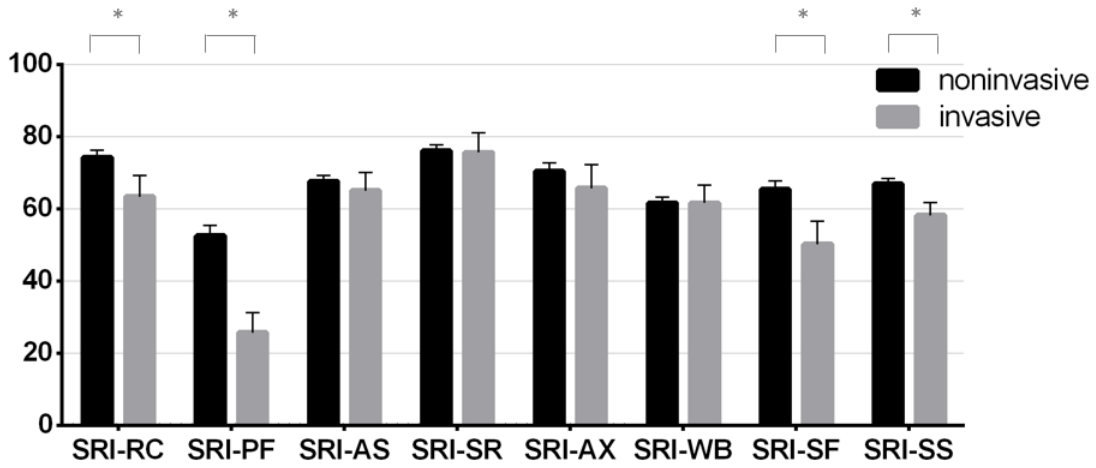

Figure 8. Boxplot of subscales in patients according to interface: *Boxes represent means, whiskers represent standard error. Significant differences are marked with asterisk. SRI-RC - respiratory complaints, SRI-PF - physical functioning, SRI-AS - attendant symptoms and sleep, SRI-SR - social relationships, SRI-AX - anxiety, SRI-WB - psychosocial well-being, SRI-SF - social functioning, SRI-SS - summary scale*

4.2.3 Viability

The time to complete the SRI was the same as the time for the SF-36: 8.6 (±3.1) minutes vs. 8.5 (±3.0); p=0.587. 72 (69.2%) questionnaires were self-administered. Self administered questionnaires were completed faster [8.1 (±2.8) vs. 9.7 (±3.6), p=0.019), diseases type and education level significantly influenced the time spent on the questionnaire (p=0.025 and p=0.002 respectively), but age of the patient did not correlate with the time to complete the SRIQ (correlation factor: -0.006, p=0.954). The reasons given for not self-administering the questionnaire were physically unable for 24 (23.1%) or eyesight problems for 11 (10.6%) patients. Overall missing items were 0.2 (±0.6) out of the 49 items for the SRI and 0.2 (±0.8) out of the 36 items for the SF-36. All questions were answered by 96-100% of patients. The question skipped most frequently for the SRIQ was question 31 (regarding the effect of the disease on relationships) by 4 (3.8%) patients, because they were not in a relationship.

4.2.4 Validity

Exploratory factor analysis explained 73.8% of the variance of the questionnaire, but it resulted in 13 scales, which is similar to results published by the Spanish validation of the SRI questionnaire (see Figure 9).

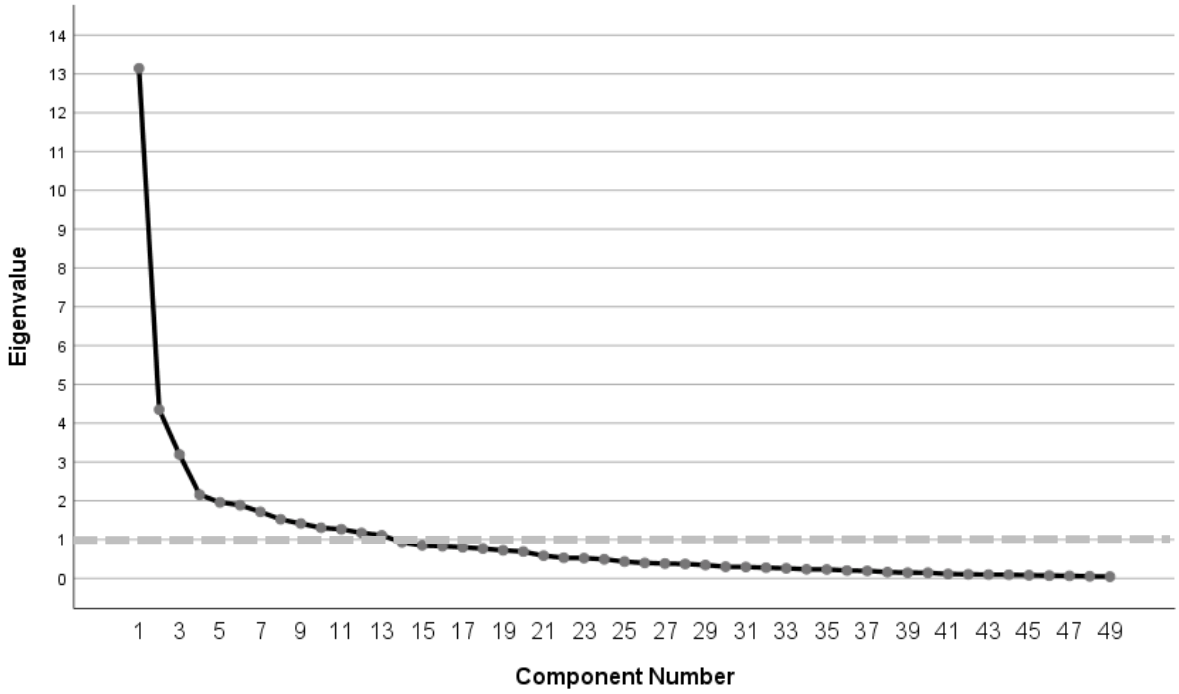

Figure 9: Scree plot for the exploratory factor analysis: *Eigenvalue of 1 is marked by dashed line verifying 13 components on the graph.*

Conformatory factor analysis for the 7 subscales showed one component for one, two components for five and three components for one of the subscales. The PF scale was the most retained, its factor analysis showing only one component. All other scales tended to be divided into two further scales, albeit showed significant correlations with each other. The RC's first scale included items related to shortness of breath while the second to the ability to cough and expectorate (correlation factor: 0.466 , p<0.001). The AS's two scales focused on general secondary symptoms and the ability to sleep through the night respectively (correlation factor: 0.257 p=0.008). The SR's first scale related to items

concerning relationships to others, while the second focused on feelings of loneliness (correlation factor: 0.210 , p=0.032). The AX was also divided into two scales with some questions focusing on disease related anxieties and others related to social anxiety (correlation factor: 0.419, p<0.001). The SF's first scale focused on activities and leisure while the other one on social interactions (correlation factor: 0.832, p<0.001). The WB was the most divided scale, with three components, the largest one with items evaluating depression while the other two related to feelings of frustration with the disease. All these also showed significant correlations (0.328 p=0.001; 0.299 p=0.002; 0.222 p=0.024).
The correlation matrix for the SRI and SF-36 questionnaires is presented in Table 5.

Table 5. SRI and SF-36 correlation matrix: *Values with p<0.05 are marked with *. Values with p<0.01 are marked with **. Values with p<0.001 are marked with ***. Strong correlations are marked with bold text. SRI-RC - respiratory complaints, SRI-PF - physical functioning, SRI-AS - attendant symptoms and sleep, SRI-SR - social relationships, SRI-AX - anxiety, SRI-WB - psychosocial well-being, SRI-SF - social functioning, SRI-SS - summary scale, SF-36-PF - physical functioning, SF36-PH - role limitations due to physical health, SF36-EP - role limitations due to emotional problems, SF36-E/F - energy/fatigue, SF36-EWB - emotional well-being, SF36-SF - social functioning, SF36-P – pain, SF36-GH - general health.*

	SF36-PF	**SF36-PH**	**SF36-EP**	**SF36-E/F**	**SF36-EWB**	**SF36-SF**	**SF36-P**	**SF36-GH**
SRI-RC	0.384***	0.499***	0.368***	0.523***	0.341***	0.397***	0.482***	0.591***
SRI-PF	**0.842*** **	0.437***	0.304*	0.432***	0.317*	0.409***	0.277**	0.343***
SRI-AS	0.290*	0.425***	0.385***	0.463***	0.432***	0.355***	0.557***	0.474***
SRI-SR	0.401***	0.390***	0.456***	0.552***	0.596***	0.537***	0.369***	0.378***
SRI-AX	0.418***	0.458***	0.340***	0.398***	0.342***	0.409***	0.330*	0.526***
SRI-WB	0.315*	0.353***	0.363***	0.611***	**0.721*** **	0.591***	0.420***	0.514***
SRI-SF	**0.732*** **	0.485***	0.428***	0.561***	0.473***	0.593***	0.385***	0.535***
SRI-SS	**0.699*** **	0.590***	0.499***	0.667***	0.590***	0.626***	0.522***	0.660***

The best correlations of the two questionnaires were achieved between both PF scales (R: 0.842 p<0.001). Other strong correlations were found between the SRI-SF and SF36-PF (0.732, p<0.001), the SRI-SS and SF36-PF (0.699, p<0.001) and the SRI-WB and SF36-

EBW scales (0.721, $p<0.001$). Moderately strong correlations were found between the SRI-WB and SF36-E/F (0.611, $p<0.001$), the SRI-SS and SF36-E/F (0.667, $p<0.001$), the SRI-SS and SF36-SF (0.626), $p<0.001$) and SRI-SS and SF36-GH scales (0.660, $p<0.001$).

4.2.5 Reliability

The Cronbach alpha coefficient was 0.928 for the summary scale of the Hungarian SRI Questionnaire. The Cronbach alpha coefficients, and correlation of each item with its own scale correcting for overlap and with the rest of the scales are listed in Table 6.

Table 6. Cronbach's alpha reliability: *ICQ- item correlation coefficient with the rest of the questionnaire; ICS - item correlation coefficient with its own scale SRI-RC - respiratory complaints, SRI-PF - physical functioning, SRI-AS - attendant symptoms and sleep, SRI-SR - social relationships, SRI-AX - anxiety, SRI-WB - psychosocial well-being, SRI-SF - social functioning, SRI-SS - summary scale*

Scale	Cronbach alpha	ICQ (min-max)	ICS (min-max)
SRI-RC	0.810	-0.053-0.621	0.758-0.866
SRI-PF	0.836	-0.382-0.704	0.781-0.880
SRI-AS	0.635	-0.330-0.584	0.516-0.734
SRI-SR	0.612	-0.350-0.620	0.484-0.717
SRI-AX	0.726	-0.451-0.569	0.633-0.802
SRI-WB	0.630	-0.492-0.591	0.513-0.728
SRI-SF	0.849	-0.452-0.704	0.800-0.890

Correlations of an item to its own scale, correcting for overlap (item correlation coefficient with its own scale [ICS]), were good compared with the correlations with the rest of the scales in the questionnaire (item correlation coefficient with the rest of the questionnaire [ICQ]), reaching higher correlations in ICS than in ICQ.

4.2.6 Reproducibility

Correlations between the results of the two SRI Questionnaires submitted at different time points are listed in Table 7.

Table 7. Correlation of repeated punctuation of the SRI Questionnaire: *SRI-RC - respiratory complaints, SRI-PF - physical functioning, SRI-AS - attendant symptoms and sleep, SRI-SR - social relationships, SRI-AX - anxiety, SRI-WB - psychosocial well-being, SRI-SF - social functioning, SRI-SS - summary scale*

Scale	**Correlation factor**	**p-value**
SRI-RC	0.778	$p<0.001$
SRI-PF	0.859	$p<0.001$
SRI-AS	0.820	$p<0.001$
SRI-SR	0.676	$p<0.001$
SRI-AX	0.774	$p<0.001$
SRI-WB	0.736	$p<0.001$
SRI-SF	0.823	$p<0.001$
SRI-SS	0.877	$p<0.001$

Reproducibility was high for most scales, resulting in a high overall correlation for the summary score (0.877, $p<0.001$).

4.3 Monitoring the efficacy of home mechanical ventilation through quality of life change

4.3.1 Patients

Out of the 75 patients enrolled, 2 were excluded because they were unable to complete HRQL forms due to cognitive impairment. One patient was deceased before study completion, and 6 patients were excluded because of missing data. A total of 66 patients completed the study. Baseline characteristics of the patients are listed in Table 8.

Table 8: Baseline demographics and patient characteristics: *Data are presented as mean (SD) for continuous and as percentages (n) for categorical variables. Lung function parameters are presented as percentage of expected value. FVC- forced vital capacity, FEV1 - forced expiratory volume in 1 sec, PEF - peak expiratory flow.*

Characteristic	**mean (SD) or n (%)**
Total	66 (100%)
Sex	
Female	20 (30.3%)
Male	46 (69.7%)
Age (years)	51.5 (±18.1)
Initiation of ventilation	
Acute	40 (60.6%)
Elective	24 (39.4%)
Interface	
Invasive	14 (21.2%)
Noninvasive	52 (78.8%)
O_2 supplementation need	
No	33 (50%)
Yes	33 (50%)
O_2 flow (L/min)	1.8 (±2.8)
Daily ventilation need (hours)	12.6 (±6.5)
Ventilator settings	
Target volume (mL)	541 (±129)
Inspiratory pressure (cmH_2O)	22.2 (±4.8)
Expiratory pressure (cmH_2O)	8.3 (±3.6)
Frequency (/min)	15.9 (±3.6)
Initial diagnosis	
Chronic obstructive pulmonary disease	9 (13.6%)
Restrictive chest wall disease	5 (7.6%)
Obesity hypoventilation syndrome	20 (30.3%)
Non progressive neuromuscular disease	19 (28.8%)
Progressive neuromuscular disease	13 (19.7%)
Pulmonary function	
FVC%	47.2 (±22.2)
FEV1%	38.7 (±21.3)
FEV1/FVC%	86.0 (±21.8)
PEF%	36.5 (±20.6)
Arterial blood gas	
p_aO_2 (mmHg)	69.7 (±14.2)
p_aCO_2 (mmHg)	49.7 (±17.5)
HCO_3 (mmol/L)	28 (±5.2)

Indication for invasive ventilation was bulbar symptoms in 10 (71.4%) and more than 16 hours of ventilation in 4 (28.6%) of the 14 cases in the study. Invasively ventilated patients had higher daily ventilation need (17.9 (±6.5) vs. 11.1 (±5.8) hours, $p<0.001$), lower FVC% (31.5 (±23.3) vs 51.1 (±20.3), $p=0.004$) and PEF% (23.9 (±20.9) vs 39.6 (±19.4), $p=0.013$) values, but had corrected blood gas parameters (pO_2: 78.4 (±16.8) vs 67.4 (±12.7) mmHg, $p=0.016$; pCO_2: 36.2 (±7.3) vs 53.2 (±17.7) mmHg, $p=0.001$) compared to noninvasively ventilated patients at baseline.

Patients initiated after acute hospitalization had no significant differences in baseline ventilation need, supplementary oxygen need, lung function or blood gas values compared to those enrolled electively.

Compliance remained stable during the study duration (>80% daily required ventilation use in 100% of patients), with slightly diminishing daily ventilator use at six months (12.6 (±6.6) vs 11.2 (±6.6) hours, $p<0.001$). Blood gas parameters showed improvement from baseline values (pO_2: 69.7 (±14.2) vs 73.7 (±14.3) mmHg, $p=0.011$; pCO_2: 49.7 (±17.5) vs 45.1 (±11.4) mmHg, $p=0.005$; HCO_3: 28.0 (±5.2) vs 26.9 (±3.3) mmol/L, $p=0.038$), despite decrease in O_2 supplement use (1.8 (±2.8) vs 1.3 (±2.2) L/min, $p=0.011$).

4.3.2 Baseline HRQL

Overall SRI score was 57.7 (±14.4) and several subscales showed values under 60, corresponding to limited HRQL with SRI-RC, -PF, -AS, -WB and -SF being the aspects with the lowest values (Figure 10).

4.3.2.1 Differences in baseline HRQL scores by interface and diagnosis

As can be seen from Figure 10, none of the baseline SRI subscales differed in patients treated through invasive or noninvasive interface. Baseline SRI-AS and -AX subscales were significantly associated with initial diagnosis ($p=0.048$ and $p=0.018$ respectively). The SRI-AS scores were the lowest in OHS and ALS patients, while SRI-AX scores were the lowest in COPD and ALS patients (Figure 10).

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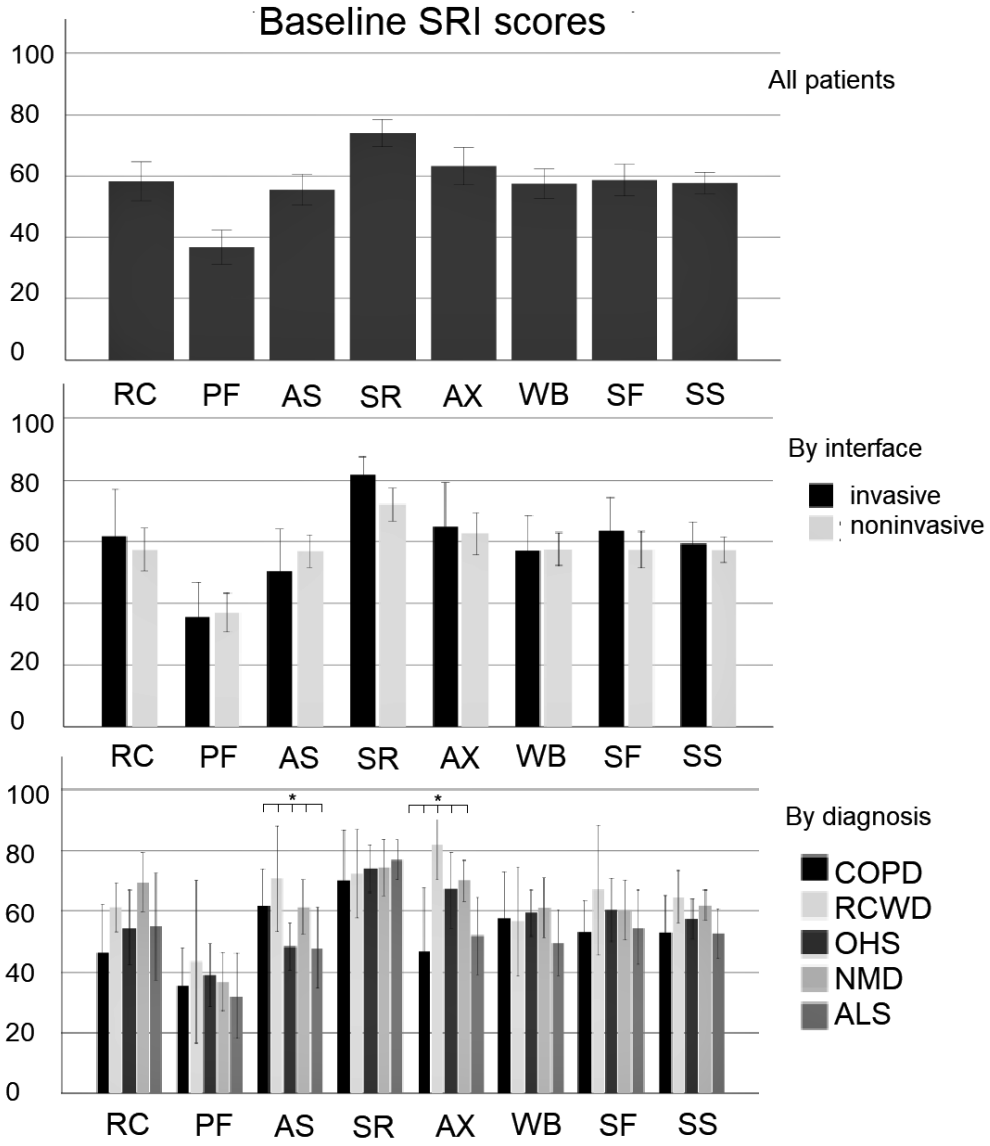

Figure 10. Bar graphs of baseline scores of the SRI subscales for the whole study group, by interface and by diagnosis: *Boxes represent means, error bars represent standard error. Significant differences are marked with asterisk. COPD - chronic obstructive pulmonary disease, RCWD - restrictive chest wall disease, OHS - obesity hypoventilation syndrome, NMD - neuromuscular disease, ALS - amyotrophic lateral sclerosis, RC - Respiratory complaints, PF - Physical functioning, AS - Attendant symptoms and sleep, SR - Social relationships, AX - Anxiety WB - Psychological well-being, SF - Social functioning, SS - Summary Score*

4.3.2.2 Differences in baseline HRQL scores by initiation type and O_2 need

In addition, there was no difference in baseline SRI scores in patients initiated acutely compared to those initiated electively, or in patients needing O_2 supplementation compared to patients who did not. Furthermore, SRI subscales showed no correlation with initial blood gas values, lung function test parameters, or hours of ventilation need (data not shown).

4.3.3 Overall HRQL change at 6-month follow-up

There was an 10.5% overall improvement of SRI summary scores from baseline to six-months [57.7 (±14.4) vs. 68.2 (±15.8), $p<0.001$]. All SRI subscales showed significant improvement during the first six months of home mechanical ventilation (Table 9.). HRQL change was clinically meaningful in RC, AS and AX subscales as well as the Summary Score (SS).

Table 9. HRQL subscale values before and 6 months after initiation of home mechanical ventilation: *RC - Respiratory complaints, PF - Physical functioning, AS - Attendant symptoms and sleep, SR - Social relationships, AX - Anxiety WB - Psychological well-being, SF - Social functioning, SS - Summary Score, HMV – home mechanical ventilation.*

	Quality of life before HMV	**Quality of life 6 months after initiation of HMV**	
RC	58.3 (±25.9)	78.7 (±17.3)	$p=0.015$
PF	36.7 (±22.5)	42.8 (±29.6)	$p<0.001$
AS	55.5 (±20.6)	74.8 (±14.0)	$p=0.006$
SR	74.1 (±18.1)	76.2 (±18.4)	$p<0.001$
AX	63.3 (±25.0)	77.7 (±22.6)	$p<0.001$
WB	57.5 (±19.7)	63.8 (±19.3)	$p<0.001$
SF	58.7 (±21.1)	63.6 (±24.6)	$p<0.001$
SS	57.7 (±14.4)	68.2 (±15.8)	$p<0.001$

4.3.4 Factors effecting HRQL change

4.3.4.1 HRQL change by interface and diagnosis

As can be seen from Figure 11, the choice of interface did not affect change in SRI subscales (p=0.660). Changes in SRI-RC, -PF, -SF and -SS subscales were significantly influenced by initial diagnosis (p=0.025, p<0.001, p=0.002 and p=0.025 respectively).
When further analyzing HRQL changes within diagnostic groups, we found that different diagnostic groups had different HRQL change patterns, which is visualized in the bubble chart depicting relative changes in different patient groups (Figure 12).
As can be seen from the figure, the patients benefiting most from HMV were COPD patients, while OHS patients improved across the most SRI subscales. SRI-RC subscale improved in all groups but ALS patients, and most prominently in COPD and OHS patients. SRI-PF and -AX scores improved only in COPD and OHS patients. SRI-SR subscales showed no change in any of the patient groups, except for OHS patients. SRI-WB and-SF improved only in OHS, and SRI-SF actually declined significantly in ALS patients. Overall SRI-SS scores improved in all patient groups except for ALS.

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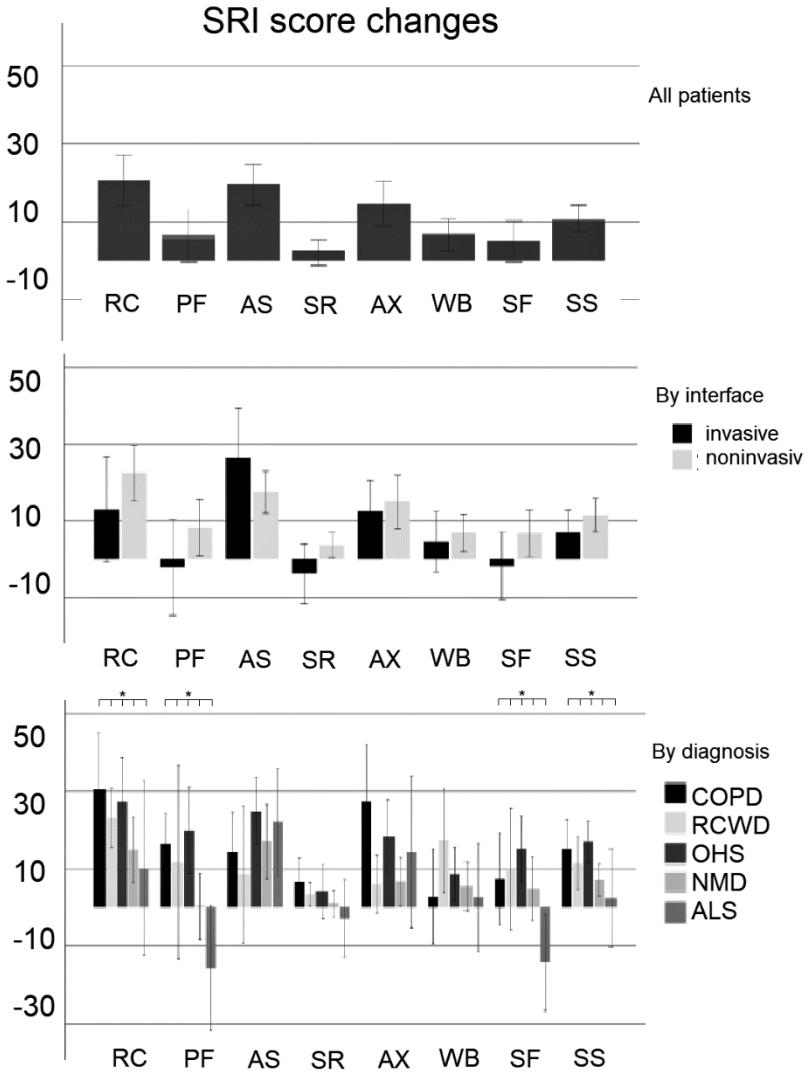

Figure 11. Bar graphs of changes in the scores of SRI subscales at the 6-month follow-up in the whole study group, by interface and by diagnostic groups: *Boxes represent means, error bars represent standard error. Significant differences are marked with asterisk. COPD - chronic obstructive pulmonary disease, RCWD - restrictive chest wall disease, OHS - obesity hypoventilation syndrome, NMD - neuromuscular disease, ALS - amyotrophic lateral sclerosis, RC - Respiratory complaints, PF - Physical functioning, AS - Attendant symptoms and sleep, SR - Social relationships, AX - Anxiety WB - Psychological well-being, SF - Social functioning, SS - Summary Score*

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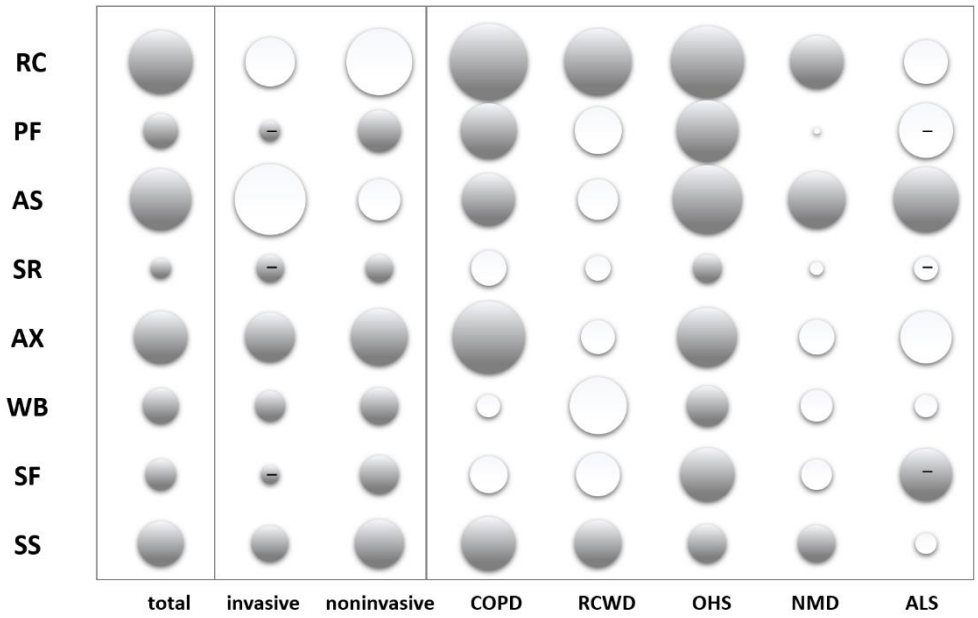

Figure 12. Bubble chart of SRI subscale changes for the whole study group and according to interface and diagnosis after 6 months of home mechanical ventilation: *Size corresponds to value of change from baseline. Significant changes are marked with gray shading. Negative changes are marked by negative sign pattern. COPD - chronic obstructive pulmonary disease, RCWD - restrictive chest wall disease, OHS - obesity hypoventilation syndrome, NMD - neuromuscular disease, ALS - amyotrophic lateral sclerosis, RC - Respiratory complaints, PF - Physical functioning, AS - Attendant symptoms and sleep, SR - Social relationships, AX - Anxiety WB - Psychological well-being, SF - Social functioning, SS - Summary Score*

4.3.4.2 HRQL change by initiation type, O_2 need, and baseline HRQL

Summary score improved significantly more in patients initiated acutely compared to patients initiated electively [12.3 (±16.8) vs. 7.4 (±9.4), p=0.029]. Change in SRI subscales showed no correlation with initial blood gas values, lung function test parameters or hours of ventilation need (data not shown). In patients using O_2 supplementation SRI-PF, -SF and -SS subscales improved significantly compared to patients that did not require O_2 supplementation [SRI-PF: 13.1 (±25.5 vs. -1.0 (±25.0) p=0.001; SRI-SF: 9.2 (±21.9) vs.0.6 (±20.3), p=0.022; SRI-SS: 12.0 (±15.6) vs. 9.0 (±13.8), p=0.006).

When further analyzing factors affecting HRQL changes in patients receiving home mechanical ventilation, we found that change in SRI subscales showed significant correlation with baseline SRI scores (SRI-RC: p<0.001; CC=-0.782; SRI-PF: p=0.0314; CC=-0.265; SRI-AS p<0.001; CC=-0.769; SRI-SR: p=0.006; CC=-0.336; SRI-AX: p<0.001; CC=-0.559; SRI-WB: p<0.001; CC=-0.465; SRI-SF: p=0.007; CC=-0.328; SRI-SS: p<0.001; CC=-0.411) (Figure 13). This phenomenon was most prominent in SRI-RC and SRI-AS scales.

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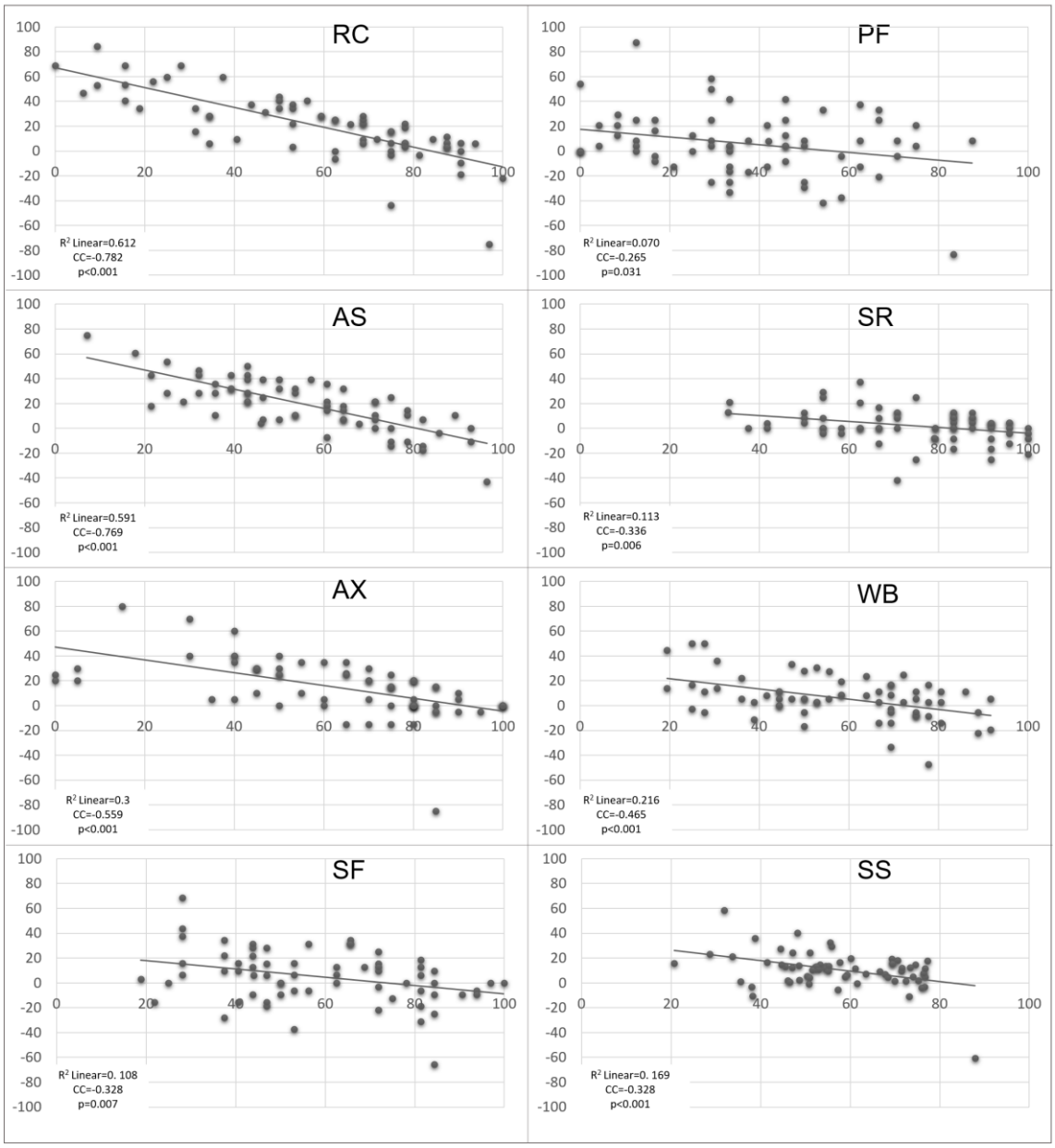

Figure 13. Subscale changes in relation to baseline subscales: *Scatterplot of SRI subscale changes according to initial SRI values. X axis shows change of SRI subscale. Y axis shows initial SRI subscale value. R^2Linear - coefficient of determination, CC - correlation coefficient, RC - Respiratory complaints, PF - Physical functioning, AS - Attendant symptoms and sleep, SR - Social relationships, AX - Anxiety WB - Psychological well-being, SF - Social functioning, SS - Summary Score*

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5. Discussion

5.1 Home mechanical ventilation in Hungary

The first study of this thesis is the first comprehensive data on the use of home mechanical ventilation in Hungary (91). The results of our survey show an overall prevalence of 3.9/100,000 for the country, with noninvasive ventilation as the most common mode of ventilation and most reported cases initiated in the last 5 years, proving the fact that HMV in Hungary has been an increasing and evolving practice in recent years. Still, the current prevalence is markedly lower than other parts of the world and even the overall prevalence of HMV in Europe identified by the Eurovent survey in 2005.

As there is no established registry for HMV and currently no assigned centers are in operation, we aimed to contact all sites possibly managing patients with failed weaning situations (intensive care units) or chronic respiratory failure patients and complex sleep related breathing disorders (pulmonology and pediatric centers). The low initial response rate of the sites contacted were thought to be indicative of the practice of home mechanical ventilation being limited to a number of sites in the country. This was verified by repeated phone contact of the non-responder sites, as 91% of nonresponding sites cited "no relevant data to share" as the reason for not completing the form.

The validity of the uncovered number of patients is further supported by reimbursement data acquired from the Hungarian National Health Insurance Fund as well as mechanical ventilator distribution data acquired from the top three distributors in the country (personal communication). As per the HNHIF, the number of patients who received active daily reimbursement for home mechanical ventilation was 97 for the month of February 2018, while an additional 102 patients were estimated to be alive who received initial government aid during the past ten years and were not transferred to active daily reimbursement (data acquired upon request through personal correspondence). This reimbursement data approximates a total of 199 patients receiving home mechanical ventilation in Hungary, but does not account for patients acquiring ventilators through alternative financing.

Distributor data identified a total of 244 ventilators purchased in the 10 years preceding the study period, not accounting for other potential distributors or ventilators acquired from abroad.

These two alternative sources of data both provide a similar, albeit lower number of patients compared to the number uncovered by our survey, pointing to the fact that some of the patients reported in our cohort might not meet the criteria for home mechanical ventilation but rather a sleep aid device for sleep apnea, which is regarded as a different group in both reimbursement and distribution databases. Overall, these data corroborate the number of patients uncovered by our survey. More precise data collection would be possible with a national registry system.

Previous data published shows an increasing prevalence of HMV in many countries across the world (25, 26, 97-100), but data is scarce on the East-Central European region. The Eurovent survey included only Poland from this region, showing a low prevalence of HMV, with patients usually treated through an invasive interface and as a result of a neuromuscular indication. Since then, Poland showed a remarkable improvement in patient recruitment and quality of care as well as prevalence of HMV, aided by newly established national recommendations (23).

Current practice in Hungary is still limited and can be described as two toned: intensive care units taking the burden of acutely admitted decompensated, highly ventilator dependent chronic respiratory failure patients and newly established noninvasive ventilation centers equipped with sleep labs prescribing therapy to less ventilator dependent patients but without regulated follow-up. Our current results prove this duality, as the small number of sites with substantial patient numbers were significantly more likely to be pulmonology affiliated than the sites with limited patient numbers, as these were more likely to be intensive care unit affiliated.

Out of the 17 sites providing care for patients in need of home mechanical ventilation, only 4 had a patient number of more than 50 and only one unit provided care for both invasively and noninvasively ventilated patients with home visits as standard follow-up care, meeting the theoretical criteria for home mechanical ventilation centers.

The relatively high ratio (89.6%) of patients receiving HMV through a noninvasive interface, is similar to recent prevalence data published from around the world (20, 21,

26), although overseeing noninvasive ventilation for home use seems to be limited to a small number of sites in Hungary.

When examining indications for HMV in Hungary, the most frequent diagnosis was central hypopnea syndromes (60%), whereas pulmonary (20%), neurological (11%) and chest wall disorder (7%) were less frequent indications for treatment. The relative high percentage of central hypopnea cases might be due to the increased awareness of complicated sleep apnea and obesity hypoventilation syndromes and it is in par with recent data from England (101) as well as Australia and New Zealand (21).

Ventilator dependence was examined in our survey. Reported cases received ventilation mostly in less than 8 hours per day, which points to the Hungarian HMV population being less ventilator dependent. Those cases with increased daily ventilation need were reported by sites with a limited case number, proving our initial theory that high ventilator dependent patients are usually initiated through an intensive care unit due to acute decompensation of chronic respiratory failure and possible consequent weaning failure.

Quality of care of HMV patients depends on follow-up visits, airway clearance methods and can be accurately described by the frequency of hospital readmissions. Our current survey on Hungarian home mechanically ventilated patients shows infrequent hospital readmission need with follow-ups provided by mostly ambulatory visits. Airway clearance techniques utilized were less state of the art, mostly done by deep suctioning in patients receiving invasive mechanical ventilation, supplied by the large number of sites caring for a limited number of invasively ventilated patients. Only 23.6% of sites provided cough assisting devices for patients if needed, despite recommendations for their use in patients with reduced peak cough flows (30).

Reimbursement for home mechanical ventilation in Hungary has been reformed in 2013, with treatment sites receiving a daily funding after eligible patients. Spending of funds, including choice of ventilator type, interface type and additional airway clearance devices is left to the discretion of the physician in charge of treatment, permitting a personalized treatment plan tailored to the need of the specific patient. Before 2013, government funding was available only as an initial aid in helping to obtain equipment for home mechanical ventilation often resulting in patients needing to take part in reimbursement or servicing of their equipment. Our current survey results show that despite a newer,

more flexible reimbursement, the most frequently used reimbursement was still initial government aid used in 73.5% of reported cases.

When comparing sites with a limited versus larger case number, we found a clear difference. Sites caring for a limited number of patients usually managed 1 to 7 patients, were more likely to treat patients with neuromuscular indications through invasive mode, with patients requiring more than 16 hours/day ventilation, home visits and more frequent readmissions. This data points to a possible gap in home mechanical ventilation provision, as patients that are more ventilator dependent but might be managed with noninvasive ventilation – a significant population according to international prevalence data - seem to be missing from current practice, despite recent data proving that even highly dependent, previously tracheostomized patients might be managed with continuous noninvasive ventilation (102).

The reasons for this missing group of patients can be as follows: lack of diagnosis or untimely diagnosis, misdiagnosis of patients with chronic respiratory failure and insufficient quality of care.

Lack of diagnosis or untimely diagnosis is especially prominent for patients with neuromuscular diseases, restrictive chest wall diseases and chronic obstructive pulmonary disease, when late diagnosis often results in acute hospitalization, at which point initiation of home mechanical ventilation is more difficult and results in a worse outcome (103). Misdiagnosis of patients with chronic respiratory failure usually affects central hypoventilation syndrome patients, as these conditions are often misdiagnosed as chronic right heart failure or as simple obstructive sleep apnea, when patients only receive oxygen therapy or CPAP therapy without adequate reevaluation. Our current study did not include sleep labs, nor focused on patients prescribed only long-term oxygen therapy or CPAP machines as ventilatory support, although in some of these patients HMV might be indicated with more precise work-up. This points to the importance of the implementation of national guidelines on the subject. Lastly, even with timely and adequate diagnosis, insufficient care and follow-up can result in worsened outcome for patients with HMV, resulting in seemingly diminished prevalence. According to our study in Hungary, so far only one established center exists that provides >16hour/day ventilation through a noninvasive interface for the majority of its patients, state of the art

secretion management devices and has a steadily growing patient number since its establishment in 2014 at Semmelweis University (see Table 2).

These described reasons are the most likely explanation for the still reduced prevalence of home mechanical ventilation in Hungary compared to other countries. Attempts to better identify and recruit these patients for HMV rest on establishing a system with a nationally approved adult HMV guideline, at least one center with sufficient diagnostic and follow-up infrastructure and a national registry to follow care of patients already under treatment, all of which are currently evolving projects at Semmelweis University.

The main limitation of the first study is that data collection was done through a voluntary basis, possibly leading to some misidentified and some not identified cases. Overall response rate was quite low, which can be explained by the wide range of sites contacted in order to identify sites with limited patient number and experience. Another limitation of the study is that survey identification of patients and treatment characteristics is less reliable, although most published prevalence data are based on surveys conducted with similar methodology.

5.2 Validation of the Hungarian version of the SRI Questionnaire

The SRI Questionnaire is a quality of life tool designed to evaluate chronic respiratory failure patients and has high psychometric properties. The goal of the second study was the transcultural adaptation of the questionnaire through the translation-back translation method involving the original author group. The results of the current validation study prove that the Hungarian version of the questionnaire has psychometric properties similar to the original version and its subsequent translations and is suitable for assessing quality of life in patients requiring home mechanical ventilation (92).

Our study population included patients with common diagnoses that are currently advised to be treated through home mechanical ventilation (30-32) with the characteristics of patients similar to the original study group (71), although there are also notable differences in the patient composition. The most common diagnosis for home mechanical ventilation in our study population was OHS/OSA, which is an increasingly common indication for HMV in recent years (104). This composition of the cohort is explained by the results of our first study, where we found that the majority of Hungary’s HMV

population has begun treatment in the last 5 years with OHS being the most frequent indication (91). Our results of the SRI Questionnaire in this patient group indicate that OHS/OSA causes similair quality of life limitation to other chronic respiratory failure conditions, with SRI-PF and -WB scales being the most affected aspects.

The second most frequent diagnosis in our cohort was NMD, while COPD and RCWD were less common. It should be noted that until recently, COPD diagnosis alone was not sufficient to apply for reimbursement in the Hungarian health care system, so most patients are predictably overlap patients (COPD and OSA) as indicated by the relatively high FEV1/FVC% values of this patient group. The relatively normal p_aCO_2 values of this patient group are notable and reflect successful achievement of treatment goals (as the institutional guideline aims for normocapnia in patients receiving HMV for COPD) and adequate patient recruitment (eg. stable patients without need for amendments to HMV treatment in the previous month).

Quality of life was different in different disease groups in our study, which has been described before, making the SRI a valid diagnostic tool (75). When comparing patients receiving ventilation through noninvasive or invasive interface, we found a difference in overall SRI score [SRI-SS: 66.8 (±15.1) vs. 58.2 (±13.6), p=0.046], as well as the SRI-RC, -PF and SF subscales [SRI-RC: 74.3 (±18.5) vs. 63.4 (±22.2), p=0.049; SRI-PF: 52.5 (±27.7) vs. 25.7 (±20.5), p=0.001; SRI-SF: 65.3 (±23.0) vs. 50.2 (±23.6), p=0.025], while other subscales showed no significant difference . This result is noteworthy despite the low ratio of invasively ventilated patients, and warrants further research of the subject.

The viability of the Hungarian version of the SRI Questionnaire was similar to the previously translated versions, with 69.2% of patients able to self-administer the tool and a time of about 9 minutes to complete the questionnaire, which was identical for the SF-36 quality of life questionnaire widely used in Hungary. Ability to self administer the questionnaire, disease type and education level significantly inlfuenced time spent on the questionnaire, but the age of the patient was not an influencing factor in our cohort. Missing items were less common with the SRI than the SF-36 questionnaire, attributing to a viable patient reported outcome tool.

Regarding validity, factor analysis explained 73.8% of the variation of the questionnaire, but it resulted in 13 scales. This is similar to results published by the Spanish and Portuguese validation of the SRI Questionnaire (76, 79) and has been explained by the

initial methodology of creating the questionnaire scales, which was done by an expert panel rather than factor analysis (71). Scale incongruencies have been described before with the SRI Questionnaire used in validation studies and are thought to be a result of limited study population numbers and differing patient composition compared to the original study (72, 87). Despite exploratory factor analysis showing an increased number of scales in previously published validation studies, within scale incongruences tend to correlate well with each other, which was also true for our data. Despite the limited but more versatile patient population in Hungary, the Hungarian SRI Questionnaire's validity proved to be similar to previously published translations with high overall Cronbach values and factor analysis results (see Table 10).

Table 10. Characteristics of previously published SRI Questionnaire translations: *SRI-SS: Summary Scale of the Severe Respiratory Insufficiency Questionnaire*

	Number of patients recruited	**Cronbach value of SRI-SS scale and (other scales)**	**Factor analysis: percentage of variance explained**	**Factor analysis: number of scales found**
German (original) (71)	226	0.89 (0.73-0.89)	59.8%	not done
Chinese (73)	149	0.95 (0.71-0.92)	59.0%	9
English (74)	152	0.93 (0.77-0.89)	70.0%	10
Finnish (105)	74	0.95 (0.67-0.88)	not done	not done
Japanese (78)	56	0.92 (0.56-0.80)	not done	not done
Norwegian (77)	127	0.94 (0.68-0.88)	not done	not done
Portuguese (79)	93	0.84 (0.44-0.78)	73.0%	13
Spanish (76)	115	0.93 (0.63-0.85)	60.0%	13
Hungarian (92)	104	0.93 (0.61-0.85)	73.8%	13

Correlations between the Hungarian version of the SRI and SF-36 were verified in several corresponding scales, most notably in scales assessing physical function and well-being and in some extent social relation and social function. The summary score of the SRI

Questionnaire and the general health score of the SF-36 questionnaire also showed reasonable correlation, verifying that the SRI Questionnaire was useful in assessing the overall quality of life in the patient group tested. The strength of the SRI Questionnaire for the HMV population is notable when studying the SRI-RC scale and it's apparent low correlation with most of the SF-36 subscales, pointing out that respiratory complaints, an aspect especially crucial when assessing chronic respiratory failure patients, tends to be poorly reflected in scales of a general quality of life questionnaire, like the SF-36. This corraborates previous views that the SRI Questionnaire is better suited to evaluate important quality of life aspects in chronic respiratory failure.

Reliability of the Hungarian SRI Questionnaire was found to be high, with an overall Cronbach alpha value of 0.93 for the questionnaire, corresponding to strong internal integrity. Cronbach alpha values were less than 0.7 for three, the SRI-AS, -SR and -WB scales, notably ones we found more incongruent. Reproducibility was also sufficiently high for the questionnaire.

The limitations of the second study include the smaller number of enrolled patients compared to those reported by some other validation studies, which can be explained by Hungary's smaller overall population and reported low prevalence of patients treated with home mechanical ventilation, however its versatile patient group makes it a valid and valuable tool for the currently growing Hungarian practice as well as a new reference for newly recruiting HMV centers.

5.3 Monitoring the efficacy of home mechanical ventilation through quality of life change

The aim of the third study was to assess HRQL change induced in a mixed case chronic respiratory failure patient population in one HMV center under optimal follow-up (93). Patients were recruited through the Semmelweis University Home Mechanical Ventilation Program, which meets the critera for the international standards for home mechanical ventilation centers (31, 32, 91). Our cohort included patients with a variety of underlying conditions, ventilated both invasively and noninvasively, initiated acutely and electively, resulting in a real-life study population. Frequent follow-up visits ensured

optimal compliance and maintained treatment goals, ensuring that HRQL changes were comparable despite the mixed case study population.

We found that overall HRQL improved significantly in the first 6 months of home mechanical ventilation and the grade of HRQL change was influenced by initial diagnosis. Furthermore, we also found that patients with worse initial HRQL, initiated acutely and needing O_2 supplementation, had a greater improvement in HRQL and that HRQL did not improve in ALS patients but was maintained despite significant progression of the disease.

The group of patients recruited for this study had baseline characteristics similar to home mechanical ventilation populations described before (see Table 1 and 8) and a composition more indicative of current world-wide HMV practice. Noninvasively ventilated patient populations have been known to be characterized by a daily ventilation need of 6.5 to 9 hours, FVC% values of 42-62%, p_aO_2 of 66-73 mmHg, and p_aCO_2 of 44-59 mmHg, while invasively ventilated patients have been reported to have higher daily ventilation needs (18-20 hours), with O_2 supplementation needed in 75% of patients (71, 75, 80, 81). In our study population, invasive and noninvasive ventilation ratio was similar to proportions noted in the Eurovent study describing patterns of HMV in Europe (19). This ratio explains the mean daily ventilator use in our study as well as the high O_2 supplementation need. Pulmonary function tests and blood gas values at baseline were consistent with values described in the previous references, with mean values showing restrictive lung function changes, hypoxia and hypercapnia (71, 75, 80, 81). The majority of patients were initiated on HMV after resolution of an acute exacerbation of a previously undiagnosed chronic condition, which might be explained by possible insufficient diagnostic algorithms and screening of patient populations with higher risk of chronic respiratory failure. This ratio makes the current study more relevant for real-life practices compared to studies performed on highly selected patient groups (see Table 1), as results are adaptable to a wider range of patients.

Baseline HRQL in our study population was similar [SRI-SS: 57.7 (±14.4)] to values described in patients suffering from chronic respiratory failure (see Table 1), with the subscales of Respiratory complaints, Attendant symptoms and sleep, Physical functioning, Social functioning and Psychological well-being being the aspects most diminished. To our knowledge, no previous study compared patients ventilated invasively

versus patients ventilated noninvasively, although patients ventilated through a tracheostomy are generally assumed to have diminished HRQL (75, 106). In our study population none of the baseline SRI subscales differed in patients treated through invasive or noninvasive interface as opposed to what we observed during the SRI validation study (91). This might be attributable to the fact that the validation study included patients who have already been established on HMV, while this current study focused on patients just starting the treatment. Since progressive neuromuscular diseases are often the indication for tracheostomy, their progression and subsequent decline of HRQL could explain this discrepancy.

There was also no significant difference in baseline values in patients initiated acutely or electively or in patients needing O_2 supplementation compared to patients who did not, and SRI subscales showed no correlation with initial blood gas values, lung function test parameters or hours of ventilation need, pointing to the fact that HRQL is not merely influenced by the severity of respiratory failure, although the relatively low number of invasively ventilated patients might contribute to this finding.

We found that quality of life increased significantly during the six-month observation period [SRI summary score changed from 57.7 (±14.4) vs. 68.2 (±15.8), $p<0.001$], which is similar to changes reported by studies in more selective patient populations (see Table 1). HRQL subscales that were most robustly improved were Respiratory complaints and Attendant symptoms and sleep, which are indeed the main goals of long-term mechanical ventilation. Anxiety subscales also showed significant improvement, which is most likely a consequence of the improvement of the two prior scales. Social relations and Social functioning showed no change, which suggests that these subscales are influenced by more complex disease attributes and are not solely related to respiratory symptoms. The change in Physical functioning also showed no significant overall improvement, which is understandable since several patient groups had stable or progressive neuromuscular impairment. When looking at specific disease groups, we found that diseases where neuromuscular involvement was not present (COPD and OHS), Physical functioning subscale actually improved significantly and considerably [16.2 (±12.2), $p=0.002$ and 19.8 (±24.9), $p<0.001$ respectively]. This is an important finding, since previous studies have suggested that NIV treatment and physical training could have an equally strong and additive positive effect on 6MWD in this patient group (107).

The overall SRI HRQL change found in our study is similar to changes previously reported in a study using solely noninvasive ventilation (81). Furthermore, our study found higher post-ventilation HRQL values than a study in a population ventilated invasively (75). As an additional interesting finding, our study suggests that an increase in HRQL does not depend on interface (108), meaning HRQL can both be increased through invasive and noninvasive ventilation. This is important because there is a general fear towards tracheostomy in patients requiring long term mechanical ventilation (109). The results of our study provide evidence that significant improvement might be achieved in HRQL even through an invasive interface. This can be attributed to patient-tailored home mechanical ventilation therapy, which is feasible under current reimbursement system in Hungary and permits complex ventilation and physiotherapy plans for patients, despite vastly different needs. The other possible reason for the consistently improved outcome might be the optimized care and frequent follow-ups provided by our program, highlighting the theory that HRQL change can in fact be a marker of efficacy of care.

Current international guidelines do not specify the frequency of follow-up for home mechanically ventilated patients (30-32), but most centers reduce the frequency of home or ambulatory visits to twice a year after successful initiation (18, 53). In our patient population, however, in order to assume best possible care, follow-up was provided monthly for patients ventilated invasively and monthly or bi-monthly for stable patients ventilated through a noninvasive interface.

When looking at other factors potentially influencing HRQL change, we found that HRQL increase was the greatest among patients with lower initial HRQL scores, patients initiated with long term mechanical ventilation in an acute setting, and patients needing supplemental O_2 therapy, implying that a lot of patients included in the current study might have received home mechanical ventilation relatively late in their course of disease progression. This is corroborated by the results of our first study that describes the current characteristics and prevalence of HMV in Hungary, which found that prevalence of home mechanical ventilation is lower than that found in other internationally published data, because many ventilator-dependent patients might not receive therapy in time (91). This finding is especially important, since there is still no clear data to help us differentiate between long term therapeutic home mechanical ventilation and palliative care with

ventilation. The results of our study suggest that even patients with very poor HRQL benefit greatly from initiation of home mechanical ventilation.

Our results regarding the HRQL influencing effect of initial diagnosis corroborate the findings published previously (75, 81). Based on our findings, COPD patients can expect the most benefit in HRQL increase, which is important, since long term home mechanical ventilation is still controversial in this indication (16, 110, 111), although it should be noted that COPD is a heterogenous disease group and our study did not analyze disease phenotypes. Moreover, when analyzing patient groups, we found that OHS patients improved most consistently, *on par* with recently published guidelines (112). Given that this disease effects a younger population and its main symptoms are debilitating daytime sleepiness and hypercapnia (113), this HRQL improvement has important socioeconomical consequences. It is also important to note that recent guidelines indicate most OHS patients might be managed with initial CPAP therapy. Prospective HRQL change studies might verify whether optimal improvement can be achieved by this approach.

In our study, the only patient group not showing improved HRQL scores were the ALS patients, which is *on par* with literature describing this progressive neuromuscular disease (114), although noninvasive ventilation has been shown to improve HRQL and even survival for a shorter period of time (60). In our study, spanning a longer period, it is especially conspicuous that ALS patients were the only ones to show significant detriment in one subscale (SRI Social functioning change), suggesting that these patients often become isolated during the progression of their disease. However, it is noteworthy that despite HRQL subscale changes due to disease progression, overall Summary scores remained stable, mainly because Attendant symptoms and sleep, Anxiety and Respiratory complaints subscales counterbalance the decrease in Social functioning and Physical functioning subscales. This suggests that home mechanical ventilation might be a valid palliative care technique in ALS even in cases where significant lifespan or HRQL improvement can’t be proven.

The main limitation of our study is the sample size that might be considered small; however previously published studies on HMV patients utilized similar sample sizes (68, 69, 75, 81). Our study was a single center, prospective HRQL change investigation under optimized care using the SRI Questionnaire, providing valuable “real-life” information

on a mixed case population previously not extensively described in the literature. Another limitation is that the study was not designed to identify outcome differences in patients with different interfaces or initial diagnosis, nor was powered for multivariate analysis to exactly define confounding factors influencing subscale changes, as subgroup analysis would have resulted in groups that would have been too small to deduct relevant clinical correlations.

6. Conclusion

In conclusion, home mechanical ventilation is an evolving therapeutic option for chronic respiratory failure patients with established indications and advanced technical possibilities. Our results are the first in the country to describe current practice and show a reasonable estimate and characterization of home mechanical ventilation in Hungary. Although a growing local practice can be assumed, current prevalence of home mechanical ventilation is still markedly reduced compared to previously reported international data. Our results uncovered a possible gap in diagnosis and care for more dependent patients that might be managed with noninvasive techniques, possibly accounting for the relatively low prevalence. These results point to the importance of establishing national guidelines and home mechanical ventilation centers, where increased experience will enable state of the art care for more dependent patients as well, helping to increase overall prevalence.

In order to aid diagnosis and management of chronic respiratory failure patients, we validated the Hungarian version of the Severe Respiratory Insufficiency Questionnaire, the most widely used quality of life tool in the field on home mechanical ventilation. We proved that the Hungarian version of the SRI Questionnaire is a viable, valid, reliable and reproduceable quality of life tool applicable for Hungarian patients treated with home mechanical ventilation and supplies additional information for the usefulness of the questionnaire in more versatile patient populations. Thus, further application of this version of the questionnaire for evaluation and monitoring of patients suffering from chronic respiratory failure is well founded.

Future research in the field should focus on efficacy of treatment and establishing clear guidelines on management and follow-up of these patients. Regarding monitoring the efficacy of home mechanical ventilation in a real-life population, we found that starting home mechanical ventilation is accompanied by improved quality of life in several patient groups suffering from chronic respiratory failure. Our findings suggest that HRQL improvement is independent of classic markers of the severity of chronic respiratory failure (e.g., baseline pulmonary function, arterial blood gas values, hours of ventilation need) or interface used for ventilation, but it is dependent on the type of disease causing the chronic respiratory failure, initiation type (acute versus elective), initial HRQL and

O_2 supplementation need. Our results further suggest that acutely initiated, O_2 dependent COPD and OHS patients with low initial HRQL can expect the most benefit, while ALS patients can expect maintenance of overall HRQL despite ongoing neurological deterioration.

Our results can provide a reference for expected HRQL change with optimal home mechanical ventilation management. Further prospective studies are needed to confirm our findings, to identify whether HRQL changes can be used as efficacy markers and correlate well with compliance, disease progression and mortality as well as how often HRQL needs to be measured during the follow-up of patients receiving home mechanical ventilation in order to better improve the lives of patients suffering from chronic respiratory failure.

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7. Summary

Home mechanical ventilation is an established mode of treatment for patients with chronic respiratory failure, resulting in increased survival, reduced costs and infection rates, optimized medical care utilization and improved health-related quality of life. Prevalence varies in different countries, as do follow-up practices. Although indications for treatment are well defined, there is limited data on optimal treatment goals and follow-up algorithms that monitor efficacy of treatment.

Our results are the first to describe current home mechanical ventilation practice in Hungary. We found that prevalence is 3.9/100,000, which is below European average, although growing practice can be assumed. We uncovered a possible gap in diagnosis and care for more dependent patients, highlighting the need for increased use of noninvasive techniques and home mechanical ventilation centers that are able to oversee these therapies.

We validated the Hungarian version of the Severe Respiratory Insufficiency Questionnaire, a quality of life tool designed and validated for chronic respiratory patients. The Hungarian version proved to be viable, valid, reliable and reproduceable and could help aid future diagnosis and management of chronic respiratory failure patients in the country.

In order to describe health-related quality of life change patterns after starting home mechanical ventilation, we conducted a single center, prospective HRQL change investigation under optimized care using the SRI Questionnaire, providing valuable “real-life” information on a mixed case population previously not extensively described in the literature. We found that improvement in health-related quality of life is dependent on disease type, initiation type and initial quality of life, suggesting that patients considered more severe might actually benefit more from treatment. Our results can provide a reference for expected health-related quality of life change with optimal home mechanical ventilation management and can aid further research on efficacy of home mechanical ventilation.

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7. Összefoglalás

Az otthoni lélegeztetés a krónikus légzési elégtelen betegek lehetséges kezelési módja, mely ismerten javítja a túlélést, csökkenti a kezelési költségeket és a fertőzések előfordulását, optimalizálja az egészségügyi ellátást és javítja a betegek életminőségét.
A kezelés prevalenciája országonként változó, ahogy az ellátás gyakorlata is. Bár az indikációs körök jól meghatározhatók, az optimális kezelési célokról és a kezelés hatékonyságát célzó ideális utánkövetési algoritmusokról még keveset tudunk.
Eredményeink először mutatják be a jelenlegi otthoni lélegeztetési gyakorlatot Magyarországon. A magyar prevalencia 3,9/100.000, mely elmarad az európai átlagtól, annak ellenére, hogy az ellátás vélhetően fejlődik. Eredményeink rámutatnak a dependens betegek potenciális diagnosztikai és ellátási hiányára és a noninvazív technikák ilyen irányú felhasználásának igényére, mely megerősíti az otthoni lélegeztetési centrumok szükségességét.
Validáltuk a Súlyos Légzési Elégtelenség Kérdőív magyar változatát, mely a krónikus légzési elégtelen betegek számára kifejlesztett életminőség felmérő eszköz. Vizsgálatunk során a magyar változat használhatónak, validnak, megbízhatónak és reprodukálhatónak bizonyult, így a krónikus légzési elégtelen betegek diagnosztizálásában és ellátásában a továbbiakban fontos szerepet tölthet be.
Annak érdekében, hogy felmérjük az otthon lélegeztetés megkezdését követően várható életminőség változás jellemzőit, egy monocentrikus, prospektív életminőség változást felmérő vizsgálatot végeztünk ideális ellátás mellett az előzőekben validált kérdőívvel, mely információval szolgál egy az irodalomban előzőleg kevéssé részletezett, de a valós életet jobban tükröző, vegyes összetételű populációról. Eredményeink szerint az egészséghez köthető életminőség javulás mértéke az alapbetegségtől, a terápia megkezdésének körülményeitől és a kezdeti életminőségtől függ, mely arra utal, hogy a súlyosabbnak minősülő eseteknél tulajdonképpen nagyobb a kezelés hatására várható javulás mértéke. Eredményeink mindazonáltal referenciaként is szolgálhatnak az optimális felügyelet mellett végzett otthoni lélegeztetés mellett várható életminőség változásról és így a továbbiakban az otthoni lélegeztetés hatékonyságára utaló vizsgálatok alapjául szolgálhatnak.

8. References

1. Affeldt JE, West HF, Landauer KS, Wendland LV, Arata NN. (1958) Functional and vocational recovery in severe poliomyelitis. Clin Orthop, 12: 16-21.
2. Engstrom CG. (1954) Treatment of severe cases of respiratory paralysis by the Engström universal respirator. Br Med J, 2: 666-669.
3. Barr M. (2010) The iron lung - a polio patient's story. J R Soc Med, 103: 256-259.
4. R H. (1994) Adatok a gyermekbénulás hazai leküzdésének történetéből. Orv Hetil, 135: 1539-1541.
5. Hermann C, Lorx A., Pénzes I. Otthoni lélegeztetés. In:Pénzes I. LA (szerk.), A lélegeztetés elmélete és gyakorlata. Medicina Könykiadó, Budapest, Hungary, 2004: 831-853.
6. Bertoye A, Garin JP, Vincent P, Giroud M, Monier P, Humbert G. (1965) [The return home of equipped chronic respiratory insufficiency patients]. Lyon Med, 214: 389-410.
7. Goldberg AI, Faure EA. (1984) Home care for life-supported persons in England. The Responaut Program. Chest, 86: 910-914.
8. Kinnear WJ, Shneerson JM. (1985) Assisted ventilation at home: is it worth considering? Br J Dis Chest, 79: 313-351.
9. Díaz Lobato S, Mayoralas Alises S. (2013) Modern non-invasive mechanical ventilation turns 25. Arch Bronconeumol, 49: 475-479.
10. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, Dowson L, Duffy N, Gibson GJ, Hughes PD, Hurst JR, Lewis KE, Mukherjee R, Nickol A, Oscroft N, Patout M, Pepperell J, Smith I, Stradling JR, Wedzicha JA, Polkey MI, Elliott MW, Hart N. (2017) Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA, 317: 2177-2186.
11. Storre JH, Seuthe B, Fiechter R, Milioglou S, Dreher M, Sorichter S, Windisch W. (2006) Average volume-assured pressure support in obesity hypoventilation: A randomized crossover trial. Chest, 130: 815-821.

12. Hess DR. (2009) How to initiate a noninvasive ventilation program: bringing the evidence to the bedside. Respir Care, 54: 232-243; discussion 243-235.
13. Vignaux L, Vargas F, Roeseler J, Tassaux D, Thille AW, Kossowsky MP, Brochard L, Jolliet P. (2009) Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Med, 35: 840-846.
14. Hess DR. (2011) Patient-ventilator interaction during noninvasive ventilation. Respir Care, 56: 153-165; discussion 165-157.
15. Hodgson LE, Murphy PB. (2016) Update on clinical trials in home mechanical ventilation. J Thorac Dis, 8: 255-267.
16. Kohnlein T, Windisch W, Kohler D, Drabik A, Geiseler J, Hartl S, Karg O, Laier-Groeneveld G, Nava S, Schonhofer B, Schucher B, Wegscheider K, Criee CP, Welte T. (2014) Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med, 2: 698-705.
17. van den Bergen JC, Ginjaar HB, van Essen AJ, Pangalila R, de Groot IJ, Wijkstra PJ, Zijnen MP, Cobben NA, Kampelmacher MJ, Wokke BH, de Coo IF, Fock JM, Horemans AM, van Tol M, Vroom E, Rijlaarsdam ME, Straathof CS, Niks EH, Verschuuren JJ. (2014) Forty-Five Years of Duchenne Muscular Dystrophy in The Netherlands. J Neuromuscul Dis, 1: 99-109.
18. MacIntyre EJ, Asadi L, McKim DA, Bagshaw SM. (2016) Clinical Outcomes Associated with Home Mechanical Ventilation: A Systematic Review. Can Respir J, 2016: 6547180.
19. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Fauroux B, Robert D, Schoenhofer B, Simonds AK, Wedzicha JA. (2005) Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. European Respiratory Journal, 25: 1025-1031.
20. Rose L, McKim DA, Katz SL, Leasa D, Nonoyama M, Pedersen C, Goldstein RS, Road JD. (2015) Home mechanical ventilation in Canada: a national survey. Respir Care, 60: 695-704.

21. Garner DJ, Berlowitz DJ, Douglas J, Harkness N, Howard M, McArdle N, Naughton MT, Neill A, Piper A, Yeo A, Young A. (2013) Home mechanical ventilation in Australia and New Zealand. Eur Respir J, 41: 39-45.
22. Chu CM, Yu WC, Tam CM, Lam CW, Hui DSC, Lai CKW. (2004) Home mechanical ventilation in Hong Kong. Eur Respir J, 23: 136-141.
23. Laub M, Berg S, Midgren B. (2004) Home mechanical ventilation in Sweden - Inequalities within a homogenous health care system. Respir Med, 98: 38-42.
24. Ambrosino N, Vitacca M, Dreher M, Isetta V, Montserrat JM, Tonia T, Turchetti G, Winck JC, Burgos F, Kampelmacher M, Vagheggini G. (2016) Tele-monitoring of ventilator-dependent patients: a European Respiratory Society Statement. Eur Respir J, 48: 648-663.
25. Janssens JP, Derivaz S, Breitenstein E, De Muralt B, Fitting JW, Chevrolet JC, Rochat T. (2003) Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. Chest, 123: 67-79.
26. Nasilowski J, Wachulski M, Trznadel W, Andrzejewski W, Migdal M, Drozd W, Pytel A, Suchanke R, Czajkowska-Malinowska M, Majszyk T, Szkulmowski Z, Chazan R. (2015) The evolution of home mechanical ventilation in poland between 2000 and 2010. Respir Care, 60: 577-585.
27. Lorx A, Bartusek D, Losonczy G, Gal J. (2012) Nem invazív légzési osztály a magyar ellátórendszerben. Orv Hetil, 153: 918-921.
28. Egészségügyi Szakmai Kollégium. (2017) Egészségügyi szakmai irányelv - A gyermekek invazív és noninvazív otthoni lélegeztetéséről. Egészségügyi Közlöny, EüK 3.
29. Lorx A, Valkó L, Gál J. (2019) Az otthoni lélegeztetés helyzete Magyarországon. Med Thorac, 72: 118-124.
30. McKim DA, Road J, Avendano M, Abdool S, Cote F, Duguid N, Fraser J, Maltais F, Morrison DL, O'Connell C, Petrof BJ, Rimmer K, Skomro R. (2011) Home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline. Can Respir J, 18: 197-215.
31. Windisch W, Geiseler J, Simon K, Walterspacher S, Dreher M. (2018) German National Guideline for Treating Chronic Respiratory Failure with Invasive and Non-Invasive Ventilation: Revised Edition 2017 - Part 1. Respiration, 96: 66-97.

32. Windisch W, Geiseler J, Simon K, Walterspacher S, Dreher M. (2018) German National Guideline for Treating Chronic Respiratory Failure with Invasive and Non-Invasive Ventilation - Revised Edition 2017: Part 2. Respiration, 96: 171-203.
33. Wilson ME, Dobler CC, Morrow AS, Beuschel B, Alsawas M, Benkhadra R, Seisa M, Mittal A, Sanchez M, Daraz L, Holets S, Murad MH, Wang Z. (2020) Association of Home Noninvasive Positive Pressure Ventilation With Clinical Outcomes in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis. JAMA, 323: 455-465.
34. Dreher M, Storre JH, Schmoor C, Windisch W. (2010) High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax, 65: 303-308.
35. Gustafson T, Franklin KA, Midgren B, Pehrsson K, Ranstam J, Strom K. (2006) Survival of patients with kyphoscoliosis receiving mechanical ventilation or oxygen at home. Chest, 130: 1828-1833.
36. Schonhofer B, Barchfeld T, Wenzel M, Kohler D. (2001) Long term effects of non-invasive mechanical ventilation on pulmonary haemodynamics in patients with chronic respiratory failure. Thorax, 56: 524-528.
37. Moxham J, Shneerson JM. (1993) Diaphragmatic pacing. Am Rev Respir Dis, 148: 533-536.
38. Mokhlesi B. (2010) Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care, 55: 1347-1362; discussion 1363-1345.
39. Berry RB, Chediak A, Brown LK, Finder J, Gozal D, Iber C, Kushida CA, Morgenthaler T, Rowley JA, Davidson-Ward SL. (2010) Best Clinical Practices for the Sleep Center Adjustment of Noninvasive Positive Pressure Ventilation (NPPV) in Stable Chronic Alveolar Hypoventilation Syndromes. J Clin Sleep Med, 6: 491-509.
40. Masa JF, Corral J, Alonso ML, Ordax E, Troncoso MF, Gonzalez M, Lopez-Martínez S, Marin JM, Marti S, Díaz-Cambriles T, Chiner E, Aizpuru F, Egea C. (2015) Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome. Pickwick Study. Am J Respir Crit Care Med, 192: 86-95.

41. Priou P, Hamel JF, Person C, Meslier N, Racineux JL, Urban T, Gagnadoux F. (2010) Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. Chest, 138: 84-90.
42. Sancho J, Servera E, Diaz J, Marin J. (2007) Predictors of ineffective cough during a chest infection in patients with stable amyotrophic lateral sclerosis. Am J Respir Crit Care Med, 175: 1266-1271.
43. Toussaint M, Steens M, Wasteels G, Soudon P. (2006) Diurnal ventilation via mouthpiece: survival in end-stage Duchenne patients. Eur Respir J, 28: 549-555.
44. Cazzolli PA, Oppenheimer EA. (1996) Home mechanical ventilation for amyotrophic lateral sclerosis: Nasal compared to tracheostomy-intermittent positive pressure ventilation. Journal of the Neurological Sciences, 139: 123-128.
45. Shavelle RM, Paculdo DR, Tran LM, Strauss DJ, Brooks JC, DeVivo MJ. (2015) Mobility, Continence, and Life Expectancy in Persons with ASIA Impairment Scale Grade D Spinal Cord Injuries. Am J Phys Med Rehab, 94: 180-191.
46. Mifsud Bonnici D, Sanctuary T, Warren A, Murphy PB, Steier J, Marino P, Pattani H, Creagh-Brown BC, Hart N. (2016) Prospective observational cohort study of patients with weaning failure admitted to a specialist weaning, rehabilitation and home mechanical ventilation centre. BMJ Open, 6: e010025.
47. McKim D, Rose L. (2015) Efficacy of mechanical insufflation-exsufflation in extubating unweanable subjects with restrictive pulmonary disorders. Respir Care, 60: 621-622.
48. Jacobs JM, Marcus EL, Stessman J. (2020) Prolonged Mechanical Ventilation: A Comparison of Patients Treated at Home Compared With Hospital Long-Term Care. J Am Med Dir Assoc, doi:10.1016/j.jamda.2020.06.038.
49. Gacouin A, Jouneau S, Letheulle J, Kerjouan M, Bouju P, Fillatre P, Le Tulzo Y, Tadie JM. (2015) Trends in Prevalence and Prognosis in Subjects With Acute Chronic Respiratory Failure Treated With Noninvasive and/or Invasive Ventilation. Respiratory Care, 60: 210-218.
50. Simonds AK, Hare A. (2013) New modalities for non-invasive ventilation. Clin Med (Lond), 13 Suppl 6: s41-45.
51. Nava S, Ferrer M, Esquinas A, Scala R, Groff P, Cosentini R, Guido D, Lin CH, Cuomo AM, Grassi M. (2013) Palliative use of non-invasive ventilation in end-

of-life patients with solid tumours: a randomised feasibility trial. Lancet Oncology, 14: 219-227.

52. Ørtenblad L, Carstensen K, Væggemose U, Løvschall C, Sprehn M, Küchen S, Nørregaard O, Jensen LG. (2019) Users' Experiences With Home Mechanical Ventilation: A Review of Qualitative Studies. Respir Care, 64: 1157-1168.
53. Hannan LM, Sahi H, Road JD, McDonald CF, Berlowitz DJ, Howard ME. (2016) Care Practices and Health-related Quality of Life for Individuals Receiving Assisted Ventilation. A Cross-National Study. Ann Am Thorac Soc, 13: 894-903.
54. Simonds AK. (2016) Home Mechanical Ventilation: An Overview. Ann Am Thorac Soc, 13: 2035-2044.
55. Schwarz EI, Mackie M, Weston N, Tincknell L, Beghal G, Cheng MCF, Ramsay M, Suh ES, Kaltsakas G, Pattani H, Marino P, Murphy PB, Hart N, Steier J. (2020) Time-to-death in chronic respiratory failure on home mechanical ventilation: A cohort study. Respir Med, 162: 105877.
56. McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catcheside PG, O'Donoghue FJ, Barnes DJ, Grunstein RR. (2009) Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax, 64: 561-566.
57. Borel JC, Burel B, Tamisier R, Dias-Domingos S, Baguet JP, Levy P, Pepin JL. (2013) Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. PLoS One, 8: e52006.
58. Saito T, Kawai M, Kimura E, Ogata K, Takahashi T, Kobayashi M, Takada H, Kuru S, Mikata T, Matsumura T, Yonemoto N, Fujimura H, Sakoda S. (2017) Study of Duchenne muscular dystrophy long-term survivors aged 40 years and older living in specialized institutions. in Japan. Neuromuscul Disord, 27: 107-114.
59. Toussaint M, Chatwin M, Soudon P. (2007) Mechanical ventilation in Duchenne patients with chronic respiratory insufficiency: clinical implications of 20 years published experience. Chron Respir Dis, 4: 167-177.
60. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. (2006) Effects of non-invasive ventilation on survival and quality of life in patients with

amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol, 5: 140-147.

61. Chatwin M, Heather S, Hanak A, Polkey MI, Simonds AK. (2010) Analysis of home support and ventilator malfunction in 1,211 ventilator-dependent patients. Eur Respir J, 35: 310-316.
62. Pasquina P, Adler D, Farr P, Bourqui P, Bridevaux PO, Janssens JP. (2012) What does built-in software of home ventilators tell us? An observational study of 150 patients on home ventilation. Respiration, 83: 293-299.
63. Borel JC, Palot A, Patout M. (2019) Technological advances in home non-invasive ventilation monitoring: Reliability of data and effect on patient outcomes. Respirology, 24: 1143-1151.
64. Radogna AV, Siciliano PA, Sabina S, Sabato E, Capone S. (2020) A Low-Cost Breath Analyzer Module in Domiciliary Non-Invasive Mechanical Ventilation for Remote COPD Patient Monitoring. Sensors (Basel), 20.
65. Chailleux E, Fauroux B, Binet F, Dautzenberg B, Polu JM. (1996) Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. A 10-year analysis of ANTADIR Observatory. Chest, 109: 741-749.
66. Güngör G, Karakurt Z, Adigüzel N, Aydin RE, Balci MK, Saltürk C, Sancar R, Solmaz S, Moçin Ö Y. (2013) The 6-minute walk test in chronic respiratory failure: does observed or predicted walk distance better reflect patient functional status? Respir Care, 58: 850-857.
67. Salturk C, Karakurt Z, Takir HB, Balci M, Kargin F, Mocin OY, Gungor G, Ozmen I, Oztas S, Yalcinsoy M, Evin R, Ozturk M, Adiguzel N. (2015) Comparison of exercise capacity in COPD and other etiologies of chronic respiratory failure requiring non-invasive mechanical ventilation at home: retrospective analysis of 1-year follow-up. Int J Chron Obstruct Pulmon Dis, 10: 2559-2569.
68. Struik FM, Sprooten RT, Kerstjens HA, Bladder G, Zijnen M, Asin J, Cobben NA, Vonk JM, Wijkstra PJ. (2014) Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. Thorax, 69: 826-834.

69. Oga T, Taniguchi H, Kita H, Tsuboi T, Tomii K, Ando M, Kojima E, Tomioka H, Taguchi Y, Kaji Y, Maekura R, Hiraga T, Sakai N, Kimura T, Mishima M, Windisch W, Chin K. (2017) Comparison of Different Disease-Specific Health-Related Quality of Life Measurements in Patients with Long-Term Noninvasive Ventilation. Can Respir J, 2017: 8295079.
70. Struik FM, Kerstjens HA, Bladder G, Sprooten R, Zijnen M, Asin J, van der Molen T, Wijkstra PJ. (2013) The Severe Respiratory Insufficiency Questionnaire scored best in the assessment of health-related quality of life in chronic obstructive pulmonary disease. J Clin Epidemiol, 66: 1166-1174.
71. Windisch W, Freidel K, Schucher B, Baumann H, Wiebel M, Matthys H, Petermann F. (2003) The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. J Clin Epidemiol, 56: 752-759.
72. Windisch W, Budweiser S, Heinemann F, Pfeifer M, Rzehak P. (2008) The Severe Respiratory Insufficiency Questionnaire was valid for COPD patients with severe chronic respiratory failure. J Clin Epidemiol, 61: 848-853.
73. Chen R, Guan L, Wu W, Yang Z, Li X, Luo Q, Liang Z, Wang F, Guo B, Huo Y, Yang Y, Zhou L. (2017) The Chinese version of the Severe Respiratory Insufficiency questionnaire for patients with chronic hypercapnic chronic obstructive pulmonary disease receiving non-invasive positive pressure ventilation. BMJ Open, 7: e017712.
74. Ghosh D, Rzehak P, Elliott MW, Windisch W. (2012) Validation of the English Severe Respiratory Insufficiency Questionnaire. Eur Respir J, 40: 408-415.
75. Huttmann SE, Windisch W, Storre JH. (2015) Invasive home mechanical ventilation: living conditions and health-related quality of life. Respiration, 89: 312-321.
76. Lopez-Campos JL, Failde I, Masa JF, Benitez-Moya JM, Barrot E, Ayerbe R, Leon-Jimenez A, Windisch W. (2008) Transculturally adapted Spanish SRI questionnaire for home mechanically ventilated patients was viable, valid, and reliable. J Clin Epidemiol, 61: 1061-1066.

77. Markussen H, Lehmann S, Nilsen RM, Natvig GK. (2015) The Norwegian version of the Severe Respiratory Insufficiency Questionnaire. Int J Nurs Pract, 21: 229-238.
78. Oga T, Taniguchi H, Kita H, Tsuboi T, Tomii K, Ando M, Kojima E, Tomioka H, Taguchi Y, Kaji Y, Maekura R, Hiraga T, Sakai N, Kimura T, Mishima M, Windisch W, Chin K. (2017) Validation of the Japanese Severe Respiratory Insufficiency Questionnaire in hypercapnic patients with noninvasive ventilation. Respir Investig, 55: 166-172.
79. Ribeiro C, Ferreira D, Conde S, Oliveira P, Windisch W. (2017) Validation of the Portuguese Severe Respiratory Insufficiency Questionnaire for home mechanically ventilated patients. Rev Port Pneumol (2006), 23: 139-145.
80. Tsolaki V, Pastaka C, Kostikas K, Karetsi E, Dimoulis A, Zikiri A, Koutsokera A, Gourgoulianis KI. (2011) Noninvasive Ventilation in Chronic Respiratory Failure: Effects on Quality of Life. Respiration, 81: 402-410.
81. Windisch W. (2008) Impact of home mechanical ventilation on health-related quality of life. Eur Respir J, 32: 1328-1336.
82. Oga T, Windisch W, Handa T, Hirai T, Chin K. (2018) Health-related quality of life measurement in patients with chronic respiratory failure. Respir Investig, 56: 214-221.
83. Howard ME, Piper AJ, Stevens B, Holland AE, Yee BJ, Dabscheck E, Mortimer D, Burge AT, Flunt D, Buchan C, Rautela L, Sheers N, Hillman D, Berlowitz DJ. (2017) A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax, 72: 437-444.
84. Murphy PB, Brignall K, Moxham J, Polkey MI, Davidson AC, Hart N. (2012) High pressure versus high intensity noninvasive ventilation in stable hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial. Int J Chron Obstruct Pulmon Dis, 7: 811-818.
85. Storre JH, Matrosovich E, Ekkernkamp E, Walker DJ, Schmoor C, Dreher M, Windisch W. (2014) Home mechanical ventilation for COPD: high-intensity versus target volume noninvasive ventilation. Respir Care, 59: 1389-1397.
86. Arellano-Maric MP, Hamm C, Duiverman ML, Schwarz S, Callegari J, Storre JH, Schmoor C, Spielmanns M, Galetke W, Windisch W. (2020) Obesity

hypoventilation syndrome treated with non-invasive ventilation: Is a switch to CPAP therapy feasible? Respirology, 25: 435-442.

87. Walterspacher S, July J, Kohlhaufl M, Rzehak P, Windisch W. (2016) The Severe Respiratory Insufficiency Questionnaire for Subjects With COPD With Long-Term Oxygen Therapy. Respir Care, 61: 1186-1191.
88. Budweiser S, Hitzl AP, Jorres RA, Schmidbauer K, Heinemann F, Pfeifer M. (2007) Health-related quality of life and long-term prognosis in chronic hypercapnic respiratory failure: a prospective survival analysis. Respir Res, 8: 92.
89. Huttmann SE, Magnet FS, Karagiannidis C, Storre JH, Windisch W. (2018) Quality of life and life satisfaction are severely impaired in patients with long-term invasive ventilation following ICU treatment and unsuccessful weaning. Ann Intensive Care, 8: 38.
90. Raveling T, Bladder G, Vonk JM, Nieuwenhuis JA, Verdonk-Struik FM, Wijkstra PJ, Duiverman ML. (2018) Improvement in hypercapnia does not predict survival in COPD patients on chronic noninvasive ventilation. Int J Chron Obstruct Pulmon Dis, 13: 3625-3634.
91. Valko L, Baglyas S, Gal J, Lorx A. (2018) National survey: current prevalence and characteristics of home mechanical ventilation in Hungary. BMC Pulm Med, 18: 190.
92. Valko L, Baglyas S, Kunos L, Terray-Horvath A, Lorx A, Gal J, Windisch W. (2020) Validation of the Hungarian version of the SRI Questionnaire. BMC Pulm Med, 20: 130.
93. Valko L, Baglyas S, Gyarmathy VA, Gal J, Lorx A. (2020) Home mechanical ventilation: quality of life patterns after six months of treatment. BMC Pulm Med, 20: 221.
94. (2018) Központi Statisztikai Hivatal. Vol. 2018
95. Czimbalmos A NZ, Varga Z, Husztik P. (1999) Páciens megelégedettségi vizsgálat SF-36 kérdőívvel, a magyarországi normálértékek meghatározása. Népegészségügy, 80: 4-19.
96. Norman GR, Sloan JA, Wyrwich KW. (2003) Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care, 41: 582-592.

97. Tan GP, McArdle N, Dhaliwal SS, Douglas J, Rea CS, Singh B. (2018) Patterns of use, survival and prognostic factors in patients receiving home mechanical ventilation in Western Australia: A single centre historical cohort study. Chron Respir Dis, doi:10.1177/1479972318755723: 1479972318755723.

98. Povitz M, Rose L, Shariff SZ, Leonard S, Welk B, Jenkyn KB, Leasa DJ, Gershon AS. (2018) Home Mechanical Ventilation: A 12-Year Population-Based Retrospective Cohort Study. Respir Care, 63: 380-387.

99. Goodwin S, Smith H, Langton Hewer S, Fleming P, Henderson AJ, Hilliard T, Fraser J. (2011) Increasing prevalence of domiciliary ventilation: changes in service demand and provision in the South West of the UK. Eur J Pediatr, 170: 1187-1192.

100. Laub M, Berg S, Midgren B. (2004) Home mechanical ventilation in Sweden--inequalities within a homogenous health care system. Respir Med, 98: 38-42.

101. Mandal S, Suh E, Davies M, Smith I, Maher TM, Elliott MW, Davidson AC, Hart N. (2013) Provision of home mechanical ventilation and sleep services for England survey. Thorax, 68: 880-881.

102. Bach JR, Goncalves MR, Hamdani I, Winck JC. (2010) Extubation of patients with neuromuscular weakness: a new management paradigm. Chest, 137: 1033-1039.

103. Duiverman ML, Bladder G, Meinesz AF, Wijkstra PJ. (2006) Home mechanical ventilatory support in patients with restrictive ventilatory disorders: a 48-year experience. Respir Med, 100: 56-65.

104. Masa JF, Pepin JL, Borel JC, Mokhlesi B, Murphy PB, Sanchez-Quiroga MA. (2019) Obesity hypoventilation syndrome. Eur Respir Rev, 28.

105. Kotanen P, Kainu A, Brander P, Bergman P, Lehtomäki A, Kreivi HR. (2020) Validation of the Finnish severe respiratory insufficiency questionnaire. Clin Respir J, 14: 659-666.

106. Marchese S, Lo Coco D, Lo Coco A. (2008) Outcome and attitudes toward home tracheostomy ventilation of consecutive patients: a 10-year experience. Respir Med, 102: 430-436.

107. Márquez-Martín E, Ruiz FO, Ramos PC, López-Campos JL, Azcona BV, Cortés EB. (2014) Randomized trial of non-invasive ventilation combined with exercise

training in patients with chronic hypercapnic failure due to chronic obstructive pulmonary disease. Respir Med, 108: 1741-1751.

108. Markstrom A, Sundell K, Lysdahl M, Andersson G, Schedin U, Klang B. (2002) Quality-of-life evaluation of patients with neuromuscular and skeletal diseases treated with noninvasive and invasive home mechanical ventilation. Chest, 122: 1695-1700.

109. Rabkin J, Ogino M, Goetz R, McElhiney M, Hupf J, Heitzman D, Heiman-Patterson T, Miller R, Katz J, Lomen-Hoerth C, Imai T, Atsuta N, Morita M, Tateishi T, Matsumura T, Mitsumoto H. (2014) Japanese and American ALS patient preferences regarding TIV (tracheostomy with invasive ventilation): a cross-national survey. Amyotroph Lateral Scler Frontotemporal Degener, 15: 185-191.

110. Ankjaergaard KL, Tonnesen P, Laursen LC, Hansen EF, Andreassen HF, Wilcke JT. (2016) Home Non Invasive Ventilation (NIV) treatment for COPD patients with a history of NIV-treated exacerbation; a randomized, controlled, multi-center study. BMC Pulm Med, 16: 32.

111. Dretzke J, Moore D, Dave C, Mukherjee R, Price MJ, Bayliss S, Wu X, Jordan RE, Turner AM. (2016) The effect of domiciliary noninvasive ventilation on clinical outcomes in stable and recently hospitalized patients with COPD: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis, 11: 2269-2286.

112. Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, Buyse B, De Backer W, Eckert DJ, Grote L, Hagmeyer L, Hedner J, Jennum P, La Rovere MT, Miltz C, McNicholas WT, Montserrat J, Naughton M, Pepin JL, Pevernagie D, Sanner B, Testelmans D, Tonia T, Vrijsen B, Wijkstra P, Levy P. (2017) Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J, 49.

113. Piper A. (2016) Obesity Hypoventilation Syndrome: Weighing in on Therapy Options. Chest, 149: 856-868.

114. Ng L, Khan F, Young CA, Galea M. (2017) Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev, 1: Cd011776.

9. List of publications

9.1 Publications included in the thesis

Valkó L, Baglyas S, Gál J, Lorx A. (2018) National survey: current prevalence and characteristics of home mechanical ventilation in Hungary. BMC Pulm Med, 18: 190. **IF: 2.184**

Valkó L, Baglyas S, Kunos L, Terray-Horváth A, Lorx A, Gál J, Windisch W. (2020) Validation of the Hungarian version of the SRI Questionnaire. BMC Pulm Med, 20: 130. **IF: 2.813**

Lorx A, **Valkó L**, Gál J. (2019) Az otthoni lélegeztetés helyzete Magyarországon. Med Thorac, 72: 119-125.

Valkó L, Baglyas S, Gyarmathy VA, Gal J, Lorx A. (2020) Home mechanical ventilation: quality of life patterns after six months of treatment. BMC Pulm Med, 20: 221. **IF: 2.813**

9.2 Other publications by the author

Sugár I, Vörös A, Diczházi C, Barabás L**, Valkó L**, Ondrejka P. (2010) Mediastinalis és retroperitonealis bronchogen cysták sikeresen operált esetei és tanulságaik. Magy Seb, 63(4): 168–171.

Lorx A, **Valkó L**, Pénzes I. Anaesthesia for interventional bronchoscopy. In: Strausz, János; Bollinger, Chris T. (editors), Interventional pulmonology. European Respiratory Society Journals Ltd, Sheffield, 2010: 18-32.

Iványi Z, **Valkó L**, Hauser B, Kristóf K, Hargitai Z, Lorx A, Madách K, Gál J. (2010) Experiences of the Department of Anesthesiology and Intensive Therapy of Semmelweis University during the 2009 pandemic H1N1 (pH1N1) influenza outbreak. Interv Med Appl Sci, 2(2), 59–65.

Lorx A, Valkó L. COPD. In: Molnár Z, Bede A (editors), A lélegeztetés gyakorlata. Medicina Könyvkiadó Zrt, Budapest, 2016: 287–298.

Valkó L, Lorx A. Restriktív tüdőbetegség – scoliosisos beteg lélegeztetése. In: Molnár Zs, Bede A (editors), A lélegeztetés gyakorlata. Medicina Könyvkiadó Zrt, Budapest, 2016: 345–350.

Valkó L, Baglyas S, Tamáska E, Lorx A, Gál J. (2018). Nem invazív lélegeztetés alkalmazása kritikus állapotú betegekben. Orv hetil, 159(45): 1831–1837. **IF: 0.564**

Valkó L, Lorx A, Baglyas S, Vincze K, Müller V, Gál J. (2019). Idiopathias pulmonalis fibrosis intenzív terápiás és aneszteziológiai vonatkozásai. Med thorac, 72(5): 268–274.

Valkó L, Csósza G, Mérei A, Mühl D, Faludi R, Karlócai K, Lorx A, Gál J. (2019). Management of acutely decompensated chronic thromboembolic pulmonary hypertension in late pregnancy: a case report. BMC Pregnancy Childbirth, 19(1): 365. **IF: 2.239**

Csósza G, **Valkó L**, Baglyas S, Losonczy G, Lorx A, Gál J, Karlócai K. (2019). Mellkasdeformitás okozta pulmonalis hipertónia oki kezelése. Card Hung, 49(3): 184-187.

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