Thesis for doctoral degree (Ph.D.)
2018

Disability and health-related quality of life in patients with amyotrophic lateral sclerosis, and caregiving experience from the perspective of next of kin

Petter Sandstedt

Karolinska Institutet

From the Department of Neurobiology, Care Sciences
and Society, Division of Physiotherapy
Karolinska Institutet, Stockholm, Sweden

DISABILITY AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS, AND CAREGIVING EXPERIENCE FROM THE PERSPECTIVE OF NEXT OF KIN

Petter Sandstedt

Karolinska Institutet

Stockholm 2018

Published by Karolinska Institutet.
Printed by Arkitektkopia AB, 2018

ISBN 978-91-7831-254-2

Disability and health-related quality of life in patients with amyotrophic lateral sclerosis, and caregiving experience from the perspective of next of kin

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Petter Sandstedt

Principal Supervisor:

PhD Marie Kierkegaard
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Physiotherapy

Co-supervisors:

Professor Lotta Widén Holmqvist
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Physiotherapy

Associate professor
Charlotte Ytterberg
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Physiotherapy

Associate professor
Sverker Johansson
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Physiotherapy

Opponent:

Professor Pernilla Åsenlöf
Uppsala University
Department of Neuroscience
Physiotherapy

Examination Board:

Associate professor Göran Solders
Karolinska Institutet
Department of Clinical Neuroscience
Division of Neurology

Associate professor Anneli Ozanne
University of Gothenburg
Institute of Health and Care Sciences

Professor Karin Nordin
Uppsala University
Department of Public Health and
Caring Sciences

ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a degenerative motor neuron disease leading to progressive muscle weakness resulting in respiratory failure and death. The average survival time from diagnosis is two to three years. The use of tracheostomy invasive ventilation (TIV) may, however, prolong life by several years. ALS has a major impact on the lives of both the patients and their next of kin/informal caregivers. There is no cure for ALS and the cornerstone of management is symptomatic treatment to alleviate symptoms and improve health-related quality of life (HRQL).

Aims: The aims of this thesis were to explore aspects of disability, contextual factors and HRQL in patients with ALS, and to explore the caregiving experiences and HRQL in their next of kin/informal caregivers. In addition, this thesis aimed to investigate the experiences of being next of kin to patients with ALS undergoing TIV.

Material and methods: Sixty patients with ALS were included at baseline (Study I) and followed-up every 6 months for three years, unless participants had deceased or declined participation (Study II). Data on disability, contextual factors and HRQL were collected from medical records, and by study-specific protocols and standardized questionnaires administrated during home visits. Forty-nine next of kin/informal caregivers to patients with ALS were included to explore caregiving experience, HRQL and life satisfaction (Study III). Data were collected by study-specific protocols and standardized questionnaires. Multivariate regression analyses were used to explore factors associated with patients' HRQL (Study I) and informal caregivers' HRQL and life satisfaction (Study III). Descriptive statistics and correlation analyses were used to present and explore data on disability and contextual factors over three years (Study II). Eight next of kin were included to investigate the experiences of being next of kin to patients with ALS undergoing TIV (Study IV). Semi-structured face-to-face interviews were conducted and analyzed with qualitative content analysis with an inductive approach.

Results: Regardless of disease severity, fatigue, anxiety, depression and pain were commonly and concurrently present in patients with ALS. Furthermore, activity limitations and participation restrictions were frequently reported. The health condition, i.e. high disease severity; the impairments fatigue, anxiety and/or depression; participation restrictions, i.e. low frequency of social and life style activities; and the contextual factors weak coping capacity and mechanical ventilator use (non-invasive and TIV) were associated with worse HRQL in patients with ALS. Both positive and negative caregiver experiences were reported by the informal caregivers. Positive experience and older age in the informal caregiver were

associated with better HRQL, while negative caregiving experiences and anxiety and/or depression in the patient with ALS were associated with worse HRQL in informal caregivers. As for life satisfaction, older age in the informal caregiver and not cohabiting with the patient were associated with being satisfied with "life as a whole". Being next of kin to patients with ALS undergoing TIV involved experiences of a turbulent care process aiming to extend life, a struggle to cope with the strains of everyday life, and of conflicting roles as next of kin and carer.

Conclusion: Patients with ALS need, throughout the course of the disease, to be regularly screened for commonly present impairments, activity limitations, participation restrictions and perceived HRQL, so that person-centred care can be applied at the right time. There is a need to consider the individual caregiver's experience when planning services, care and support. Furthermore, it is important to adopt person-centred care, not only for patients but also for their informal caregivers, as factors related to both parties were associated with the informal caregivers' HRQL and life satisfaction. It is important to involve next of kin to patients with ALS undergoing TIV throughout the whole care process, and to consider the specific needs of the next of kin. Furthermore, specific support interventions for next of kin to facilitate their everyday life and to ease their burden need to be developed.

SAMMANFATTNING

Bakgrund: Amyotrofisk lateral skleros (ALS) är en degenerativ motorneuronsjukdom som leder till progressiv muskelsvaghet vilket resulterar i respiratorisk svikt och att den drabbade avlider. Den genomsnittliga överlevnadstiden efter diagnos är två till tre år. Genom invasiv ventilation via trakeostomi (TIV) kan dock livet förlängas med flera år. ALS har en stor inverkan på livet för både patienterna och deras närstående/informella vårdgivare. Det finns inget botemedel mot ALS och det grundläggande för hälso- och sjukvården är symptomatisk behandling för att lindra symptom och förbättra hälso-relaterad livskvalitet (HRQL).

Syfte: Det övergripande syftet med avhandlingen var att utforska funktionshinder, kontextuella faktorer och HRQL hos patienter med ALS, och att utforska vårdgivarerfarenheter och HRQL hos deras närstående/informella vårdgivare. Dessutom var syftet att undersöka erfarenheter av att vara närstående till patienter med ALS som har TIV.

Material och metod: Sextio patienter med ALS inkluderades vid baslinjen (Studie I) och följdes sedan var sjätte månad under tre år, med undantag för de patienter som hade avlidit eller avböjt deltagande i studien (Studie II). Data gällande funktionshinder, kontextuella faktorer och HRQL samlades in från medicinska journaler, studiespecifika protokoll och standardiserade frågeformulär vid hembesök. Fyrtionio närstående/informella vårdgivare till patienter med ALS inkluderades för att utforska vårdgivarerfarenheter, HRQL och livstillfredsställelse (Studie III). Data samlades in med studiespecifika protokoll och standardiserade frågeformulär. Multivariata regressionsanalyser användes för att utforska faktorer som hade samband med patienternas HRQL (Studie I) och informella vårdgivares HRQL och livstillfredsställelse (Studie III). Beskrivande statistik och korrelationsanalyser användes för att presentera och utforska data om funktionshinder och kontextuella faktorer (Studie II). Åtta närstående inkluderades för att undersöka erfarenheterna av att vara närstående till patienter med ALS som har TIV (Studie IV). Semi-strukturerade intervjuer genomfördes och analyserades med kvalitativ innehållsanalys med induktiv ansats.

Resultat: Oavsett sjukdomsgrad så var fatigue, ångest, depression och smärta vanligt och samtidigt förekommande hos patienter med ALS. Dessutom var aktivitetsbegränsningar och delaktighetsinskränkningar frekvent förekommande. Hälsotillståndet, d.v.s. hög sjukdomsgrad; funktionsnedsättningarna fatigue, ångest och/eller depression; delatighetsinskränkning, d.v.s. låg frekvens av sociala och livsstilsrelaterade aktiviteter; och de kontextuella faktorerna svag copingförmåga och mekanisk ventilation (icke-invasiv och TIV) hade ett samband med sämre HRQL hos patienter med ALS. Både positiva och negativa vårdgivarerfarenheter

rapporterades från informella vårdgivare. Positiva erfarenheter och högre ålder hos den informella vårdgivaren hade ett samband med bättre livskvalitet, medan negativa erfarenheter och ångest och/eller depression hos patienten med ALS hade ett samband med sämre HRQL. Gällande livstillfredsställelse, så hade högre ålder hos den informella vårdgivaren och att inte sammanbo med patienten ett samband med att vara tillfredsställd med ”livet som helhet”. Att vara närstående till patienter med ALS som har TIV innefattar erfarenheter av en turbulent vårdprocess med syfte att förlänga livet, att kämpa för att hantera ett ansträngt vardagsliv och konflikten i rollerna att vara både närstående och vårdare.

Konklusion: Patienter med ALS behöver, under hela sjukdomsförloppet, regelbundet undersökas för vanligt förekommande funktionsnedsättningar, aktivitetsbegränsningar, delatighetsinskränkningar och upplevd HRQL så att personcentrerad vård kan implementeras vid rätt tidpunkt. Den informella vårdgivarens erfarenheter behöver tas i beaktande när service, vård och stöd planeras. Dessutom är det viktigt att anpassa den personcentrerade vården, inte bara riktat till patienter utan även till deras informella vårdgivare, eftersom faktorer relaterade till båda parter hade ett samband med informella vårdgivares HRQL och livstillfredsställelse. Det är viktigt att närstående till patienter med ALS som har TIV är involverade genom hela vårdprocessen och att deras specifika behov beaktas. Vidare behöver särskilda stödinsatser utvecklas för att underlätta närståendes vardagsliv och minska deras börda.

LIST OF SCIENTIFIC PAPERS

I. Sandstedt P, Johansson S, Ytterberg C, Ingre C, Widén Holmqvist L, Kierkegaard M. Predictors of health-related quality of life in people with amyotrophic lateral sclerosis. J Neurol Sci. 2016;370:269-273.

II. Sandstedt P, Littorin S, Johansson S, Gottberg K, Ytterberg C, Kierkegaard M. Disability and contextual factors in patients with amyotrophic lateral sclerosis – a three-year observational study. J Neuromuscul Dis. 2018;5:439-449.

III. Sandstedt P, Littorin S, Cröde Widsell G, Johansson S, Gottberg K, Ytterberg C, Olsson M, Widén Holmqvist L, Kierkegaard M. Caregiver experience, health-related quality of life and life satisfaction among informal caregivers to patients with amyotrophic lateral sclerosis: A cross-sectional study. J Clin Nurs. 2018;27:4321-4330.

IV. Ytterberg C, Gottberg K, Sandstedt P, Johansson S, Kierkegaard M. Experiences of next of kin to patients with amyotrophic lateral sclerosis requiring invasive ventilation via tracheostomy. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of daily living
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	ALS Functioning Rating Scale-Revised
BMI	Body mass index
CIS	Checklist Individual Strength
CRA	Caregiver Reaction Assessment
EQ VAS	EuroQol Visual Analogue Scale
FAI	Frenchay Activities Index
HADS	Hospital Anxiety and Depression Scale
HRQL	Health-related quality of life
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile range
Katz I-ADL	Katz Instrumental-ADL index
Katz P-ADL	Katz Personal-ADL index
LiSat-11	Life Satisfaction Checklist-11
MoCA	Montreal Cognitive Assessment
NRS	Numeric Rating Scale
QoL	Quality of life
SD	Standard deviation
SF-36	Short-Form (36) Health Survey
SIP	Sickness Impact Profile
SOC	Sense of Coherence Scale
TIV	Tracheostomy invasive ventilation
WHO	World Health Organization

1 INTRODUCTION

1.1 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is an adult-onset motor neuron disease that primarily affects upper and lower motor neurons in the motor cortex, brainstem and spinal cord, leading to progressive weakness and wasting in voluntary muscles, and eventually resulting in respiratory failure and death. Cognitive and behavioural impairments are today considered to be present in ALS (1), and there is, reportedly, an overlap between ALS and frontotemporal dementia (2, 3). Other examples of motor neuron diseases related to ALS are primary lateral sclerosis with pure involvement of upper motor neurons and progressive muscle atrophy with pure lower motor neuron involvement (2).

The incidence rate of ALS in European populations is approximately 3 per 100,000 person-years (4, 5). The disease is more common in men than in women, and the reported male and female incidence is 3.1 and 2.2 per 100,000 person-years, respectively (6). Most cases of ALS are sporadic, and around 5-10% are familial (hereditary) (2). Peak age at onset is 58-63 years for sporadic ALS and 47-52 years for familial (7). Occurrence of the disease declines rapidly after 80 years of age (6).

There is no biological marker for ALS, and diagnosis is based on the revised El Escorial criteria (8). These criteria require evidence of both upper and lower motor neuron degeneration in combination with a progressive spread of symptoms and signs in the absence of electrophysiological, pathological and neuroimaging evidence of other disease processes (8). ALS can, based on levels of certainty, be categorized as definite, probable, possible or suspected ALS (8).

Depending on the site of onset, ALS is often classified as spinal (limb muscles) or bulbar (speech and swallowing muscles) form. Most common is the spinal form, and spinal onset is reported in 80% of patients (9). The average survival time from diagnosis is two to three years, although some patients with ALS will live for decades (10). Younger age at onset (10), male sex and spinal onset have been found to be predictors of longer survival (9, 10).

There is a high number of different mutations and variable penetrance of genes causing familial ALS (2). Most common are mutations in the C9orf72 (11) and SOD1 (12) genes. The causes of sporadic ALS are of unknown aetiology. Suggested potential risk factors for ALS are the environmental factor smoking and the personal factors older age and male sex (13).

1.2 International classification of functioning, disability and health

The International Classification of Functioning, Disability and Health (ICF) (14) is used in the present thesis as a conceptual framework for describing and exploring functioning, disability and contextual factors in patients with ALS and their next of kin. The interactions between the components of the ICF are described in Figure 1 (14).

The ICF was developed by the World Health Organization (WHO) and provides a framework for the scientific structure of functioning, disability and health in individuals or groups of people. The ICF provides a common language for describing health and enables comparisons of data in a scientific context. In the ICF, *health condition* is an umbrella term for a disease (such as ALS), disorder, injury or trauma.

The ICF classifies information in two parts, each containing two components. The first part pertains to functioning and disability. *Functioning* is an overarching term that refers to body functions and body structures, as well as to activities and participation. The term *disability* describes impairments in body functions and body structures, as well as limitations in activities and restrictions in participation.

The second part addresses *contextual factors*, including distinctions between personal and environmental factors. Personal factors are individual characteristics, such as age, sex, education and ability to cope. Personal factors are not classified in the ICF. Environmental factors are aspects of the physical, social and attitudinal environment in which a person lives. These factors are outside the person and can either facilitate or hinder functioning and disability (14). Products and technology, e.g. medicines and aids for use in daily living, mobility and communication; support and relationships, e.g. from family, personal care providers, personal assistants and health professionals; and services, systems and policies are all examples of environmental factors.

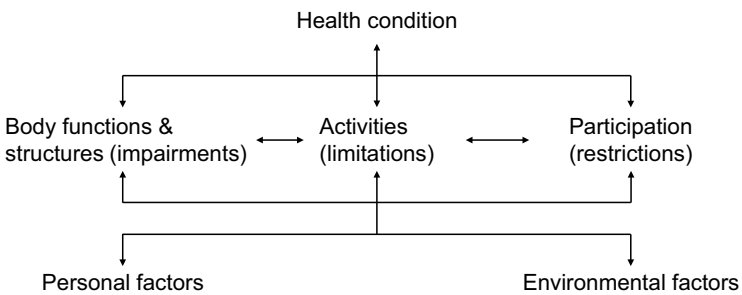

Figure 1. *Interactions between components of the ICF.*

1.3 Disability in ALS

1.3.1 Impairments in body functions and structures

Common impairments in patients with ALS due to the process of upper motor neuron degeneration are spasticity, progressive weakness and brisk tendon reflexes in limbs (2). Degeneration of lower motor neuron typically presents signs of fasciculation, wasting and progressive weakness in muscles (2). Bulbar motor neuron degeneration causes dysarthria (15) and dysphagia (16). The latter leads to weight loss and malnutrition. Other reported impairments are thickened saliva and hypersalivation (2).

The earlier view of ALS as a pure motor neuron disease has been challenged, as studies have shown that approximately 35% of ALS patients have cognitive impairment and an additional 15% fulfil the criteria for frontotemporal dementia (17, 18). Reported behavioural changes are apathy (1, 19, 20), irritability (19), loss of empathy, perseveration and disinhibition (1).

Fatigue (21, 22), anxiety (23, 24), depression (22, 24) and pain (25, 26) are other reported impairments in patients with ALS. Fatigue has been found in approximately 40% to 50% of patients (21, 22) and is reported to be associated with disease severity (21, 22). Anxiety has been reported in 19% to 35% of patients (27, 28) and depression in 22% to 36% (22, 28). Patients with ALS have scored worse than the general population on anxiety and depression measures (29); however, neither anxiety nor depression have been found to be associated with disease severity (23). Approximately 40% to 70% of patients with ALS experience pain (25, 30, 31), which is a greater share than has been found for compared controls (25, 31). The variation in reported pain frequency is probably due to differences in studied patient groups and in the methods used. The relation between pain and disease severity is contradictory, as both an association and a lack of association have been reported (25, 26). The variations in reported frequencies of the above-mentioned impairments might be due to differences in small and heterogeneous samples and in the methods used.

1.3.2 Activity limitations and participation restrictions

A loss of independence in activities of daily living (ADL) is reported in patients with ALS, for example, in eating and drinking, toileting, dressing, cleaning or shopping (32). Studies have reported that both activity limitations and participation restrictions, e.g. in social and lifestyle activities such as domestic chores, work, leisure and outdoor activities, are common (33, 34). Communication limitations due to dysarthria and various neuropsychiatric disturbances are reported in patients with ALS (35). Speech intelligibility is reported to decline over time and is associated with a limitation in communication effectiveness (36).

1.4 Contextual factors in ALS

1.4.1 Personal factors

Personal factors such as age, sex and body mass index (BMI) are important to consider when describing ALS. Older age, male sex and a family history of ALS (37) are risk factors for ALS. Greater physical fitness, but not muscle strength, at age 18 years is also associated with a higher risk of ALS (38). Furthermore, low BMI and high BMI reduction rates are reported to be associated with shorter survival (39-41).

An important personal factor is the ability to handle or cope with stressful situations in life (42). Individuals with a poor ability to cope when living with a disease may experience increased disability (43). Studies report that patients with ALS use both problem-focused and emotion-focused strategies and that coping strategies change during the course of the disease (44, 45). Sense of coherence, as described by Antonovsky (42), is one way of looking at coping ability and has been used in a number of studies of people with chronic conditions (46-49). Sense of coherence describes whether individuals see their existence as meaningful, comprehensible and manageable, and individuals with a stronger sense of coherence are more likely to cope with stressful situations (42). Studies on coping ability as measured with sense of coherence in patients with ALS have not yet been published.

1.4.2 Environmental factors

Environmental factors can be either facilitators or barriers in ALS management. Medical treatment, aids and services are described as potential facilitators (2), while lack of the above mentioned may be considered potential barriers.

Riluzole is today the only registered disease modifying therapy in Sweden and is reported to increase the median survival time by two to three months (50). Medical symptomatic treatments for anxiety, depression, insomnia, fatigue, cramps, spasticity and hypersalivation are recommended (51). To facilitate mobility, including walking and moving around, orthoses and aids such as walking sticks and wheelchairs are recommended, as are aids to facilitate ADL, communication, ventilation and nutrition (2).

Specialized multidisciplinary care with collaboration between various health professionals is recommended for patients with ALS (52) and is usually provided for patients in Sweden. Besides improving health-related quality of life (HRQL) (52), multidisciplinary care can reduce the number of hospital admissions and days in hospital (53), and prolong survival (54).

To reduce impact of disability, regardless of illness, all Swedish citizens have the opportunity to apply for transportation services and for home care services and personal assistance.

Respiratory insufficiency is to be treated through health care (51), and, in addition to physiotherapy treatment, mechanical ventilation is used. The primary option is commonly non-invasive ventilation, i.e. treatment by air pressure thru a fascial- or nasal mask (51). Non-invasive ventilation is found to alleviate symptoms of respiratory insufficiency and, to some extent, increase survival (55-58). Less common is tracheostomy invasive ventilation (TIV), i.e. treatment by air pressure through a tracheostomy tube. TIV is currently the only way to prolong life by years in patients with ALS (59, 60). The disease will, however, still progress with the risk of the patient developing a "locked-in" state (51). After receiving TIV, most patients live in their home (59, 61).

Treatment with TIV varies between countries, reportedly from 0-11% in Europe and the USA (59, 62, 63) to 30% in Japan (64). Initiation of TIV is influenced by uncertainties of its impact on patients' quality of life (QoL) (51), the economic means to maintain the treatment (64, 65), and the attitudes of physicians (66), patients (67) and their next of kin (68). Since 2010, the Karolinska University Hospital clinical guidelines state that TIV should be considered when non-invasive ventilation is insufficient. Approximately 8% of patients with ALS in Stockholm County undergo TIV today (69).

1.5 Next of kin to patients with ALS

In addition to the support provided by society, there is an increased need for informal care, i.e. unpaid care, during the course of the disease (32). Internationally, it has been reported that next of kin to patients with ALS assume a great responsibility for this informal care (70, 71), and both the amount of time spent on informal care and the burden of caregiving are reported to be substantial (72-74). Studies show that next of kin spend approximately 50-60 hours per week on caregiving (70, 74) and that time spent on informal care is associated with high self-reported caregiver burden (70). Reported factors modulating caregiver burden are the caregiver's age, employment status and social support (70); and the patients' cognitive impairments (73) and behavioural changes (73, 75). Caregiving is described as a multi-faceted construct with both positive and negative experiences (76), though only a few studies explore both the positive and negative sides of caregiving in next of kin to patients with ALS (77, 78).

The experiences of next of kin to patients with ALS undergoing non-invasive ventilation are found to be both positive and negative (79, 80), e.g. feelings of stress and relief, which alternate during the course of the disease (81). It is also reported that as the ALS disease progresses, it causes an increased emotional burden on the next of kin (70, 80).

Big differences are reported in studies (68, 82) on the attitudes next of kin hold toward TIV as a treatment option for family members with ALS. It is reported that 5% to 53% of next of kin are in favour of and that 10% to 86% are opposed to TIV as a treatment option (68, 82). The results are based on investigations conducted in the USA (68, 82) and in Japan (68), and show that a much more positive attitude towards TIV is held by next of kin from Japan than from in the USA. Different cultures and different attitudes among health care professionals, e.g. different ways of presenting opportunities to receive TIV, may have influenced the discrepancy of the results. Important factors contributing to whether next of kin are in favour of TIV are that the use gives hope for the future and that the family member with ALS can maintain their QoL. Next of kin to patients with ALS using TIV express that they must spend more time on care than they wish to, and that they experience health problems and are unable to hold salaried jobs (83). Also reported are feelings of having to give up their own lives and loss of control over their own life situations (84).

1.6 HRQL and life satisfaction

Even though the ICF provides a framework for obtaining a comprehensive view of an individual's functioning, disability and health, it lacks a reference to QoL, which is needed to make a complete description of an individual's health status. QoL is described as a multi-dimensional construct (85), but there is little consensus in the literature on what should be included in the construct. The WHO defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (86). Further, QoL is described as a broad ranging construct affecting the psychological states, physical health, social relations and beliefs of individuals and their relationship to prominent features of the environment in complex structures (86).

The concept of HRQL is often used in medicine to distinguish between QoL in a more general sense and aspects of QoL that are concerned with functioning and well-being in relation to illness and its treatment (87). Questionnaires on HRQL generally reflect the multi-dimensional construct of QoL and focus on items covering physical, emotional (mental) and social functioning, as well as general health (88).

Life satisfaction is described as a measure of happiness (89). By mobilizing resources within an individual, that individual may achieve optimal life satisfaction (90). Life satisfaction is generally agreed to be part of the multi-dimensional construct of QoL (88). In this thesis, life satisfaction is used as a complement to HRQL in next of kin to patients with ALS to cover aspects other than HRQL.

1.6.1 HRQL in patients with ALS

Patients with ALS rate their HRQL worse than a general population (29), and it is reported that patients' HRQL become worse with increasing disease severity (91). The physical dimension of HRQL is found to deteriorate during the course of the disease while the mental dimension remains stable (23, 92). Impairments like fatigue (93), anxiety (94), depression (93, 95, 96) and pain (97) are reported to worsen HRQL. A strong ability to cope when living with a deadly disease like ALS (98, 99) is associated with better HRQL. Mechanical ventilation is found to be associated with both better and worse HRQL (100-102).

1.6.2 HRQL in next of kin

It is important to consider the HRQL of the next of kin, as they often act as informal caregivers to family members with ALS as they become weaker, more dependent, and in need of increased care as the disease progresses (103). There is evidence that HRQL is negatively impacted in next of kin to patients with ALS (104, 105). Negative experiences of informal caregiving such as psychological distress and impact on relations are found to be associated with worse HRQL in next of kin (74). Others report that more time spent on informal caregiving (106), younger age, female gender (104) and presence of depression (75) among caregivers are factors associated with worse HRQL. In addition, factors related to patients with ALS are also associated with worse HRQL in next of kin, e.g. disease severity (94), inability to communicate (107), changes in behaviour (75) and TIV use (83, 102), although the latter is less impacted if the patient has formal caregiving (102).

Life satisfaction has been reported to be associated with both positive and negative caregiving experiences in informal caregivers to patients with stroke (108, 109). There are, however, few studies on life satisfaction in informal caregivers to patients with ALS (94), and we lack knowledge of factors associated with life satisfaction among informal caregivers to patients with ALS.

1.7 Rationale for the thesis

Although disability and contextual factors have previously been described in patients with ALS (21-23), few studies give a comprehensive view of concurrent body-function impairments, as well as activity limitations and participation

restrictions over time. There is no cure for ALS, and the cornerstone of management is symptomatic treatment to alleviate symptoms and improve HRQL. Thus, it is important to investigate factors impacting patients' HRQL, as some might be amenable to health-care interventions.

ALS is a disease that not only affects patients but also their next of kin, who often become informal caregivers. It is therefore important to investigate their experiences in caregiving, and factors related to their HRQL and life satisfaction, so that appropriate measures can be taken to develop support and care.

The average survival time after diagnosis of ALS is two to three years. The use of TIV may, however, prolong life by several years, although the disease will still progress with a risk of the patient developing a "locked-in" state. As most patients live in their homes after receiving TIV, the life of next of kin is likely imposed upon. Studies investigating the experiences of next of kin to patients with ALS undergoing TIV are scarce (83, 84). Thus, there is an urgent need for such studies.

In summary, the knowledge gaps described above need to be addressed so that health care can develop interventions to meet the needs of patients with ALS and their next of kin.

2 AIMS

The overall aim of this thesis were to explore aspects of disability, contextual factors and HRQL in patients with ALS, and to investigate the experiences and HRQL in their next of kin.

The specific aims were:

1. To describe and explore the impact of disease severity, fatigue, anxiety, depression, frequency of social and lifestyle activities, coping capacity and mechanical ventilator use on HRQL in persons with ALS (Study I).
2. To describe and explore disease severity and impairments, activity limitations, participation restrictions and contextual factors in patients with ALS over time. In particular, to explore concurrent presence of cognitive impairment, fatigue, anxiety, depression and pain, and whether these impairments were related to disease severity in patients with ALS (Study II).
3. To describe caregiver experience, HRQL and life satisfaction among informal caregivers to patients with ALS, and to explore factors associated with caregivers' HRQL and life satisfaction (Study III).
4. To investigate the experience of being next of kin to patients with ALS undergoing TIV (Study IV).

3 MATERIAL AND METHODS

3.1 Study designs

Studies I and III used cross-sectional designs, Study II a prospective observational design over three years, and Study IV a qualitative design.

3.2 Participants

3.2.1 Studies I and II

Figure 2 presents a flow chart of patient inclusion and retention in Studies I and II. In September 2012, 102 patients with ALS were identified through the Department of Neurology at the Karolinska University Hospital in Stockholm, Sweden. Inclusion criteria were an ALS diagnosis according to the El Escorial criteria; an age of over 18 years; and the ability to understand Swedish. Sixty patients were enrolled in Study I, and they were contacted six months later and invited to participate in a follow-up study. The process of contacting the patients with ALS who were still included in the subject pool was then repeated prior to every additional six-month follow-up for two and a half years, i.e. in total, data was collected for three years, at baseline (T1) and at six follow-ups (T2 to T7).

3.2.2 Study III

Participants in Study III were identified by patients with ALS included in Study I. Of a total of 58 next of kin, 9 declined participation; thus, 49 were included in Study III.

3.2.3 Study IV

Next of kin participating in Study IV were recruited via patients with ALS who used TIV and were registered at an ALS clinic in Sweden. A total of 12 patients were identified in May 2017, and all but one were regarded suitable for contacting according to their neurologist. Six of the eleven patients who received information about the study identified one or more next of kin who were able to communicate in Swedish to be approached by the researchers. Included in Study IV were eight next of kin, three of whom were related to the same patient.

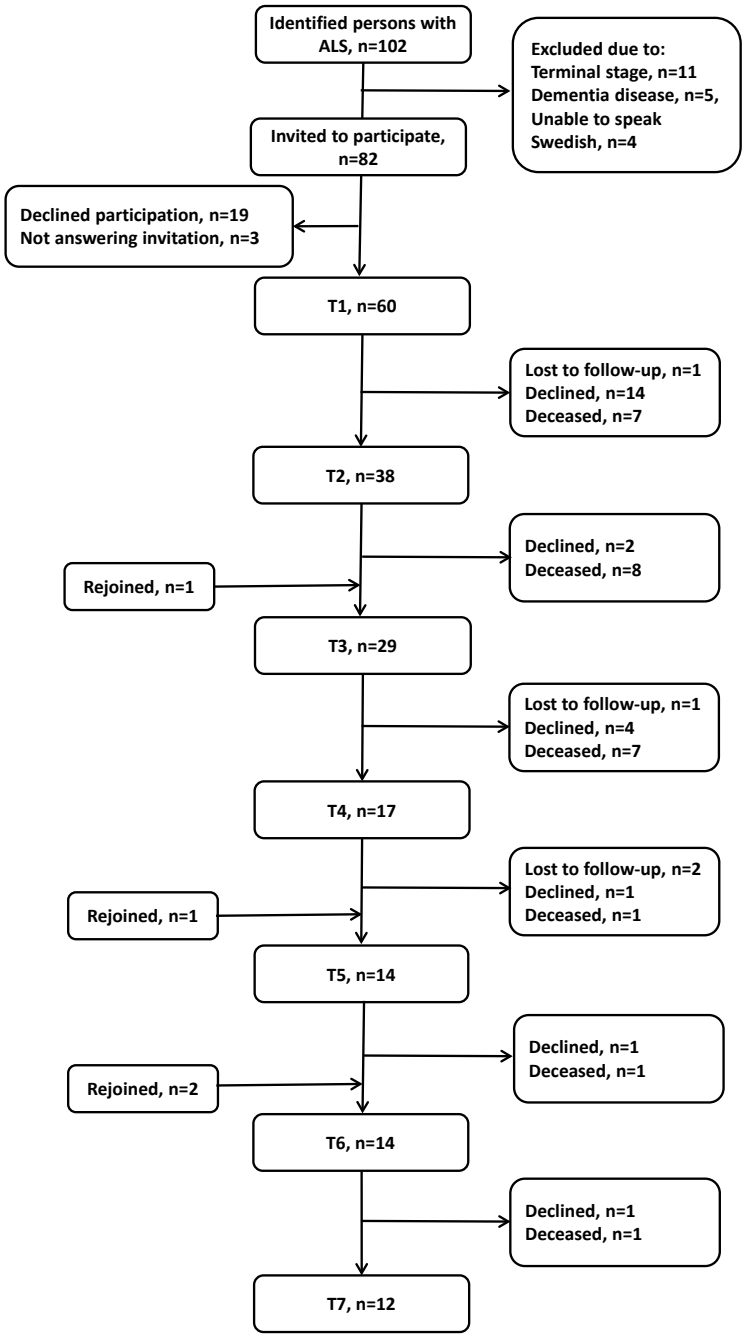

Figure 2. *A flowchart of the inclusion and retention of patients with ALS during the three-year study period.*

3.3 Procedures

Data collection in Studies I and II were performed during home visits to patients with ALS by one of three physiotherapists or an occupational therapist who guided the patient through the data collection. The duration of each home visit was in average 2.5 hours, and extra visits were offered if needed. Data collection comprised study-specific protocols administered as interviews and self-reported standardized questionnaires in a standardized order. Patients could either fill out the questionnaires themselves or get help from the data collector.

Data for Study III were collected by study-specific protocols and self-reported standardized questionnaires filled out by the next of kin, either during the home visits to the patient with ALS or later, i.e. they received the protocols and questionnaires and returned them to the data collector by post.

Data for Study IV were collected through face-to-face interviews conducted by either a pair of registered physiotherapists or a registered physiotherapist and a registered nurse. Interviews were performed in a place chosen by the next of kin, most often in their home.

3.4 Measures (Studies I, II and III)

Medical records, study-specific protocols and self-reported standardized questionnaires were used to collect information from patients with ALS and their next of kin. See Table 1 for an overview of variables from medical records and study-specific protocols, and Table 2 for an overview of variables and self-reported standardized questionnaires that were used.

3.4.1 The ALS Functioning Rating Scale-Revised

The ALS Functioning Rating Scale-Revised (ALSFRS-R) was used as a proxy for disease severity in patients with ALS (110). The ALSFRS-R concerns impairments in gross motor tasks, fine motor tasks, bulbar functions and respiratory function. The scale consists of 12 items, each graded from 0 to 4. A total score ranging from 0 to 48 is calculated, and lower scores indicate more disease severity. The ALSFRS-R is considered valid (110) and reliable (111, 112).

In Study I, an ALSFRS-R score of ≤ 29 (median score) was used as the cut-off for severe disease. In Study II, disease severity was categorized as mild (ALSFRS-R score 37-48), moderate (ALSFRS-R score 25-36), and severe (ALSFRS-R score 0-24), as previously suggested (113). In Study III, an ALSFRS-R score of ≤ 24 (lower half of the scale) was used as cut-off for severe disease.

Table 1. Overview of variables from medical records and study-specific protocols in Studies I, II and III.

Variable	Study		
	I	II	III
Medical records			
Site of onset	X	X	
Time since diagnosis	X	X	
Medications	X	X	
Study-specific protocol			
Age	X	X	X
Sex	X	X	X
Education level	X	X	X
Living conditions	X	X	
Cohabiting with patient			X
Civil status	X		
Relation to patient			X
Work status	X	X	X
Changed working time			X
Informal caregiving (hours/week)			X
Ventilation	X	X	
Gastrostomy	X	X	
Aid for			
Mobility	X	X	X
Activities of daily living	X	X	X
Communication	X	X	X
Home adaptations	X	X	X
Home care	X	X	X
Personal assistance	X	X	X
Transport service	X	X	

Table2. Overview of variables and self-reported standardized questionnaires in Studies I, II and III.

Variable	Self-reported questionnaire	Study		
		I	II	III
Disease severity	ALS Functioning Rating Scale-Revised	X	X	X
Coping capacity	Sense of Coherence Scale	X		X
Cognitive impairment	Montreal Cognitive Assessment		X	
Fatigue	Checklist Individual Strength	X	X	X
Anxiety	Hospital Anxiety and Depression Scale	X	X	X
Depression	Hospital Anxiety and Depression Scale	X	X	X
Pain	Numeric Rating Scale		X	
Activities of daily living	Katz Personal-ADL index		X	
Activities of daily living	Katz Instrumental-ADL index		X	
Frequency of social and lifestyle activities	Frenchay Activities Index	X	X	X
Health-related quality of life	Sickness Impact Profile	X		
Health-related quality of life	EuroQol Visual Analogue Scale	X		X
Health-related quality of life	Short-Form (36) Health Survey			X
Life satisfaction	Life Satisfaction Checklist-11			X
Experiences of caregiving	Caregiver Reaction Assessment			X

3.4.2 The Sense of Coherence Scale

The Sense of Coherence Scale (SOC) was used to assess coping capacity in patients with ALS (42). The SOC consists of 13 items, each graded from 1 to 7. A total score, ranging from 13 to 91, is calculated. The SOC is considered valid (114) and reliable (115).

In Studies I and III, a SOC score of ≤ 54 was used as the cut-off for indicating a weak coping capacity (116).

3.4.3 The Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) was used to assess cognitive impairment in patients with ALS (117). The MoCA consists of eight domains covering short time/work memory, visuospatial abilities, executive functions, attention,

concentration, language and orientation to time. A total score ranging from 0 to 30 is calculated and lower scores indicate more severe cognitive impairment. The MoCA is considered valid (117, 118) and reliable (118).

In study II, a score of < 26 was used as cut-off for indicating cognitive impairment (117).

3.4.4 The Checklist Individual Strength

The Checklist Individual Strength (CIS) was used to assess fatigue in patients with ALS (119). The CIS consists of 20 items, each graded from 1 to 7. A total score ranging from 20 to 140 is calculated, and a higher score indicates more severe disability. The scale comprises four subscale scores: subjective fatigue (score 8-56), concentration (score 5-35), motivation (score 4-28), and physical activity (score 3-21). The CIS is considered valid (119, 120) and reliable (120).

In Studies I, II and III, a score of ≥ 35 on the subjective fatigue subscale was used as the cut-off for indicating fatigue (21, 121).

3.4.5 The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression in patients with ALS (122). The scale comprises two sub-scales (anxiety and depression), both with seven items graded from 0 to 3. A total score ranging from 0 to 21 is calculated for each subscale, and a score of ≥ 8 indicates possible/probable anxiety and depression, respectively. A higher score indicates more severe disability. The HADS is considered valid (123) and reliable (123, 124).

In Studies I and III, a score of ≥ 8 in either of the two subscales was used as the cut-off for indicating possible/probable anxiety and/or depression. In Study II, scores ≥ 8 in the anxiety and depression subscales were used as the cut-offs for indicating anxiety and depression.

3.4.6 The Numeric Rating Scale of pain

A Numeric Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain) was used to assess pain in patients with ALS. The question from the Brief Pain Inventory Short-Form (125) was used to identify patients perceiving pain: "Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday kinds of pain the last week?" Patients answering yes were asked to rate their average pain experience using the NRS. Patients were asked to mark the number that best reflected their perceived pain. The NRS is considered valid (126, 127) and reliable (127).

In Study II, a score of ≥ 4 was used as the cut-off for indicating clinically relevant pain. The cut-off for this impairment was chosen in accordance with Karolinska University Hospital clinical guidelines, which state that pain scoring ≥ 4 on a 0-10 NRS should be treated.

3.4.7 The Katz Personal-ADL index

The Katz Personal (P)-ADL index was used to assess P-ADL in patients with ALS (128). The index consists of the six items; feeding, bathing, dressing, continence, toileting and transfer, each scoring 0 if the patient is dependent and 1 if independent. A total score ranging from 0 to 6 is calculated. The Katz P-ADL index is considered valid and reliable (129).

In Study II, a score of ≤ 5 (less than the full sum score) was used as the cut-off for indicating dependency in P-ADL, which was considered to be an activity limitation.

3.4.8 The Katz Instrumental-ADL index

The Katz Instrumental (I)-ADL index was used to assess I-ADL in patients with ALS (128). The Katz I-ADL consists of the four items; cooking, cleaning, transportation and shopping, each scoring 0 if the patient is dependent and 1 if independent. A total score ranging from 0 to 4 is calculated. The Katz I-ADL index is considered valid and reliable (129).

In Study II, a score of ≤ 3 (less than the full sum score) was used as the cut-off for indicating dependency in I-ADL, which was considered to be an activity limitation.

3.4.9 The Frenchay Activities Index

The Frenchay Activities Index (FAI) was used to assess the frequency of social and lifestyle activities in patients with ALS (130). The FAI consists of 15 items graded from 0 (inactive) to 3 (highly active) relating to domestic chores, work/leisure and outdoor activities. A total score ranging from 0 to 45 is calculated, and lower scores indicate more severe participation restrictions. The FAI is considered valid (131) and reliable (130, 132).

In Studies I, II and III, a score equal to or less than the 25th percentile of published sex- and age predictive normative values (131) was used as the cut-off for indicating below norm frequency in social and lifestyle activities, which was considered to be a participation restriction.

3.4.10 The Sickness Impact Profile

The Sickness Impact Profile (SIP) was used to assess HRQL in patients with ALS (133). The SIP consists of 136 items covering 12 categories: sleep and rest, emotional

behaviour, body care and movement, home management, mobility, social interaction, ambulation, alertness behaviour, communication, work, recreation and pastimes, and eating. Scores for all categories are calculated, as well as a total score (SIP overall) that consists of all 12 categories, a physical score (SIP physical) including 3 categories (ambulation, mobility, body care and movement) and a psychosocial score (SIP psychosocial), which includes 4 categories (social interaction, alertness behaviour, emotional behaviour, communication). Total scores from 0 to 100 are calculated, with higher scores indicating worse HRQL. The scores are expressed as percentage of impact of disease. The SIP is considered valid (134) and reliable (134).

3.4.11 The EuroQol Visual Analogue Scale

The EuroQol Visual Analogue Scale (EQ VAS) was used to assess HRQL in patients with ALS and in their next of kin (135). The EQ VAS consists of a vertical thermometer graded from 0 (worst imaginable health) to 100 (best imaginable health) on which the respondent marks their perceived overall health status today. The EQ VAS is considered valid (136) and reliable (136, 137).

3.4.12 The Short-Form (36) Health Survey

The Short-Form (36) Health Survey (SF-36) was used to assess HRQL in next of kin (87). The survey consists of 36 items, of which 1 question measures change in health status during the last year, while the other 35 items group into 8 subscales (physical functioning, role limitation, bodily pain, general health, vitality, social functioning, role limitation and emotional problems). An SF-36 Physical Component Summary (SF-36 physical) and an SF-36 Mental Component Summary (SF-36 mental) index score can be calculated, both ranging from 0 to 100. Lower scores indicate worse HRQL. The SF-36 is considered valid and reliable (87).

3.4.13 The Life Satisfaction Checklist-11

The Life Satisfaction Checklist-11 (LiSat-11) was used to assess life satisfaction in next of kin (89). The LiSat-11 consists of 11 items, of which 1 item measures global satisfaction with life, ‘life as a whole’, and 10 items capture satisfaction with life in the following domains: vocation, economy, leisure, contacts, sexual life, family life, partner relationship, ADL, physical health and psychological health. Each item is graded from 1 (very dissatisfied) to 6 (very satisfied), and scores can be categorized into “satisfied” (≥ 5) or “not satisfied” (scores ≤ 4) (89).

In Study III, a score of ≥ 5 was used as the cut-off for indication of satisfaction with “life as a whole” (LiSat-11, item 1).

3.4.14 The Caregiver Reaction Assessment

The Caregiver Reaction Assessment (CRA) was used to assess experiences of caregiving in next of kin (138). The scale captures both positive and negative experiences of informal caregiving. The CRA consists of 24 items graded from 1 (does not apply at all) to 5 (applies completely) that can be grouped into five dimensions: self-esteem, family support, finances, schedule and health. Positive experiences are captured by the self-esteem dimension, whereas the other four dimensions describe negative experiences of caregiving. Dimension scores, ranging from 1 to 5, are calculated, and higher scores indicate higher impact on the dimension. The CRA is considered valid (139) and reliable (139, 140).

In Study III, a score of ≥ 4 in the self-esteem dimension was considered to indicate a high positive impact in caregiving esteem. For the other four dimensions (family support, finances, schedule and health), a score of ≥ 3 was considered to indicate a high negative impact by describing lack of family support, financial problems, disrupted schedules and health problems.

3.5 Data collection (Study IV)

Data on age, sex, relation to patient with ALS and work status in next of kin, as well as on time since diagnosis and duration of TIV in patients with ALS, were collected using standardized questions administered as an interview.

A semi-structured interview guide was developed in order to delve into the experience of being next of kin to someone with ALS who is undergoing TIV. The guide started with the question: "Can you tell us about an ordinary day in your everyday life?" This main question was followed by additional questions on, e.g., impact on daily life, involvement in care, expectations on social and health care personnel, thoughts about the situation with TIV, communication with the patient and, finally, advice to others including health care. All interviews were audio-taped and transcribed verbatim.

3.6 Data analyses (Studies I, II and III)

An overview of the statistical methods used in Studies I, II and III is presented in Table 3. Descriptive statistics were used to present data, i.e., mean and standard deviation (SD), median and interquartile range (IQR), minimum and maximum values, frequency and percent. The Kolmogorov-Smirnov test, normality plots, and kurtosis and skewness values were used to check for normal distribution. The Mann-Whitney U and the Chi-squared tests were used to analyse differences in age and sex, respectively, between patients participating in Study I and those who declined/did not answer, and in Study II between patients still in the study after three years and those who dropped out of the study.

Table 3. An overview of statistical methods used in Studies I, II and III.

Statistical method	Study I	Study II	Study III
Descriptive statistics	X	X	X
Mann-Whitney U test	X	X	
Chi-squared test	X	X	X
Spearman rank correlation test		X	
Univariate linear regression analysis			X
Multivariate linear regression analysis	X		X
Binary multivariate logistic regression analysis			X

In Study I, stepwise multivariate linear regression analyses were used to explore associations between HRQL and the independent variables disease severity, fatigue, anxiety and/or depression, frequency of social and lifestyle activities, coping capacity and mechanical ventilator use, categorized according to the described cut-offs (Table 4).

In Study II, fatigue, anxiety, depression and clinically relevant pain were categorized according to the described cut-offs in section 3.4, and each patient's total number of impairments was calculated. Descriptive statistics were used to explore relations between impairments and the three levels of disease severity (mild, moderate and severe). The Spearman rank correlation test was used to explore associations between disease severity and impairments. To facilitate interpretation, scores on fatigue, anxiety, depression and pain were inverted in these analyses so that higher scores reflected better functioning in all measures. The correlation coefficients were considered low if ≤ 0.49, moderate if 0.50 to 0.69, and high if ≥ 0.70 (141).

In Study III, stepwise multivariate linear regression analyses were used to explore associations between HRQL and independent variables i.e. caregiver experiences and factors related to informal caregivers and to the patient with ALS, categorized according to the described cut-offs (Table 4). The selection of independent variables to be used in the multivariate regression analyses was based on univariate analyses, i.e. a variable was selected if it was significantly associated with the dependent variable. A binary multivariate logistic regression analysis was used to explore the associations between satisfaction in "life as a whole" and the independent variables described above.

Assumptions of regression models in Studies I and III were performed by analysing outliers, independence and the normality distribution of residuals, and multicollinearity. The level of significance was set to $p < 0.05$, and analyses were performed with IBM SPSS Statistics 22 and 24 for windows.

Table 4. Cut-offs for categorization of independent variables used in univariate and multivariate regression analyses (Studies I and III).

Independent variable	Cut-off	Study I	Study III
Patient-related			
Disease severity	Severe (ALSFRS-R ≤29)	X	
Disease severity	Severe (ALSFRS-R ≤24)		X
Coping capacity	Weak (SOC ≤54)	X	X
Fatigue	Fatigue (CIS fatigue subscale ≥35)	X	X
Anxiety and/or depression	Anxiety and/or depression (HADS ≥8)	X	X
Social and lifestyle activities	Below norm (FAI ≤25th percentile of norm values)	X	X
Mechanical ventilation	Yes	X	
Homecare/personal assistance	Yes		X
Next of kin-related			
Age	≥65 years		X
Sex	Man		X
Education level	University		X
Cohabiting with patient	No		X
Time spent on caregiving	>7 h/week		X
Caregiving esteem	High positive impact (CRA self-esteem ≥4)		X
Lack of family support	High negative impact (CRA family support ≥3)		X
Financial problems	High negative impact (CRA finances ≥3)		X
Disrupted schedule	High negative impact (CRA schedule ≥3)		X
Health problems	High negative impact (CRA health ≥3)		X

ALSFRS-R: ALS Functioning Rating Scale-Revised, SOC: Sense of Coherence Scale, CIS: Checklist Individual Strength, HADS: Hospital Anxiety and Depression Scale, FAI: Frenchay Activities Index, CRA: Caregiver Reaction Assessment

3.7 Data analysis (Study IV)

Qualitative content analysis with an inductive approach (142, 143) was used for analysis of interviews on the experiences of next of kin to patients with ALS undergoing TIV. The units of analysis were the recorded interviews, which were transcribed verbatim. The steps of the analysis are described below:

1. The transcribed interviews were read through several times to get a sense of their content.
2. The text was divided into meaning units comprising words, sentences or paragraphs related to each other by their content and context.
3. The meaning units were condensed, i.e. the text was shortened without interpretation and still contained the core of the meaning units.
4. Each condensed meaning unit was, in a process to interpret the underlying meaning, labelled with a code.
5. Codes were compared, and those with similar content were grouped into subthemes. The initial number of subthemes was reduced after a process of re-reading codes and reconsidering the interpretation of the underlying meaning and the whole context, and thus, moving between the whole and parts of the text.
6. The subthemes were analysed by their latent content in a process to answer how next of kin experienced TIV for their relative with ALS. Three main themes were constructed based on the underlying meaning of the subthemes.

3.8 Ethical considerations

Ethical approvals were obtained from the ethical review board in Stockholm, Sweden, registration number 2012/842-31/2 (Studies I, II and III) and registration number 2016/1086-31 (Study IV). All procedures were conducted in accordance with the Helsinki Declaration, and all participants received oral and written information and had to give their consent before inclusion.

Studies in patients with the progressive fatal disease ALS and their next of kin require serious ethical considerations, as both patients and next of kin might be psychologically and emotionally vulnerable. It is important to respect individuals' situations and not to induce any additional strain. In the present studies, care was taken to assert that the time and day for the data collections were according to the participants' wishes and that procedures were not too tiring. The data collectors had clinical experience in ALS but were not involved in actual care of participants. If needed, data collectors informed participants about where to go for professional support in different matters.

4 RESULTS

4.1 Patient inclusion and retention, patient characteristics and contextual factors (Studies I and II)

The inclusion and retention of patients with ALS during the three-year study period is presented in Figure 2. Twelve of the sixty patients included at baseline (T1) were still in the study at the last data collection. The median time since diagnosis at baseline was longer for those 12 (41 months) compared to the other 48 patients (16 months). Altogether, 23 patients declined participation at some time point after baseline, with the most common reasons being that the participants were too fatigued or in a terminal stage of ALS.

Information on patient characteristics and contextual factors at each data collection during the three-year study period is presented in Table 5. At baseline, the median age was 61 years, and the proportion of men and women was almost equal, with 53% of patients being men. The spinal form of ALS was more common than the bulbar, ranging from 75% of the patients at baseline to 92% at the last data collection (not shown in Table 5). All but three patients with ALS lived in their own home during the study period. Depending on data collection time point, disease modifying medication was prescribed to 76-86% and anti-depressives to 18-48%. Furthermore, having aids, home adaptations and services such as home care, personal assistance and transport service were reported by 52-100% of the patients. At baseline, 7 (14%) of 52 patients who answered the questionnaire on coping capacity (SOC) were classified as having weak coping capacity (not shown in Table 5).

4.2 Disease severity and disability in patients with ALS (Studies I and II)

Disease severity and disability at each data collection during the three-year study period is presented in Table 6. As expected, disease severity (ALSFRS-R) progressed over time, and no one was categorized as having mild disease after two years. Depending on data collection time point, fatigue was found in 31-61% of the patients, anxiety in 0-25%, depression in 11-36% and clinically relevant pain in 24-38%. Anti-depressive medication was prescribed for patients scoring above and under the cut-off for depression (not shown in tables). No results on cognitive impairment are presented, as 60-80% of the patients were unable to complete all parts of the used measure (MoCA) due to physical disability. Activity limitations and participation restrictions were common, and most patients were already at baseline dependent in ADL and reported severely reduced frequency (below norm) in social and lifestyle activities.

Table 5. Information on patient characteristics and contextual factors at each data collection (T1-T7) during the three-year study period. N represents the number of patients participating at each time point.

	T1 (N=60)	T2 (N=38)	T3 (N=29)	T4 (N=17)	T5 (N=14)	T6 (N=14)	T7 (N=12)
Age, years, median (IQR)	61 (55-69)	60 (54-67)	61 (53-66)	61 (48-68)	63 (58-68)	62 (50-67)	63 (48-68)
Men, n (%)	32 (53)	21 (55)	17 (59)	11 (65)	10 (71)	8 (57)	6 (50)
Time since diagnosis, months, median (IQR)	17 (8–35)	24 (14–57)	35 (20–82)	52 (32–107)	60 (36–123)	65 (45–129)	77 (50–152)
Own accommodation, n (%)	58 (97)	36 (95)	28 (97)	16 (94)	14 (100)	14 (100)	12 (100)
Living with family member, n (%)	45 (75)	31 (82)	23 (79)	14 (82)	12 (86)	12 (86)	10 (83)
Medications							
Disease modifying, n (%)	46 (77)	29 (76)	23 (79)	13 (77)	12 (86)	12 (86)	10 (83)
Symptomatic, n (%)	27 (45)	22 (58)	15 (52)	10 (59)	7 (50)	8 (57)	10 (83)
Anti-depressive, n (%)	16 (27)	11 (29)	14 (48)	3 (18)	5 (36)	3 (21)	4 (33)
Ventilation							
Non-invasive, n (%)	18 (30)	11 (29)	5 (17)	3 (18)	3 (21)	3 (21)	3 (25)
Invasive, n (%)	4 (7)	3 (8)	3 (10)	3 (18)	3 (21)	5 (36)	4 (33)
Gastrostomy, n (%)	18 (30)	11 (29)	11 (38)	5 (29)	6 (43)	7 (50)	7 (58)
Aids							
Mobility, n (%)	49 (82)	35 (92)	28 (97)	16 (94)	13 (93)	14 (100)	12 (100)
Activities of daily living, n (%)	43 (72)	31 (82)	24 (83)	15 (88)	12 (86)	13 (93)	12 (100)
Communication, n (%)	36 (60)	23 (61)	17 (59)	11 (65)	11 (79)	13 (93)	11 (92)
Home adaptations, n (%)	34 (57)	27 (71)	23 (79)	13 (77)	12 (86)	13 (93)	12 (100)
Home care, n (%)	15 (25)	9 (24)	7 (24)	2 (12)	2 (14)	2 (14)	3 (25)
Personal assistance, n (%)	16 (27)	15 (39)	16 (55)	10 (59)	8 (57)	9 (64)	7 (58)
Transport service, n (%)	40 (67)	32 (84)	27 (93)	17 (100)	14 (100)	14 (100)	12 (100)

IQR: interquartile range.

Table 6. Disease severity and disability in patients with ALS at each data collection (T1-T7) during the three-year study period. N represents the number of patients participating at each time point and n indicates the number of patients having answered the questionnaires.

	T1 (N=60) n (%)	T2 (N=38) n (%)	T3 (N=29) n (%)	T4 (N=17) n (%)	T5 (N=14) n (%)	T6 (N=14) n (%)	T7 (N=12) n (%)
Disease severity							
Mild	20 (33)	6 (16)	5 (17)	1 (6)	1 (7)	-	-
Moderate	17 (28)	19 (50)	10 (35)	9 (53)	4 (29)	6 (43)	4 (33)
Severe	23 (39)	13 (34)	14 (48)	7 (41)	9 (64)	8 (57)	8 (67)
Fatigue							
Yes	31 (61)	21 (58)	13 (50)	7 (41)	6 (43)	4 (31)	6 (50)
No	20 (39)	15 (42)	13 (50)	10 (59)	8 (57)	9 (69)	6 (50)
Anxiety							
Yes	14 (25)	9 (25)	3 (11)	2 (12)	2 (14)	0 (0)	2 (17)
No	42 (75)	27 (75)	24 (89)	15 (88)	12 (86)	14 (100)	10 (83)
Depression							
Yes	12 (21)	10 (28)	3 (11)	4 (31)	5 (36)	3 (21)	2 (17)
No	44 (79)	26 (72)	24 (89)	13 (69)	9 (64)	11 (79)	10 (83)
Pain							
Yes, clinically relevant	14 (24)	12 (32)	11 (38)	6 (35)	3 (21)	5 (36)	3 (25)
Yes, below cut-off	7 (12)	4 (10)	3 (10)	2 (12)	0 (0)	1 (7)	3 (25)
No	38 (64)	22 (58)	15 (52)	9 (53)	11 (79)	8 (57)	6 (50)
Personal ADL							
Dependent	41 (68)	29 (76)	25 (86)	16 (94)	12 (86)	14 (100)	12 (100)
Independent	19 (32)	9 (24)	4 (14)	1 (6)	2 (14)	0 (0)	0 (0)
Instrumental ADL							
Dependent	52 (87)	37 (97)	28 (97)	16 (94)	14 (100)	14 (100)	12 (100)
Independent	8 (13)	1 (3)	1 (3)	1 (6)	0 (0)	0 (0)	0 (0)
Social and lifestyle activities							
Below norm	47 (78)	35 (92)	27 (93)	16 (94)	14 (100)	14 (100)	12 (100)
Within norm	13 (22)	3 (8)	2 (7)	1 (6)	0 (0)	0 (0)	0 (0)

The number of patients having fatigue, anxiety, depression and clinically relevant pain in relation to disease severity level at each data collection during the three-year study period is presented in Figure 3. Presence of these impairments was found in all disease severity levels, i.e. in those categorized as having mild, moderate and severe disease. Concurrent presence of fatigue, anxiety, depression and clinically relevant pain at each data collection is presented in Figure 4. Depending on data collection time point, between 23% and 42% of the patients had two or more of these impairments concurrently. The impairments (fatigue, anxiety, depression and clinically relevant pain) were not considered to be related to disease severity as correlation coefficients were low.

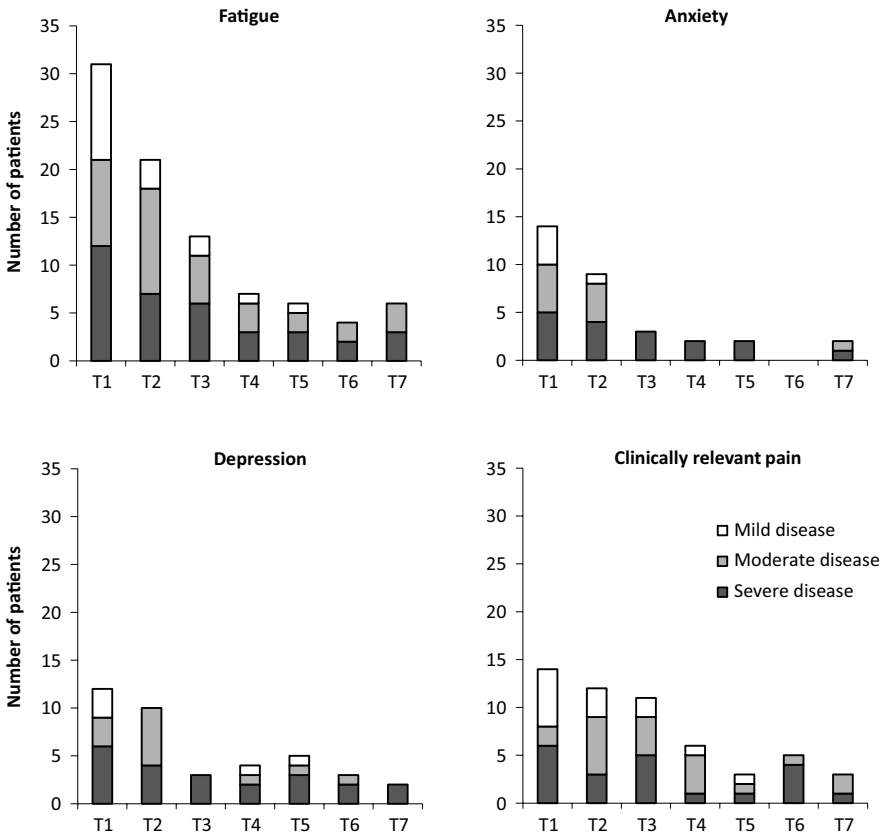

Figure 3. *Presence of fatigue, anxiety, depression and clinically relevant pain in relation to disease severity (mild, moderate and severe) at each data collection (T1-T7) during the three-year study period.*

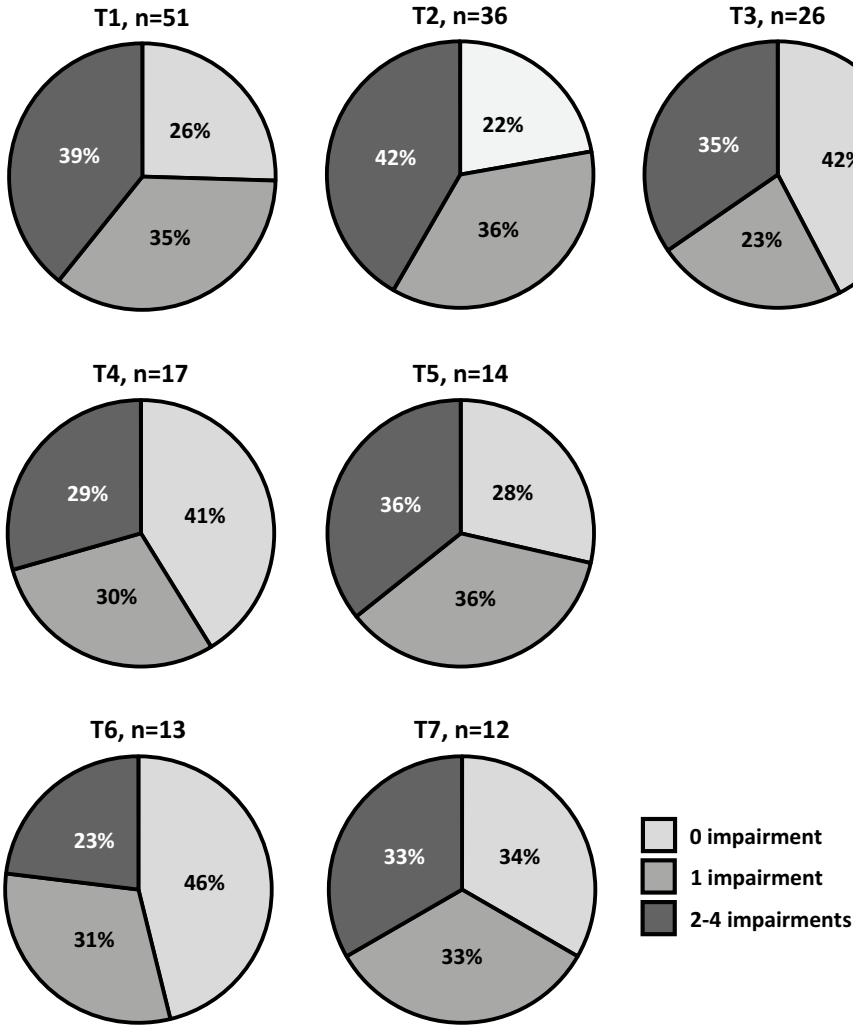

Figure 4. *Concurrent presence of the impairments fatigue, anxiety, depression and clinically relevant pain at each data collection (T1-T7) during the three-year study period.*

4.3 Predictors of HRQL in patients with ALS (Study I)

Results of HRQL measures at baseline in patients with ALS are presented in Figure 5. The physical dimension of HRQL (SIP physical) was more severely affected than the psychosocial dimension (SIP psychosocial). The variation in patients' ratings of their perceived overall health status today (EQ VAS) was wide, with a median value of 50, i.e. precisely between worst and best imaginable health.

The results from the multivariate regression analyses of predictors of HRQL in patients with ALS are presented in Table 7. Participation restriction, i.e. below the norm frequency in social and lifestyle activities, severe disease and weak coping capacity predicted worse overall HRQL (SIP overall). Participation restriction in social and lifestyle activities and severe disease predicted worse physical HRQL (SIP physical), and severe disease, weak coping capacity and presence of anxiety and/or depression were predictors of worse psychosocial HRQL (SIP psychosocial). Fatigue and use of mechanical ventilator were predictors of worse overall health status (EQ VAS).

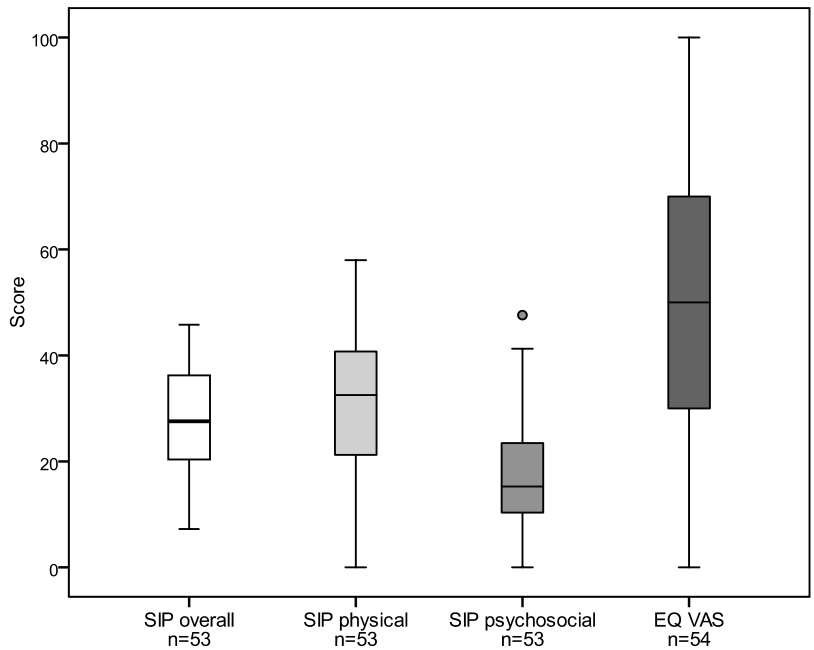

Figure 5. *Box plots of health-related quality (HRQL) measures at baseline in patients with ALS. Higher scores in Sickness Impact Profile (SIP) overall, SIP physical and SIP psychosocial indicate worse HRQL, and lower scores in EuroQol Visual Analogue Scale (EQ VAS) indicate worse HRQL.*

Table 7. Results of multivariate regression analyses on predictors of health-related quality of life in patients with ALS.

Dependent variable	Independent variable	Unstandardized coefficients		P-value	Adjusted R^2	Total variance explained
		B	95% CI			
SIP overall (n=51)	Participation restriction (FAI ≤25th percentile of norm values)	10.3	5.4 to 15.3	<0.001	0.42	42%
	Severe disease (ALSFRS-R ≤29)	9.1	5.0 to 13.2	<0.001	0.12	54%
	Weak coping capacity (SOC ≤54)	6.2	0.8 to 11.5	0.025	0.04	58%
SIP physical (n=51)	Participation restriction (FAI ≤25th percentile of norm values)	17.5	10.2 to 24.9	<0.001	0.44	44%
	Severe disease (ALSFRS-R ≤29)	11.6	5.6 to17.7	<0.001	0.13	57%
SIP psychosocial (n=51)	Severe disease (ALSFRS-R ≤29)	7.3	2.4 to 12.1	0.004	0.17	17%
	Weak coping capacity (SOC ≤54)	8.4	1.3 to 15.4	0.021	0.11	28%
	Anxiety and/or depression (HADS ≥8)	5.2	0.1 to 10.3	0.045	0.05	33%
EQ VAS (n=50)	Fatigue (CIS fatigue subscale ≥35)	-18.4	-32.2 to -4.6	0.010	0.10	10%
	Mechanical ventilator (yes)	-17.0	-32.1 to -2.0	0.027	0.07	17%

CI: Confidence interval, SIP: Sickness Impact Profile, EQ VAS: EuroQol Visual Analogue Scale, FAI: Frenchay Activities Index, ALSFRS-R: ALS Functional Rating Scale Revised, SOC: Sense of Coherence Scale, HADS: Hospital Anxiety and Depression Scale, CIS fatigue: Checklist Individual Strength fatigue subscale.

4.4 Informal caregiver characteristics (Study III)

All next of kin in Study III performed unpaid caregiving and were therefore considered to be informal caregivers. (See Table 8 for information on informal caregiver characteristics.) Most informal caregivers were women (69%), and 67% of all informal caregivers cohabitated with the patient with ALS. The reported median (IQR) time spent on informal caregiving was 18 (6-50) hours per/week (not shown in Table 8).

Table 8. Information on informal caregiver characteristics.

Informal caregivers	
Age, years, median (IQR)	60 (49-67)
Women, n (%)	34 (69)
Work status, full/part time, n (%)	14/16 (29/33)
Changed working time (after ALS diagnosis), n (%)	15 (31)
Relation to patient with ALS, n (%)	
Partner/ex-partner	31/2 (63/4)
Child	8 (26)
Parent/sibling/friend	1/6/1 (2/12/2)
Cohabiting with patient with ALS, n (%)	33 (67)
Informal caregiving >7 hours/week, n (%)	35 (71)

IQR: interquartile range

4.5 Caregiver experience, HRQL and life satisfaction in informal caregivers (Study III)

Results on positive and negative caregiver experiences (CRA) are presented in Figure 6. High positive impact on self-esteem was reported by 30 (63%) informal caregivers. High negative impact was reported by 30 (63%) in schedule and by 20 (42%) in health, i.e. many informal caregivers had disrupted schedules and health problems.

Results of HRQL measures in informal caregivers to patients with ALS are presented in Figure 7. The mental dimension of HRQL (SF-36 mental) was more severely affected than the physical dimension (SF-36 physical). The variation in informal caregivers' ratings of their perceived overall health status today (EQ VAS) was wide with a median value of 75.

Results of life satisfaction in informal caregivers to patients with ALS are presented in Figure 8. Fourteen (30%) informal caregivers were satisfied with "life as a whole" (LiSat-11, item 1), and 11 (23%) and 7 (15%) reported being satisfied in the leisure and sexual life domains, respectively.

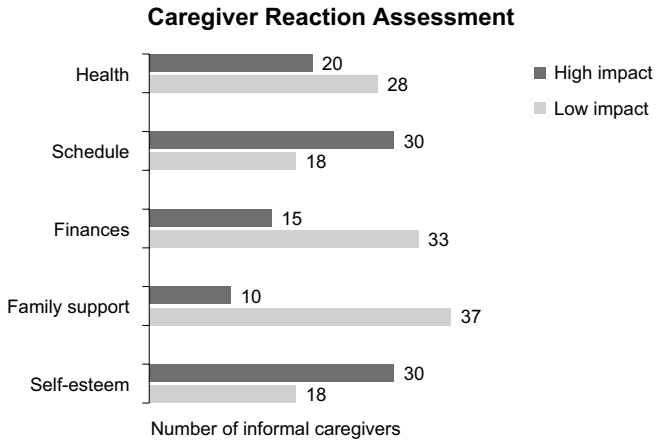

Figure 6. *Results on positive (self-esteem) and negative (health, schedule, finances and family support) caregiver experiences in informal caregivers to patients with ALS. Numbers of patients reporting high and low impact in the five dimensions of the Caregiver Reaction Assessment questionnaire.*

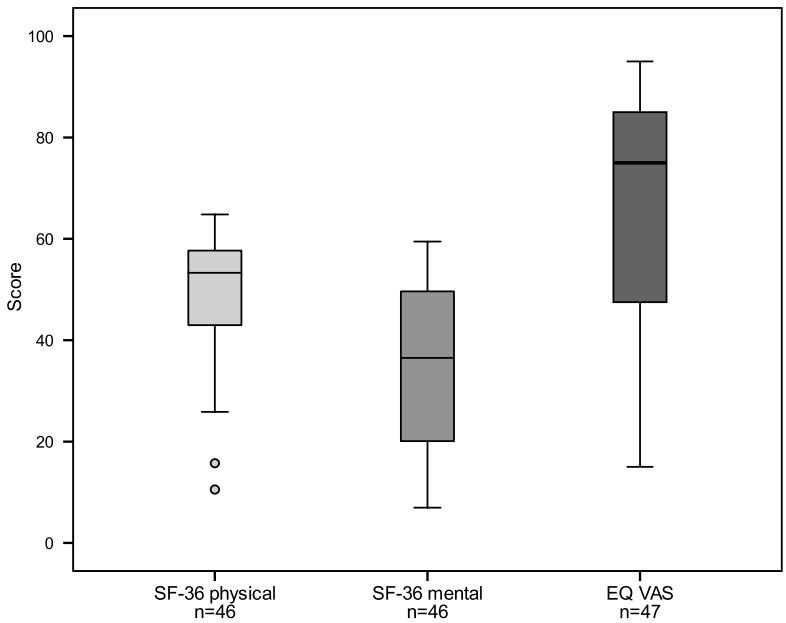

Figure 7. *Box plots on health-related quality of life (HRQL) measures in informal caregivers to patients with ALS. Lower scores in SF-36 Physical Component Summary (SF-36 physical), SF-36 Mental Component Summary (SF-36 mental), and EuroQol Visual Analogue Scale (EQ VAS) indicate worse HRQL.*

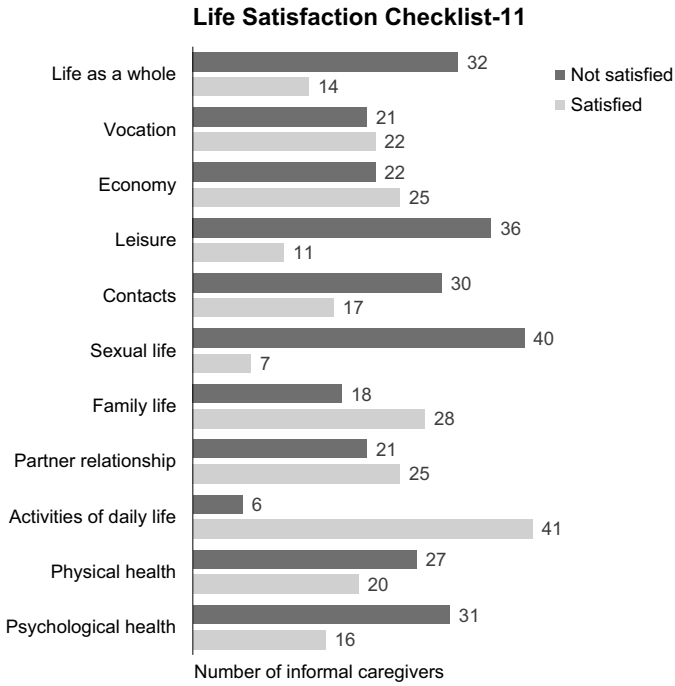

Figure 8. *Results on life satisfaction in informal caregivers to patients with ALS. Numbers of patients reporting being satisfied and not satisfied in the 11 domains of the Life Satisfaction Checklist-11 questionnaire.*

4.6 Factors associated with HRQL and life satisfaction in informal caregivers (Study III)

Results of multivariate regression analyses on factors associated with informal caregivers' HRQL are presented in Table 9. Anxiety and/or depression in patients with ALS was associated with worse physical HRQL (SF-36 physical), while the disrupted schedules of informal caregivers were associated with better physical HRQL. Older age and high self-esteem in informal caregivers were associated with better mental HRQL (SF-36 mental), while informal caregivers' disrupted schedules and health problems were associated with worse mental HRQL. Male sex and health problems in informal caregivers were associated with worse overall health status (EQ VAS).

The binary multivariate logistic regression analysis showed that older age in informal caregivers and not cohabiting with patients with ALS were associated with being satisfied with "life as a whole" (LiSat-11, item 1). The odds ratio (95% CI) for older age was 11 (2-61), p=0.006 and for not cohabiting 7 (1-41), p=0.028.

Table 9. Results of multivariate regression analyses on factors associated with health-related quality of life in informal caregivers to patients with ALS.

Dependent variable	Independent variable	Unstandardized coefficients		P-value	Adjusted R^2	Total variance explained
		B	95% CI			
SF-36 physical (n=45)	Anxiety and/or depression in patient (HADS ≥8)	-9.3	-16.4 to -2.2	0.011	0.12	12%
	Disrupted schedule (CRA schedule ≥3)	7.8	0.8 to 14.7	0.028	0.07	19%
SF-36 mental (n=46)	Age (≥65 years)	15.1	8.4 to 21.8	<0.001	0.27	27%
	Health problems (CRA health ≥3)	-8.7	-15.7 to -1.7	0.016	0.18	45%
	Disrupted schedule (CRA schedule ≥3)	-9.4	-16.5 to -2.3	0.011	0.05	50%
	Caregiving esteem (CRA self-esteem ≥4)	7.2	0.6 to 13.8	0.033	0.04	54%
EQ VAS (n=47)	Sex (man)	-19.7	-31.8 to -7.5	0.002	0.15	15%
	Health problems (CRA health ≥3)	-21.1	-32.6 to -9.7	0.001	0.13	28%

CI: confidence interval, SF-36 physical: SF-36 Physical Component Summary, SF-36 mental: SF-36 Mental Component Summary, EQ VAS: EuroQol Visual Analogue Scale, HADS: Hospital Anxiety and Depression Scale, CRA: Caregiver Reaction Assessment.

4.7 Experiences of next of kin to patients with ALS undergoing TIV (Study IV)

Characteristics of next of kin and patients are presented in Table 10. Three main themes and nine subthemes emerged from the qualitative content analysis (Table 11).

The first theme, "A turbulent care process aiming to extend life", described the perceived chaotic situation that emerged when a tracheostomy had been carried out in an emergency situation. Although TIV had been discussed and sometimes planned, next of kin felt they lacked knowledge and were uncertain of the reasons underlying the patient's choice of invasive ventilation. However, TIV meant that the focus changed from thoughts of the patient's immediate death to prolonging life. The period after the emergency surgery was described as turbulent with inadequate support and information, and that the care was of a low standard until the patient was transferred to the Respiratory Centre. The period of hospitalization after TIV was initiated was perceived as surprisingly long.

Table 10. Characteristics of next of kin (n=8) and patients with ALS requiring invasive ventilation via tracheostomy (n=6).

Study IV	
Next of kin	
Age, years, median (min-max)	49 (27-64)
Women/men, n	6/2
Relation	
Wife, n	3
Parent, n	2
Children	3
Cohabiting with patient, n	4
Work status	
Full time/part time as personal assistant, n	3/4
Patients with ALS	
Time since diagnosis, years, median (min-max)	4 (3-12)
Invasive ventilation, years, median (min-max)	2 (1-7)

Table 11. The results of the qualitative content analysis of experiences in next of kin to patients with ALS undergoing invasive ventilation via tracheostomy.

Theme	Subtheme
A turbulent care process aiming to extend life	Feeling insecure in a tense emergency situation
	A roller-coaster care process
Struggling to cope with the strains of everyday life	Putting one's own life on hold
	The challenge of coping with life-giving TIV
	Reliance on personal assistance needed to feel secure
	The struggle to communicate when the power of speech is lost
Conflicting roles as next of kin and carer	Being an unofficial guardian
	Contradictory relationship roles
	A desire for support and guidance in the carer role

The second theme, "Struggling to cope with the strains of everyday life", described the experiences of having to adapt to the situation of home care of a patient with TIV. Next of kin put their own lives on hold and adapted to the needs of the patient. Some perceived TIV as terrifying, as the patient would die without it, while others described it as one of several aids that made life easier. Home care brought about a change to a more hospital-like home with a constant presence of employed formal caregivers. A well-functioning situation regarding these caregivers was, however, a prerequisite for next of kin to be able to feel secure. In everyday life, the patient's loss of ability to communicate was perceived as a major difficulty and involved uncertainties in the understanding of the patient and a feeling that the patient had changed as a person.

The third theme, "Conflicting roles as next of kin and carer", described how next of kin felt that they had become the patient's unofficial guardian. This task was accompanied by a heavy work load, and they lacked help in co-ordinating the care of the patient. Difficulties in maintaining their relationship as a close relative while also working as a formal caregiver were described. They expressed a need for psychological and social support as next of kin and as carers and in issues related to ALS and TIV.

5 DISCUSSION

This thesis aimed to explore aspects of disability, contextual factors and HRQL in patients with ALS, and to explore informal caregivers' HRQL and life satisfaction. Further, to investigate the experiences of being next of kin to patients with ALS undergoing TIV.

5.1 Main findings

Regardless of disease severity, patients with ALS were found to experience fatigue, anxiety, depression and pain concurrently. The health condition, i.e. high disease severity; the impairments fatigue, anxiety and/or depression; participation restrictions, i.e. low frequency of social and lifestyle activities; and the contextual factors weak coping capacity and mechanical ventilator use (non-invasive and TIV) were associated with worse HRQL in patients with ALS. Anxiety and/or depression in patients with ALS, and informal caregivers' negative caregiving experiences and male sex were associated with worse HRQL in informal caregivers, while positive caregiving experiences and older age were associated with better HRQL. As for life satisfaction, older age and not cohabiting with the patient were associated with being satisfied with "life as a whole". The following main themes were identified in the qualitative analyses of the experiences of being next of kin to patients with ALS undergoing TIV: "A turbulent care process aiming to extend life"; "Struggling to cope with the strains of everyday life"; and "Conflicting roles as next of kin and carer".

5.2 Disability in patients with ALS (Studies I and II)

Although patients with ALS present many various impairments, the focus in this thesis were on such impairments that are amenable to health care interventions. Fatigue was the most common impairment at all data collection time points. Fatigue can be said to consist of a physiological (central and peripheral fatigue) and a psychological dimension (depression, concentration and motivational influences) (144). Both dimensions are thought to influence patients' perceptions of fatigue as adaptation mechanisms in the central nervous system early in the development of the disease, and there is obvious psychological stress related to having ALS. Although fatigue was common among the patients studied here, it did not seem to increase over time. It can be speculated that patients became less physically active due to progressive muscle weakness and, thus, were less fatigued. Such explanation would be in accordance with a previous report that patients with ALS describe fatigue as a use-dependent reversible muscle weakness and a whole-body tiredness (145). Both pharmacological and non-pharmacological interventions for

fatigue have been studied, but it is not possible to draw any conclusion on their effectiveness, as the quality of the available evidence is low (146). It was recently reported that fatigue is the most prevalent symptom in patients with ALS, and at the same time it is the least treated (147). Thus, there is a great need for scientific studies regarding interventions to reduce fatigue.

The number of patients with anxiety and depression seemed to decrease over time. Perhaps this was due to the shorter time from diagnosis in patients at baseline. i.e. the perceived psychological strain might decrease over time due to acceptance and other coping strategies. Regardless of data collection time point, there were patients with anxiety and/or depression who lacked anti-depressive medication, indicating possible under-treatment. In addition to medication, non-pharmacological interventions should be considered, e.g. cognitive behavioural therapy which has shown the potential to decrease anxiety and depression in patients with ALS (148).

Pain has been highlighted as a largely neglected impairment in patients with ALS (149). The findings that, regardless of data collection time point, approximately half of the patients experienced pain, and that most were categorized as having clinically relevant pain and thereby were considered as undertreated, provide new and important knowledge. There are many underlying causes for that pain that patients with ALS experience, e.g. there may be pain due to muscle weakness, cramps, spasticity, contractures and immobilization, which is why proper pharmacological and non-pharmacological interventions to reduce pain are needed (149).

Activity limitations in P- and I-ADL and participation restrictions were present in patients with ALS at all data collection time points and increased over time. This was found despite that, on a group level, patients apparently had access to aids, support and services. It would therefore be interesting to explore the timing, use and satisfaction of the prescribed aids, as well as the granted support and services from an individual perspective, to get a better understanding of how to reduce activity limitations and participation restrictions. Although multidisciplinary care, including physio- and occupational therapy-related interventions, are thought to be beneficial, the knowledge of the impact of such interventions to decrease participation restrictions in patients with ALS is limited and, thus, needed (150, 151).

The findings that patients with ALS, regardless of disease severity, experienced fatigue, anxiety, depression and pain over time, with approximately one-third having two or more impairments at the same time, and further, that activity limitations and participation restrictions were common, indicate the need for regular screening so that person-centred care can be applied at the right time.

5.3 Predictors of HRQL in patients with ALS (Study I)

That disease severity was associated with both physical and psychosocial dimensions of HRQL, i.e. severe disease with worse HRQL, corroborates what has previously been reported (91, 95, 101). The results indicate that is valuable to monitor disease severity in patients as it influences their HRQL, and furthermore, that patients might need enhanced care and support during severe stages of the disease.

In line with the results presented in this thesis, the relationship between fatigue and HRQL in patients with ALS seems to be inconclusive, as both an association with worse HRQL and a lack of association have been reported (93, 99, 152). The use of different measures, both for fatigue and HRQL, is a possible explanation for the discrepancies found in these associations. However, as HRQL is a multidimensional construct, it can be necessary to have complementary measures when exploring the impact of fatigue on HRQL.

Anxiety and/or depression were found to be associated with worse HRQL, a finding in line with previous reports (93, 94, 153). It is important to screen for these impairments, as in addition to having a negative impact on HRQL, it was found that anxiety and depression might be under-treated in patients with ALS.

Participation restrictions, i.e. low frequency of social and lifestyle activities, were associated with worse overall and physical HRQL, which underlines the importance of intervention and support for facilitating activities in domestic life and social participation.

The finding of an association between weak coping capacity and worse HRQL indicates that coping capacity, as captured by SOC, is an important factor to consider in the ALS population. The result is also in line with findings in patients with other various diseases where a stronger sense of coherence is found to be associated with better HRQL (154). It has been debated whether a person's sense of coherence is a stable entity, formed in young adulthood and stabilized around the age of 30, as proposed by Antonovsky (155), or if it is subject to change. The latter is supported by the evidence found of increasing SOC scores as one ages across the entire life span (114). Thus, it may be possible to change a person's sense of coherence/coping capacity. Suggested crucial components for interventions aiming to strengthen coping capacity are empowerment and reflection processes (156).

Mechanical ventilator use was found to be associated with worse HRQL. Although a bit surprising, the finding might be related to the fact that mechanical ventilation included both non-invasive ventilation and TIV. It has previously been reported that non-invasive ventilation is associated with better HRQL (100, 101), while invasive ventilation might worsen patients' HRQL (102). That most patients with

ALS in need of mechanical ventilation have a high degree of disease severity and that disease severity has an impact on HRQL (91, 95, 101) might be another possible explanation of the result.

5.4 Caregiver experience, HRQL and life satisfaction in informal caregivers (Study III)

That informal caregivers spent a substantial amount of time on caregiving are in line with previous findings on caregiving in both patients with ALS (71, 74, 157, 158) and other neurological diseases (159-161). The Swedish disability policy includes the right for people with disabilities to apply for social services such as personal assistance and home care, and many of the patients in this study made use of these services. Despite this, informal caregivers provided care for several hours almost every day. However, it is likely that these caregiving efforts made it possible for patients to live in their homes.

Caregiving experience is a multi-faceted construct with both positive and negative sides (76). Most studies on caregiving for patients with ALS explore negative aspects (74, 162, 163), and only a few studies report on positive caregiving experiences (77, 78). That approximately two-thirds of the informal caregivers had a high positive impact in the self-esteem dimension is therefore an important finding. In line with previous studies, where high time-consuming burden (164, 165) and time restrictions (74, 166) are reported as negative caregiver experiences, a high negative impact was found in the schedule dimension. These findings on caregiver experiences provide knowledge that can be used in health care. For example, informal caregivers with positive experiences in caregiving could be valuable as role models or facilitators in support groups for informal caregivers to patients with ALS. Further, it is possible that the enhanced involvement of informal caregivers in the care-planning of the patient with ALS might reduce negative caregiver experience. Whether the involvement of informal caregivers in care planning has this effect, however, needs to be further studied.

Negative caregiver experiences are reported to be associated with worse HRQL in caregivers to ALS patients (74). That disrupted schedule was associated with better physical HRQL was therefore a bit surprising. A possible explanation might be that informal caregivers with better physical HRQL are more active and therefore perceive a high negative impact on their schedule dimension, as caregiving interrupts other activities. Interestingly, a positive caregiver experience was associated with better mental HRQL, which underscores the importance of exploring both positive and negative sides of caregiving. Older age in informal caregivers was associated with better mental HRQL, a result in line with a previous study (104). That male sex in informal caregivers was associated with worse

HRQL contradicted a previous study where females rated their HRQL worse than males (167). Female informal caregivers are also reported to experience higher caregiver burden than men (165). These findings highlight the need for studies on gender differences in this area. Anxiety and/or depression in patients were associated with worse physical HRQL in informal caregivers. There was, however, no association between patients' disease severity and HRQL in informal caregivers, which corroborates what others report (29, 167-169). Thus, one can assume that patients' mental issues have a greater impact on informal caregivers' HRQL than patients' disease severity.

Life satisfaction in informal caregivers to patients with ALS was low compared to both informal caregivers to stroke patients (108, 109) and to Swedish reference levels (89). Although approximately one-third were satisfied with "life as a whole", few informal caregivers were satisfied in the domains concerning leisure and sexual life. Sexual interest, activity and satisfaction have been reported to decrease in patients with ALS and in their partners compared to the time before disease onset; however, the issue of sexuality is seldom addressed by health care professionals in general (170). Given the importance of sexuality, this is an area where health care needs to develop both strategies and interventions to support patients and their caregivers/partners.

It has been reported that younger age is associated with being satisfied with life (94), a finding in contrast to the result in this study that older age ($\geq$ 65 years) is associated with being satisfied with "life as a whole". Although not studied, older informal caregivers might be more satisfied because they do not need to combine informal caregiving with work demands. Furthermore, the aspirations for a healthy life and the expectations of life satisfaction possibly change with age. Not cohabiting with the patient was another factor associated with being satisfied with "life as a whole". Such an association might be because cohabiting with the patient possibly increases the strain in the lives of informal caregivers and reduces the time they can devote to their own activities.

5.5 Experiences of next of kin to patients with ALS undergoing TIV (Study IV)

Next of kin described the implementation of TIV as a turbulent care process that leads to continued life for their family member. Even though TIV had been discussed, tracheostomy was mostly performed in an acute setting. That patients with ALS undergo tracheostomy in emergencies is not unusual: it is reported to be the case in 44-67% of those undergoing TIV (59, 62, 171). This indicates a need for improving the protocol for implementing TIV in a safe and timely fashion, e.g. by establishing a care plan for management before respiratory complications occur,

a plan that both next of kin and patient feel comfortable with. That the hospitalization period after undergoing a tracheostomy was described as being turbulent and surprisingly long, implies that next of kin were not prepared for all the matters to be sorted out before the patient could return home. Though not available for patients and next of kin at the time of the tracheostomy in this study, there are now local guidelines (172) on how to implement TIV and how follow-up care after discharge from the Respiratory Centre. The extent to which next of kin are actively involved is, however, unknown.

It is known that the burden of care for caregivers to patients with ALS is substantial. Furthermore, it is known that next of kin providing care to TIV patients, ALS and other diagnoses perceive high levels of physical and emotional burden, and worse QoL than others (83, 173-176). Next of kin participating in Study IV described struggling to cope with the strains of everyday life, of placing all their focus on their patients, and of feeling that their own lives had been put on hold. That next of kin centre on the situations of their patients and set aside their own needs are consistent with the findings of other studies (166, 177, 178). The need for support for next of kin to patients with ALS has previously been highlighted (71, 166, 173, 179), but there is less literature describing how this support can be organized and delivered. Next of kin in Study IV described the dramatic shift in the situation at home that home care for a patient undergoing TIV brought about. If individually adapted information about the inevitable changes in the home situation were supplied, with regular follow-ups giving opportunity for reflection, next of kin might be better prepared and able to cope with the new situation better.

Next of kin described experiencing conflicting roles as next of kin and carer. That most were employed as formal caregivers, i.e. personal assistants, indicates that the lines between formal and informal care might be blurred, as well as those between work and free time. They also expressed a need for psychological and social support for them as next of kin and carers and in issues related to ALS and TIV. As for issues related to TIV, it is reported that a hands-on education programme for patients and their next of kin, in addition to providing the best available information, also assists in decision-making with respect to ventilatory support (180).

5.6 Methodological considerations

Patients with ALS participating in Studies I and II were recruited from the ALS clinic at the Karolinska University Hospital. This clinic serves all patients with ALS living in Stockholm County, a county with approximately two million inhabitants, i.e. one-fifth of Sweden's population. All patients had been diagnosed as having ALS according to the El Escorial criteria, i.e. there were signs of both upper and lower motor neuron involvement. Although 22 of 82 eligible patients declined to

participate in the study, the patient characteristics, including age, sex and onset form, of the 60 included at baseline were in agreement with reports from European population-based studies (6, 181, 182). Furthermore, no significant differences concerning age and sex were found between the 22 who declined and the 60 patients participating.

Participants in Study III were identified by patients with ALS (Study I) as being next of kin to them. Forty-nine of 58 identified as next of kin agreed to participate, and they were regarded as informal caregivers, as all provided unpaid care for patients with ALS. The relationship to the patient with ALS differed among the informal caregivers, and there was a variety in age and sex. Thus, it can be argued that the study samples were representative of patients with ALS and their informal caregivers, which strengthens the external validity of the study.

Next of kin participating in Study IV were recruited via patients with ALS undergoing TIV. As treatment with TIV is uncommon, it is not surprising that the study sample was small. There were, however, differences in age, sex, and the relationship to the patient undergoing TIV among the six next of kin, meaning that existing differences in experiences could be captured. However, that three next of kin came from the same family might limit the study's external validity.

The ICF was in the present thesis used as a conceptual framework, primarily when designing studies and when choosing measures to be used to describe and explore disability and contextual factors in patients with ALS and their next of kin. Even though the ICF provides a framework for obtaining a coherent view of health, it lacks a reference to HRQL, which is needed for a comprehensive view. Thus, HRQL measures were used in addition to the selected measures covering the different components of the ICF.

Studies I and III used cross-sectional designs, which are useful when studying the occurrence and severity of, e.g., health problems. Although this design is applicable for studying relationships, it cannot with certainty explain cause-effect relations (183). Study II used a prospective observational design, as the aim was to perform repeated observations of the same variables in patients with ALS over a three-year period. Study IV used a qualitative design, as the aim was to gain insight into experiences of next of kin to patients with ALS undergoing TIV. Qualitative designs are useful when the aim is to learn from participants why and how they experience a situation, process or setting, as well as the meaning and interpretation of their experiences.

Most data used in the present thesis were collected during home visits. This method was chosen because it was previously used successfully in other neurological cohorts (47, 184, 185). The home visits were much appreciated by the participat-

ing patients with ALS and contributed to high patient compliance during data collections. It was an advantage to interview participants, patients and next of kin in their own environment, as it empowered them, and that detailed information could be obtained in a way not possible during a hospital visit or via a postal survey. Further, it can be argued that this method provides ecological validity, as the real-world was studied.

The selection of measures used in the present thesis was based on previous knowledge and experience, literature reviewing, and reported psychometric properties. There was, however, a lack of measures evaluated concerning validity, reliability and responsiveness in the ALS population. This might be considered a limitation, but it is not unusual in the study of rare diseases. The self-reported questionnaires that were used, however, were standardized and well-known in the clinical settings and in the research context, and psychometric properties had been evaluated in the general population or in people with other neurological diseases. Even though the MoCA has previously been used in studies of patients with ALS (186, 187), it had obvious shortcomings, as most patients could not complete all parts of the assessment. Like many other cognitive tests, the MoCA relies on patients' physical abilities (pen-and-paper items), which makes it less useful in ALS. Another example of a questionnaire based on physical abilities and performance is the FAI. This questionnaire, which was used to map the frequency of social and lifestyle activities among the patients, was developed before the use of internet with its possibilities for, e.g., social interaction or shopping. Thus, the findings on participation restrictions should be interpreted with some caution, as patients might use technology to compensate for lack of physical performance.

The well-known and generic measure SIP was used as a measure of HRQL in patients with ALS. Although SIP can be criticized for having many items, it is rather easy for patients to complete, as they only need to answer yes or no. Furthermore, the questionnaire has previously been used in patients with other neurological diseases (47, 184, 185, 188, 189). SIP was, however, considered less suitable for next of kin, as it evaluates the impact of disease. Another generic HRQL measure, the SF-36, was therefore chosen for next of kin. In addition to these standardized questionnaires, the EQ-VAS was used. The EQ-VAS provides important, complementary information on individuals' views about their HRQL. It can be argued that the EQ-VAS has some important advantages when the individuals' views are paramount.

Although patients were recruited from the Karolinska University Hospital's ALS clinic, a major clinic in Sweden, the study sample had considerably reduced already after one year. This hampered the possibility for longitudinal analyses, such as repeated measures analysis, and descriptive statistics was therefore used

to present the available data at each time point. Cross-sectional data were used in analyses of factors associated with HRQL, in both patients with ALS and their next of kin. Even though the cause-effect relationship cannot be established, it is likely that the associated factors influenced HRQL and not the other way around. For example, it is more likely that disease severity influenced HRQL rather than that HRQL had an impact on the disease. Interestingly, the explained variance in the multivariate regression analyses was generally considerably higher when the dependent variable was the SIP or SF-36 compared to when the EQ-VAS was used. This highlights the value of using complementary measures, and further that anamnestic information is needed to understand what is important for the individual patient or next of kin.

Content analysis with an inductive approach was used in Study IV, a method considered useful for investigating both individual experiences and the wholeness of being next of kin. That the interviews were performed by two data collectors, one of whom led the interview and the other followed up on important matters, was a strength and probably enrichened the interviews. Furthermore, the trustworthiness of the results was increased by the frequent discussions between the authors in the process of analysis.

5.7 Conclusions and clinical implications

Regardless of disease severity, fatigue, anxiety, depression and pain were commonly and concurrently present in patients with ALS. Furthermore, activity limitations and participation restrictions were frequently reported. Factors associated with patients' HRQL were identified. Some of these factors are amenable to health care interventions; e.g. fatigue, anxiety and depression, and others might serve as "red flags" for health care, i.e. that these patients might need extra care and support, e.g. patients with low coping capacity. The results indicate that patients with ALS need to be regularly screened for commonly present impairments, activity limitations, participation restrictions and perceived HRQL, so that person-centred interventions can be applied at the right time.

Positive and negative experiences of caregiving were reported by the next of kin who all served as informal caregivers. Factors associated with the informal caregivers' HRQL and life satisfaction were identified. As for patients with ALS, some of the identified factors might be amenable to health care interventions, and others can serve as "red flags" for health care, e.g. that younger caregivers, men, and those who cohabit with the patient might need extra support and services. Next of kin to patients undergoing TIV described the care process related to TIV as turbulent, that their everyday life was strained, and that they perceived a conflict in being next of kin and a formal caregiver. Taken together, the results indicate that

health care should support and promote positive aspects of caregiving, provide services and support to reduce negative caregiving experiences, and to consider the individual next of kin/ informal caregivers' experience and involve them when planning care, service and support.

5.8 Future studies

Besides being a frequently occurring impairment in ALS, fatigue was also associated with patients' HRQL. The phenomenon of fatigue is complex, with both physiological and psychological dimensions, and there is a lack of research exploring these dimensions in the ALS population. Further, few studies have investigated interventions aiming to reduce fatigue. Thus, future studies are required to explore the fatigue phenomenon in ALS, and to develop and evaluate treatment strategies.

Although not present in the majority, there was a fair number of patients being categorized as having possible or probable anxiety and/or depression at each timepoint. Anxiety and/or depression in patients with ALS was also associated with informal caregivers' HRQL. Most published studies have explored the prevalence of these impairments in the ALS population, and few have evaluated effects of interventions. Future studies are therefore needed to monitor the effectiveness of pharmacological treatments and to evaluate the effects of non-pharmacological interventions, e.g. cognitive behavioural therapy, mindfulness or meditation. In addition, future studies should also evaluate combinations of pharmacological and non-pharmacological treatments.

Pain has been described as a largely neglected impairment in patients with ALS. The results showed that approximately half of the patients reported pain at each timepoint. Previous studies have mainly focused on the prevalence of pain, and thus, there is a need for future studies on the pathophysiology of pain and the effectiveness of treatment strategies.

ALS is a disease that impacts the patients' life as well as the life of their next of kin. Most literature in the past has focused on describing caregiver burden among next of kin and their need for care, service and support. There appears to be a lack of studies describing how this care and support should be delivered and organized. It would therefore be interesting in the future to study whether a self-management program, developed in a co-design process where next of kin and health professionals take an equal role in the development, could be beneficial for the next of kin to patients with ALS.

6 ACKNOWLEDGEMENTS

Även om det är mitt namn som finns på framsidan av denna avhandling så är jag inte på något sätt den enda person som bidragit till dess innehåll. Jag vill framföra min djupa tacksamhet till alla personer med ALS och deras närstående för att de delat med sig av sina erfarenheter och till alla andra som gjorde detta möjligt. Jag vill framföra ett särskilt tack till:

Marie Kierkegaard, min huvudhandledare, tack för allt stöd, engagemang och ett oändligt tålamod genom hela detta fyra år långa doktorand projekt. Du har alltid varit närvarande och tillgänglig för att svara på mina frågor vilket har varit till stor hjälp.

Lotta Widén Holmqvist, min bihandledare, för att du så generöst delat med dig av dina stora kunskaper och erfarenheter kring forskning och för inspiration till att bli mer noggrann.

Lotta Ytterberg, min bihandledare, för all kompetens du delat med dig av och för att du bidragit med konstruktiv kritik.

Sverker Johansson, min bihandledare, för att du delat med dig av din kunskap, samt ditt stöd och uppmuntran.

Helena Grönstedt, min mentor, för ditt stöd och för att du gett mig nya perspektiv på frågor stora som små.

Tidigare och nuvarande ledning på sektionen för fysioterapi, Maria Hagströmer, Anette Heijne, Malin Nygren-Bonnier och Joanna Kvist för att jag har fått möjligheten att genomföra mina doktorandstudier vid sektionen.

Mina tidigare och nuvarande chefer på Karolinska Universitetssjukhuset, Åsa Dedering och Caroline Björck för möjligheten att genomföra min utbildning.

Magnus Anderson, temachef på Tema Neuro, för möjligheten att genomföra studierna.

Neurologerna Rayomand Press, Ann Zachau, Jan Weinberg, Caroline Ingre och Lars-Olof Ronnevi på Tema Neuro, för er tillgänglighet och era bidrag till att studierna kunnat genomföras.

Susanne Littorin, för hjälp med datainsamling och för att du delat med dig av din stora kunskap. Det har varit otroligt värdefullt.

Gunilla Cröde-Widsell, för hjälp med datainsamling och för givande reflektioner.

Jens Werner och Anna Wide för att ni delat med er av er erfarenhet och kunskap.

Elisabeth Berg, för tålamod och vägledning i statistik.

Lisbet Broman, för praktisk hjälp med bildhantering.

Mariann Olsson, för vägledning i kvalitativ metodik.

Balbir Dhuper and Kerstin Dencker, för allt stöd och hjälp med administrativa praktikaliteter.

Ulrika Einarsson, för allt stöd och uppmuntran och för att du lotsade mig mot en forskarutbildning.

Kollegorna i forskargruppen, Disa Sommerfeld, Kristina Gottberg, Sebastian Lindblom och Mia Forslin, för alla era givande kommentarer och våra diskussioner.

Alla mina vänner för ert stöd och intresse.

Min mor Irene och min syster Tina med familj för att ni alltid finns där.

Mina svärföräldrar, Maria och Tomas, för att ni alltid ställer upp.

Mira, William och Novali, också kända som Mira-Li, Slobodan och Zero, för att ni finns i mitt liv och för allt bra vi har tillsammans.

Min älskade hustru Hanna, för att du gör mig till en bättre person än jag egentligen är. Du är den värdefullaste i mitt liv.

7 REFERENCES

1. Crockford C, Newton J, Lonergan K, Chiwera T, Booth T, Chandran S, et al. ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS. Neurology. 2018;91(15):e1370-e1380.

2. Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, et al. Amyotrophic lateral sclerosis. Lancet. 2011;377(9769):942-55.

3. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. Lancet Neurol. 2007;6(11):994-1003.

4. Fang F, Valdimarsdottir U, Bellocco R, Ronnevi LO, Sparen P, Fall K, et al. Amyotrophic lateral sclerosis in Sweden, 1991-2005. Arch Neurol. 2009;66(4):515-9.

5. Uenal H, Rosenbohm A, Kufeldt J, Weydt P, Goder K, Ludolph A, et al. Incidence and geographical variation of amyotrophic lateral sclerosis (ALS) in Southern Germany--completeness of the ALS registry Swabia. PLoS One. 2014;9(4):e93932.

6. Logroscino G, Traynor BJ, Hardiman O, Chio A, Mitchell D, Swingler RJ, et al. Incidence of amyotrophic lateral sclerosis in Europe. J Neurol Neurosurg Psychiatry. 2010;81(4):385-90.

7. Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. Brain. 1995;118 (Pt 3):707-19.

8. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron D. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1(5):293-9.

9. Moura MC, Novaes MR, Eduardo EJ, Zago YS, Freitas Rdel N, Casulari LA. Prognostic Factors in Amyotrophic Lateral Sclerosis: A Population-Based Study. PLoS One. 2015;10(10):e0141500.

10. Lavernhe S, Antoine JC, Court-Fortune I, Dimier N, Costes F, Lacour A, et al. Home care organization impacts patient management and survival in ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(7-8):562-8.

11. Majounie E, Renton AE, Mok K, Dopper EG, Waite A, Rollinson S, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012;11(4):323-30.

12. van Es MA, Dahlberg C, Birve A, Veldink JH, van den Berg LH, Andersen PM. Large-scale SOD1 mutation screening provides evidence for genetic heterogeneity in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2010;81(5):562-6.

13. Ingre C, Roos PM, Piehl F, Kamel F, Fang F. Risk factors for amyotrophic lateral sclerosis. Clin Epidemiol. 2015;7:181-93.

14. International classification of functioning, disability and health (ICF). Geneva: World Health Organization; 2001.

15. Yunusova Y, Green JR, Lindstrom MJ, Ball LJ, Pattee GL, Zinman L. Kinematics of disease progression in bulbar ALS. J Commun Disord. 2010;43(1):6-20.

16. Fattori B, Grosso M, Bongioanni P, Nacci A, Cristofani R, AlSharif A, et al. Assessment of swallowing by oropharyngoesophageal scintigraphy in patients with amyotrophic lateral sclerosis. Dysphagia. 2006;21(4):280-6.

17. Goldstein LH, Abrahams S. Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. Lancet Neurol. 2013;12(4):368-80.

18. Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry. 2012;83(1):102-8.

19. Gibbons ZC, Richardson A, Neary D, Snowden JS. Behaviour in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2008;9(2):67-74.

20. Saxon JA, Thompson JC, Jones M, Harris JM, Richardson AM, Langheinrich T, et al. Examining the language and behavioural profile in FTD and ALS-FTD. J Neurol Neurosurg Psychiatry. 2017;88(8):675-80.

21. Panitz S, Kornhuber M, Hanisch F. The checklist individual strength (CIS20-R) in patients with amyotrophic lateral sclerosis - A longitudinal study. Acta Neurol Scand. 2015;131(6):372-80.

22. McElhiney MC, Rabkin JG, Gordon PH, Goetz R, Mitsumoto H. Prevalence of fatigue and depression in ALS patients and change over time. J Neurol Neurosurg Psychiatry. 2009;80(10):1146-9.

23. Olsson AG, Markhede I, Strang S, Persson LI. Differences in quality of life modalities give rise to needs of individual support in patients with ALS and their next of kin. Palliat Support Care. 2010;8(1):75-82.

24. Carvalho TL, de Almeida LM, Lorega CM, Barata MF, Ferreira ML, de Brito-Marques PR, et al. Depression and anxiety in individuals with amyotrophic lateral sclerosis: a systematic review. Trends Psychiatry Psychother. 2016;38(1):1-5.

25. Chio A, Canosa A, Gallo S, Moglia C, Ilardi A, Cammarosano S, et al. Pain in amyotrophic lateral sclerosis: a population-based controlled study. Eur J Neurol. 2012;19(4):551-5.

26. Stephens HE, Lehman E, Raheja D, Yang C, Walsh S, McArthur DB, et al. Pain in amyotrophic lateral sclerosis: Patient and physician perspectives and practices. Amyotroph Lateral Scler Frontotemporal Degener. 2015;17(1-2):21-9.

27. Lillo P, Mioshi E, Zoing MC, Kiernan MC, Hodges JR. How common are behavioural changes in amyotrophic lateral sclerosis? Amyotroph Lateral Scler. 2011;12(1):45-51.

28. Prado LGR, Bicalho ICS, Vidigal-Lopes M, Prado VGR, Gomez RS, de Souza LC, et al. Depression and anxiety in a case series of amyotrophic lateral sclerosis: frequency and association with clinical features. Einstein (Sao Paulo). 2017;15(1):58-60.

29. Olsson Ozanne, Strang S, Persson LI. Quality of life, anxiety and depression in ALS patients and their next of kin. J Clin Nurs. 2011;20(1-2):283-91.

30. Rivera I, Ajroud-Driss S, Casey P, Heller S, Allen J, Siddique T, et al. Prevalence and characteristics of pain in early and late stages of ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(5-6):369-72.

31. Wallace VC, Ellis CM, Burman R, Knights C, Shaw CE, Al-Chalabi A. The evaluation of pain in amyotrophic lateral sclerosis: a case controlled observational study. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(7-8):520-7.

32. Chio A, Gauthier A, Vignola A, Calvo A, Ghiglione P, Cavallo E, et al. Caregiver time use in ALS. Neurology. 2006;67(5):902-4.

33. De Groot IJ, Post MW, Van Heuveln T, Van Den Berg LH, Lindeman E. Measurement of decline of functioning in persons with amyotrophic lateral sclerosis: responsiveness and possible applications of the Functional Independence Measure, Barthel Index, Rehabilitation Activities Profile and Frenchay Activities Index. Amyotroph Lateral Scler. 2006;7(3):167-72.

34. Van Groenestijn AC, Schroder CD, Kruitwagen-Van Reenen ET, Van Den Berg LH, Visser-Meily JMA. Participation restrictions in ambulatory amyotrophic lateral sclerosis patients: Physical and psychological factors. Muscle Nerve. 2017;56(5):912-8.

35. Bak TH, Hodges JR. The effects of motor neurone disease on language: further evidence. Brain Lang. 2004;89(2):354-61.

36. Joubert K, Bornman J, Alant E. Speech Intelligibility and Marital Communication in Amyotrophic Lateral Sclerosis: An Exploratory Study. Communication Disorders Quarterly. 2010;33(1):34-41.

37. Armon C. An evidence-based medicine approach to the evaluation of the role of exogenous risk factors in sporadic amyotrophic lateral sclerosis. Neuroepidemiology. 2003;22(4):217-28.

38. Mattsson P, Lonnstedt I, Nygren I, Askmark H. Physical fitness, but not muscle strength, is a risk factor for death in amyotrophic lateral sclerosis at an early age. J Neurol Neurosurg Psychiatry. 2012;83(4):390-4.

39. Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional status is a prognostic factor for survival in ALS patients. Neurology. 1999;53(5):1059-63.

40. Shimizu T, Nagaoka U, Nakayama Y, Kawata A, Kugimoto C, Kuroiwa Y, et al. Reduction rate of body mass index predicts prognosis for survival in amyotrophic lateral sclerosis: a multicenter study in Japan. Amyotroph Lateral Scler. 2012;13(4):363-6.

41. Jawaid A, Murthy SB, Wilson AM, Qureshi SU, Amro MJ, Wheaton M, et al. A decrease in body mass index is associated with faster progression of motor symptoms and shorter survival in ALS. Amyotroph Lateral Scler. 2010;11(6):542-8.

42. Antonovsky A. Unraveling the mystery of health: how people manage stress and stay well. 1. ed. San Fransisco, Calif: Jossey-Bass; 1987.

43. Hugel H, Pih N, Dougan CP, Rigby S, Young CA. Identifying poor adaptation to a new diagnosis of motor neuron disease: A pilot study into the value of an early patient-led interview. Amyotroph Lateral Scler. 2010;11(1-2):104-9.

44. Jakobsson Larsson B, Nordin K, Askmark H, Nygren I. Coping strategies among patients with newly diagnosed amyotrophic lateral sclerosis. J Clin Nurs. 2014;23(21-22):3148-55.

45. Jakobsson Larsson B, Nordin K, Nygren I. Coping with amyotrophic lateral sclerosis; from diagnosis and during disease progression. J Neurol Sci. 2016;361:235-42.

46. Johansson S, Ytterberg C, Hillert J, Widen Holmqvist L, von Koch L. A longitudinal study of variations in and predictors of fatigue in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2008;79(4):454-7.

47. Chruzander C, Ytterberg C, Gottberg K, Einarsson U, Widen Holmqvist L, Johansson S. A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: changes in health-related quality of life and the value of different factors in predicting health-related quality of life. J Neurol Sci. 2014;339(1-2):57-63.

48. Gottberg K, Einarsson U, Fredrikson S, von Koch L, Holmqvist LW. A population-based study of depressive symptoms in multiple sclerosis in Stockholm county: association with functioning and sense of coherence. J Neurol Neurosurg Psychiatry. 2007;78(1):60-5.

49. Palmcrantz S, Holmqvist LW, Sommerfeld DK, Tistad M, Ytterberg C, von Koch L. Differences between younger and older individuals in their use of care and rehabilitation but not in self-perceived global recovery 1year after stroke. J Neurol Sci. 2012;321(1-2):29-34.

50. Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2007(1):Cd001447.

51. Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme P, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360-75.

52. Van den Berg JP, Kalmijn S, Lindeman E, Veldink JH, de Visser M, Van der Graaff MM, et al. Multidisciplinary ALS care improves quality of life in patients with ALS. Neurology. 2005;65(8):1264-7.

53. Chio A, Bottacchi E, Buffa C, Mutani R, Mora G. Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities. J Neurol Neurosurg Psychiatry. 2006;77(8):948-50.

54. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996-2000. J Neurol Neurosurg Psychiatry. 2003;74(9):1258-61.

55. Lo Coco D, Marchese S, Pesco MC, La Bella V, Piccoli F, Lo Coco A. Noninvasive positive-pressure ventilation in ALS: predictors of tolerance and survival. Neurology. 2006;67(5):761-5.

56. Lechtzin N, Scott Y, Busse AM, Clawson LL, Kimball R, Wiener CM. Early use of non-invasive ventilation prolongs survival in subjects with ALS. Amyotroph Lateral Scler. 2007;8(3):185-8.

57. Mandrioli J, Malerba SA, Beghi E, Fini N, Fasano A, Zucchi E, et al. Riluzole and other prognostic factors in ALS: a population-based registry study in Italy. J Neurol. 2018;265(4):817-27.

58. Dreyer P, Lorenzen CK, Schou L, Felding M. Survival in ALS with home mechanical ventilation non-invasively and invasively: a 15-year cohort study in west Denmark. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(1-2):62-7.

59. Chio A, Calvo A, Ghiglione P, Mazzini L, Mutani R, Mora G. Tracheostomy in amyotrophic lateral sclerosis: a 10-year population-based study in Italy. J Neurol Neurosurg Psychiatry. 2010;81(10):1141-3.

60. Spataro R, Bono V, Marchese S, La Bella V. Tracheostomy mechanical ventilation in patients with amyotrophic lateral sclerosis: clinical features and survival analysis. J Neurol Sci. 2012;323(1-2):66-70.

61. Vianello A, Arcaro G, Palmieri A, Ermani M, Braccioni F, Gallan F, et al. Survival and quality of life after tracheostomy for acute respiratory failure in patients with amyotrophic lateral sclerosis. J Crit Care. 2011;26(3):329.e7-14.

62. Tsou AY, Karlawish J, McCluskey L, Xie SX, Long JA. Predictors of emergent feeding tubes and tracheostomies in amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler. 2012;13(3):318-25.

63. Neudert C, Oliver D, Wasner M, Borasio GD. The course of the terminal phase in patients with amyotrophic lateral sclerosis. J Neurol. 2001;248(7):612-6.

64. Tagami M, Kimura F, Nakajima H, Ishida S, Fujiwara S, Doi Y, et al. Tracheostomy and invasive ventilation in Japanese ALS patients: decision-making and survival analysis: 1990-2010. J Neurol Sci. 2014;344(1-2):158-64.

65. Andersen PM, Kuzma-Kozakiewicz M, Keller J, Aho-Oezhan HEA, Ciecwierska K, Szejko N, et al. Therapeutic decisions in ALS patients: cross-cultural differences and clinical implications. J Neurol. 2018;265(17):1600-1606.

66. Rabkin J, Ogino M, Goetz R, McElhiney M, Marziliano A, Imai T, et al. Tracheostomy with invasive ventilation for ALS patients: neurologists' roles in the US and Japan. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(2):116-23.

67. Rabkin J, Ogino M, Goetz R, McElhiney M, Hupf J, Heitzman D, et al. Japanese and American ALS patient preferences regarding TIV (tracheostomy with invasive ventilation): a cross-national survey. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(3-4):185-91.

68. Christodoulou G, Goetz R, Ogino M, Mitsumoto H, Rabkin J. Opinions of Japanese and American ALS caregivers regarding tracheostomy with invasive ventilation (TIV). Amyotroph Lateral Scler Frontotemporal Degener. 2015;17(1-2):47-54.

69. Longinetti E, Regodon Wallin A, Samuelsson K, Press R, Zachau A, Ronnevi LO, et al. The Swedish motor neuron disease quality registry. Amyotroph Lateral Scler Frontotemporal Degener. 2018:1-10.

70. Qutub K, Lacomis D, Albert SM, Feingold E. Life factors affecting depression and burden in amyotrophic lateral sclerosis caregivers. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(3-4):292-7.

71. Galvin M, Carney S, Corr B, Mays I, Pender N, Hardiman O. Needs of informal caregivers across the caregiving course in amyotrophic lateral sclerosis: a qualitative analysis. BMJ Open. 2018;8(1):e018721.

72. Creemers H, de Moree S, Veldink JH, Nollet F, van den Berg LH, Beelen A. Factors related to caregiver strain in ALS: a longitudinal study. J Neurol Neurosurg Psychiatry. 2016;87(7):775-81.

73. Burke T, Elamin M, Galvin M, Hardiman O, Pender N. Caregiver burden in amyotrophic lateral sclerosis: a cross-sectional investigation of predictors. J Neurol. 2015;262(6):1526-32.

74. Galvin M, Corr B, Madden C, Mays I, McQuillan R, Timonen V, et al. Caregiving in ALS - a mixed methods approach to the study of Burden. BMC Palliat Care. 2016;15(1):81.

75. Chio A, Vignola A, Mastro E, Giudici AD, Iazzolino B, Calvo A, et al. Neurobehavioral symptoms in ALS are negatively related to caregivers' burden and quality of life. Eur J Neurol. 2010;17(10):1298-303.

76. Nijboer C, Triemstra M, Tempelaar R, Mulder M, Sanderman R, van den Bos GA. Patterns of caregiver experiences among partners of cancer patients. Gerontologist. 2000;40(6):738-46.

77. Rabkin JG, Wagner GJ, Del Bene M. Resilience and distress among amyotrophic lateral sclerosis patients and caregivers. Psychosom Med. 2000;62(2):271-9.

78. Weisser FB, Bristowe K, Jackson D. Experiences of burden, needs, rewards and resilience in family caregivers of people living with Motor Neurone Disease/Amyotrophic Lateral Sclerosis: A secondary thematic analysis of qualitative interviews. Palliat Med. 2015;29(8):737-45.

79. Baxter SK, Baird WO, Thompson S, Bianchi SM, Walters SJ, Lee E, et al. The use of non-invasive ventilation at end of life in patients with motor neurone disease: a qualitative exploration of family carer and health professional experiences. Palliat Med. 2013;27(6):516-23.

80. Stutzki R, Weber M, Reiter-Theil S, Simmen U, Borasio GD, Jox RJ. Attitudes towards hastened death in ALS: a prospective study of patients and family caregivers. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(1-2):68-76.

81. Sundling I-M, Ekman S-L, Weinberg J, Klefbeck B. Patients with ALS and caregivers experiences of non-invasive home ventilation. Advances in Physiotherapy, 2009, Vol11(3), p114-120. 2009;11(3):114-20.

82. Trail M, Nelson ND, Van JN, Appel SH, Lai EC. A study comparing patients with amyotrophic lateral sclerosis and their caregivers on measures of quality of life, depression, and their attitudes toward treatment options. J Neurol Sci. 2003;209(1-2):79-85.

83. Kaub-Wittemer D, Steinbuchel N, Wasner M, Laier-Groeneveld G, Borasio GD. Quality of life and psychosocial issues in ventilated patients with amyotrophic lateral sclerosis and their caregivers. J Pain Symptom Manage. 2003;26(4):890-6.

84. Akiyama MO, Kayama M, Takamura S, Kawano Y, Ohbu S, Fukuhara S. A study of the burden of caring for patients with amyotrophic lateral sclerosis (MND) in Japan. British Journal of Neuroscience Nursing. 2006;2(1):38-43.

85. Self-rated health : a useful concept in research, prevention and clinical medicine. Bjørner JB, Forskningsrådsnämnden, editors. Stockholm: Stockholm : Swedish Council for Planning and Coordination of Research Forskningsrådsnämnden FRN; 1996.

86. World Health Organization. WHOQOL: Measuring Quality of Life 2017 [cited 2017 0105]. Available from: http://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/.

87. Sullivan M. SF-36 hälsoenkät : svensk manual och tolkningsguide = (Swedish manual and interpretation guide). 2. uppl. ed. Karlsson J, Taft C, Ware JE, editors. Göteborg: Sahlgrenska sjukhuset, Sektionen för vårdforskning; 2002.

88. Fayers PM. Quality of life : assessment, analysis and interpretation. Machin D, editor. Chichester: Wiley; 2000.

89. Fugl-Meyer, Melin R, Fugl-Meyer KS. Life satisfaction in 18- to 64-year-old Swedes: in relation to gender, age, partner and immigrant status. J Rehabil Med. 2002;34(5):239-46.

90. Fugl-Meyer AR, Bränholm I-B, Fugl-Meyer KS. Happiness and domain-specific life satisfaction in adult northern Swedes. Clinical rehabilitation. 1991;5(1):25-33.

91. Kiebert GM, Green C, Murphy C, Mitchell JD, O'Brien M, Burrell A, et al. Patients' health-related quality of life and utilities associated with different stages of amyotrophic lateral sclerosis. J Neurol Sci. 2001;191(1-2):87-93.

92. De Groot IJ, Post MW, van Heuveln T, Van den Berg LH, Lindeman E. Cross-sectional and longitudinal correlations between disease progression and different health-related quality of life domains in persons with amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2007;8(6):356-61.

93. Lou JS, Reeves A, Benice T, Sexton G. Fatigue and depression are associated with poor quality of life in ALS. Neurology. 2003;60(1):122-3.

94. Vignola A, Guzzo A, Calvo A, Moglia C, Pessia A, Cavallo E, et al. Anxiety undermines quality of life in ALS patients and caregivers. Eur J Neurol. 2008;15(11):1231-6.

95. Winter Y, Schepelmann K, Spottke AE, Claus D, Grothe C, Schroder R, et al. Health-related quality of life in ALS, myasthenia gravis and facioscapulohumeral muscular dystrophy. J Neurol. 2010;257(9):1473-81.

96. Lule D, Hacker S, Ludolph A, Birbaumer N, Kubler A. Depression and quality of life in patients with amyotrophic lateral sclerosis. Dtsch Arztebl Int. 2008;105(23):397-403.

97. Pizzimenti A, Aragona M, Onesti E, Inghilleri M. Depression, pain and quality of life in patients with amyotrophic lateral sclerosis: a cross-sectional study. Funct Neurol. 2013;28(2):115-9.

98. Matuz T, Birbaumer N, Hautzinger M, Kubler A. Coping with amyotrophic lateral sclerosis: an integrative view. J Neurol Neurosurg Psychiatry. 2010;81(8):893-8.

99. Gibbons C, Thornton E, Ealing J, Shaw P, Talbot K, Tennant A, et al. The impact of fatigue and psychosocial variables on quality of life for patients with motor neuron disease. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(7-8):537-45.

100. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol. 2006;5(2):140-7.

101. Lou JS, Moore D, Gordon PH, Miller R. Correlates of quality of life in ALS: Lessons from the minocycline study. Amyotroph Lateral Scler. 2010;11(1-2):116-21.

102. Veronese S, Valle A, Chio A, Calvo A, Oliver D. The last months of life of people with amyotrophic lateral sclerosis in mechanical invasive ventilation: a qualitative study. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(7-8):499-504.

103. Mitsumoto H. Caregiver assessment: Summary. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2002;3:31-4.

104. Roach AR, Averill AJ, Segerstrom SC, Kasarskis EJ. The dynamics of quality of life in ALS patients and caregivers. Ann Behav Med. 2009;37(2):197-206.

105. Bromberg MB, Forshew DA. Comparison of instruments addressing quality of life in patients with ALS and their caregivers. Neurology. 2002;58(2):320-2.

106. Chio A, Gauthier A, Calvo A, Ghiglione P, Mutani R. Caregiver burden and patients' perception of being a burden in ALS. Neurology. 2005;64(10):1780-2.

107. Londral A, Pinto A, Pinto S, Azevedo L, De Carvalho M. Quality of life in amyotrophic lateral sclerosis patients and caregivers: Impact of assistive communication from early stages. Muscle Nerve. 2015;52(6):933-41.

108. Bergstrom AL, Eriksson G, von Koch L, Tham K. Combined life satisfaction of persons with stroke and their caregivers: associations with caregiver burden and the impact of stroke. Health Qual Life Outcomes. 2011;9:1.

109. Kruithof WJ, Visser-Meily JM, Post MW. Positive caregiving experiences are associated with life satisfaction in spouses of stroke survivors. J Stroke Cerebrovasc Dis. 2012;21(8):801-7.

110. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999;169(1-2):13-21.

111. Kaufmann P, Levy G, Montes J, Buchsbaum R, Barsdorf AI, Battista V, et al. Excellent inter-rater, intra-rater, and telephone-administered reliability of the ALSFRS-R in a multicenter clinical trial. Amyotroph Lateral Scler. 2007;8(1):42-6.

112. Miano B, Stoddard GJ, Davis S, Bromberg MB. Inter-evaluator reliability of the ALS functional rating scale. Amyotroph Lateral Scler Other Motor Neuron Disord. 2004;5(4):235-9.

113. Geng D, Ou R, Miao X, Zhao L, Wei Q, Chen X, et al. Patients' self-perceived burden, caregivers' burden, and quality of life for ALS patients: a cross-sectional study. J Clin Nurs. 2017;(19-20):3188-3199.

114. Eriksson M, Lindstrom B. Validity of Antonovsky's sense of coherence scale: a systematic review. J Epidemiol Community Health. 2005;59(6):460-6.

115. Antonovsky A. The structure and properties of the sense of coherence scale. Soc Sci Med. 1993;36(6):725-33.

116. Langius A, Bjorvell H. Coping ability and functional status in a Swedish population sample. Scand J Caring Sci. 1993;7(1):3-10.

117. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.

118. Freitas S, Simoes MR, Maroco J, Alves L, Santana I. Construct Validity of the Montreal Cognitive Assessment (MoCA). J Int Neuropsychol Soc. 2012;18(2):242-50.

119. Beurskens AJ, Bultmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: validity of a questionnaire measure. Occup Environ Med. 2000;57(5):353-7.

120. Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven HWM, van Engelen BGM, van Riel P, et al. The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. J Psychosom Res. 2017;98:40-6.

121. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res. 1994;38(5):383-92.

122. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.

123. Marrie RA, Zhang L, Lix LM, Graff LA, Walker JR, Fisk JD, et al. The validity and reliability of screening measures for depression and anxiety disorders in multiple sclerosis. Mult Scler Relat Disord. 2018;20:9-15.

124. Kjaergaard M, Arfwedson Wang CE, Waterloo K, Jorde R. A study of the psychometric properties of the Beck Depression Inventory-II, the Montgomery and Asberg Depression Rating Scale, and the Hospital Anxiety and Depression Scale in a sample from a healthy population. Scand J Psychol. 2014;55(1):83-9.

125. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23(2):129-38.

126. Rahu MA, Grap MJ, Ferguson P, Joseph P, Sherman S, Elswick RK, Jr. Validity and sensitivity of 6 pain scales in critically ill, intubated adults. Am J Crit Care. 2015;24(6):514-23.

127. Young IA, Cleland JA, Michener LA, Brown C. Reliability, construct validity, and responsiveness of the neck disability index, patient-specific functional scale, and numeric pain rating scale in patients with cervical radiculopathy. Am J Phys Med Rehabil. 2010;89(10):831-9.

128. Asberg KH, Sonn U. The cumulative structure of personal and instrumental ADL. A study of elderly people in a health service district. Scand J Rehabil Med. 1989;21(4):171-7.

129. Sonn U. Longitudinal studies of dependence in daily life activities among elderly persons. Scand J Rehabil Med Suppl. 1996;34:1-35.

130. Wade DT, Legh-Smith J, Langton Hewer R. Social activities after stroke: measurement and natural history using the Frenchay Activities Index. Int Rehabil Med. 1985;7(4):176-81.

131. Turnbull JC, Kersten P, Habib M, McLellan L, Mullee MA, George S. Validation of the Frenchay Activities Index in a general population aged 16 years and older. Arch Phys Med Rehabil. 2000;81(8):1034-8.

132. Green J, Forster A, Young J. A test-retest reliability study of the Barthel Index, the Rivermead Mobility Index, the Nottingham Extended Activities of Daily Living Scale and the Frenchay Activities Index in stroke patients. Disabil Rehabil. 2001;23(15):670-6.

133. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care. 1981;19(8):787-805.

134. Bowling A. Measuring health : a review of quality of life measurement scales. 3. ed. Buckingham: Open University Pr.; 2004.

135. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

136. Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). Br J Rheumatol. 1997;36(5):551-9.

137. Hunger M, Sabariego C, Stollenwerk B, Cieza A, Leidl R. Validity, reliability and responsiveness of the EQ-5D in German stroke patients undergoing rehabilitation. Qual Life Res. 2012;21(7):1205-16.

138. Given CW, Given B, Stommel M, Collins C, King S, Franklin S. The caregiver reaction assessment (CRA) for caregivers to persons with chronic physical and mental impairments. Res Nurs Health. 1992;15(4):271-83.

139. Nijboer C, Triemstra M, Tempelaar R, Sanderman R, van den Bos GA. Measuring both negative and positive reactions to giving care to cancer patients: psychometric qualities of the Caregiver Reaction Assessment (CRA). Soc Sci Med. 1999;48(9):1259-69.

140. Persson C, Wennman-Larsen A, Sundin K, Gustavsson P. Assessing informal caregivers' experiences: a qualitative and psychometric evaluation of the Caregiver Reaction Assessment Scale. Eur J Cancer Care (Engl). 2008;17(2):189-99.

141. Domholdt E. Physical therapy research : principles and applications. 2. ed. Philadelphia: Saunders; 2000.

142. Elo S, Kyngas H. The qualitative content analysis process. J Adv Nurs. 2008;62(1):107-15.

143. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today. 2004;24(2):105-12.

144. Zwarts MJ, Bleijenberg G, van Engelen BG. Clinical neurophysiology of fatigue. Clin Neurophysiol. 2008;119(1):2-10.

145. Gibbons CJ, Thornton EW, Young CA. The patient experience of fatigue in motor neurone disease. Front Psychol. 2013;4:788.

146. Gibbons C, Pagnini F, Friede T, Young CA. Treatment of fatigue in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2018;1:Cd011005.

147. Nicholson K, Murphy A, McDonnell E, Shapiro J, Simpson E, Glass J, et al. Improving symptom management for people with amyotrophic lateral sclerosis. Muscle Nerve. 2018;57(1):20-4.

148. Diaz JL, Sancho J, Barreto P, Banuls P, Renovell M, Servera E. Effect of a short-term psychological intervention on the anxiety and depression of amyotrophic lateral sclerosis patients. J Health Psychol. 2016;21(7):1426-35.

149. Chio A, Mora G, Lauria G. Pain in amyotrophic lateral sclerosis. Lancet Neurol. 2017;16(2):144-57.

150. Ng L, Khan F, Mathers S. Multidisciplinary care for adults with amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database Syst Rev. 2009(4):Cd007425.

151. Morris ME, Perry A, Bilney B, Curran A, Dodd K, Wittwer JE, et al. Outcomes of physical therapy, speech pathology, and occupational therapy for people with motor neuron disease: a systematic review. Neurorehabil Neural Repair. 2006;20(3):424-34.

152. Ramirez C, Piemonte ME, Callegaro D, Da Silva HC. Fatigue in amyotrophic lateral sclerosis: frequency and associated factors. Amyotroph Lateral Scler. 2008;9(2):75-80.

153. Thakore NJ, Pioro EP. Depression in ALS in a large self-reporting cohort. Neurology. 2016;86(11):1031-8.

154. Eriksson M, Lindstrom B. Antonovsky's sense of coherence scale and its relation with quality of life: a systematic review. J Epidemiol Community Health. 2007;61(11):938-44.

155. Antonovsky A. Health, stress and coping. 1. ed. San Fransisco, Calif: Jossey-Bass; 1979.

156. Super S, Wagemakers MA, Picavet HS, Verkooijen KT, Koelen MA. Strengthening sense of coherence: opportunities for theory building in health promotion. Health Promot Int. 2016;31(4):869-878.

157. Peters M, Fitzpatrick R, Doll H, Playford ED, Jenkinson C. The impact of perceived lack of support provided by health and social care services to caregivers of people with motor neuron disease. Amyotroph Lateral Scler. 2012;13(2):223-8.

158. Bruletti G, Comini L, Scalvini S, Morini R, Luisa A, Paneroni M, et al. A two-year longitudinal study on strain and needs in caregivers of advanced ALS patients. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(3-4):187-95.

159. Forsberg A, de Pedro-Cuesta J, Widen Holmqvist L. Use of healthcare, patient satisfaction and burden of care in Guillain-Barre syndrome. J Rehabil Med. 2006;38(4):230-6.

160. Gottberg K, Chruzander C, Einarsson U, Fredrikson S, Johansson S, Widen Holmqvist L. Health-related quality of life in partners of persons with MS: a longitudinal 10-year perspective. BMJ Open. 2014;4(12):e006097.

161. Miyashita M, Narita Y, Sakamoto A, Kawada N, Akiyama M, Kayama M, et al. Care burden and depression in caregivers caring for patients with intractable neurological diseases at home in Japan. J Neurol Sci. 2009;276(1-2):148-52.

162. Burke T, Hardiman O, Pinto-Grau M, Lonergan K, Heverin M, Tobin K, et al. Longitudinal predictors of caregiver burden in amyotrophic lateral sclerosis: a population-based cohort of patient-caregiver dyads. J Neurol. 2018;265(4):793-808.

163. Foley G, Timonen V, Hardiman O. “I hate being a burden”: The patient perspective on carer burden in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2016;17(5-6):351-7.

164. Gauthier A, Vignola A, Calvo A, Cavallo E, Moglia C, Sellitti L, et al. A longitudinal study on quality of life and depression in ALS patient-caregiver couples. Neurology. 2007;68(12):923-6.

165. Tramonti F, Bongioanni P, Leotta R, Puppi I, Rossi B. Age, gender, kinship and caregiver burden in amyotrophic lateral sclerosis. Psychol Health Med. 2015;20(1):41-6.

166. Olsson Ozanne, Graneheim UH, Persson L, Strang S. Factors that facilitate and hinder the manageability of living with amyotrophic lateral sclerosis in both patients and next of kin. J Clin Nurs. 2012;21(9-10):1364-73.

167. Olsson AG, Markhede I, Strang S, Persson LI. Well-being in patients with amyotrophic lateral sclerosis and their next of kin over time. Acta Neurol Scand. 2010;121(4):244-50.

168. Burke T, Galvin M, Pinto-Grau M, Lonergan K, Madden C, Mays I, et al. Caregivers of patients with amyotrophic lateral sclerosis: investigating quality of life, caregiver burden, service engagement, and patient survival. J Neurol. 2017;264(5):898-904.

169. Lo Coco G, Lo Coco D, Cicero V, Oliveri A, Lo Verso G, Piccoli F, et al. Individual and health-related quality of life assessment in amyotrophic lateral sclerosis patients and their caregivers. J Neurol Sci. 2005;238(1-2):11-7.

170. Wasner M, Bold U, Vollmer TC, Borasio GD. Sexuality in patients with amyotrophic lateral sclerosis and their partners. J Neurol. 2004;251(4):445-8.

171. Sancho J, Servera E, Diaz JL, Banuls P, Marin J. Home tracheotomy mechanical ventilation in patients with amyotrophic lateral sclerosis: causes, complications and 1-year survival. Thorax. 2011;66(11):948-52.

172. Karolinska University Hospital. Riktlinjer för initiering och avbrytande av invasiv ventilation vid ALS 2017 [cited 2018 1026]. Available from: https://lis.sll.se/prod/karolinska/lis/verksamhetshandbok/vhandbok.nsf//87E9924B75C070BAC125815A0030881B/$File/AVINAUFDLU.pdf?OpenElement.

173. Evans R, Catapano MA, Brooks D, Goldstein RS, Avendano M. Family caregiver perspectives on caring for ventilator-assisted individuals at home. Can Respir J. 2012;19(6):373-9.

174. Rossi Ferrario S, Zotti AM, Zaccaria S, Donner CF. Caregiver strain associated with tracheostomy in chronic respiratory failure. Chest. 2001;119(5):1498-502.

175. Liu JF, Lu MC, Fang TP, Yu HR, Lin HL, Fang DL. Burden on caregivers of ventilator-dependent patients: A cross-sectional study. Medicine (Baltimore). 2017;96(27):e7396.

176. van Kesteren RG, Velthuis B, van Leyden LW. Psychosocial problems arising from home ventilation. Am J Phys Med Rehabil. 2001;80(6):439-46.

177. Larsson BJ, Frojd C, Nordin K, Nygren I. Relatives of patients with amyotrophic lateral sclerosis: Their experience of care and support. Palliat Support Care. 2015;13(6):1569-77.

178. Ozanne AO, Graneheim UH, Strang S. Struggling to find meaning in life among spouses of people with ALS. Palliat Support Care. 2015;13(4):909-16.

179. Bergin S, Mockford C. Recommendations to support informal carers of people living with motor neurone disease. Br J Community Nurs. 2016;21(10):518-24.

180. McKim DA, King J, Walker K, Leblanc C, Timpson D, Wilson KG, et al. Formal ventilation patient education for ALS predicts real-life choices. Amyotroph Lateral Scler. 2012;13(1):59-65.

181. Pupillo E, Messina P, Logroscino G, Beghi E. Long-term survival in amyotrophic lateral sclerosis: a population-based study. Ann Neurol. 2014;75(2):287-97.

182. Jakobsson Larsson B, Ozanne AG, Nordin K, Nygren I. A prospective study of quality of life in amyotrophic lateral sclerosis patients. Acta Neurol Scand. 2017;136(6):631-638.

183. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003;20(1):54-60.

184. Einarsson U, Gottberg K, Fredrikson S, Bergendal G, von Koch L, Holmqvist LW. Multiple sclerosis in Stockholm County. A pilot study exploring the feasibility of assessment of impairment, disability and handicap by home visits. Clin Rehabil. 2003;17(3):294-303.

185. Forsberg A, Press R, Einarsson U, de Pedro-Cuesta J, Holmqvist LW. Disability and health-related quality of life in Guillain-Barre syndrome during the first two years after onset: a prospective study. Clin Rehabil. 2005;19(8):900-9.

186. Osborne RA, Sekhon R, Johnston W, Kalra S. Screening for frontal lobe and general cognitive impairment in patients with amyotrophic lateral sclerosis. J Neurol Sci. 2014;336(1-2):191-6.

187. Ohta Y, Sato K, Takemoto M, Takahashi Y, Morihara R, Nakano Y, et al. Behavioral and affective features of amyotrophic lateral sclerosis patients. J Neurol Sci. 2017;381:119-25.

188. Ytterberg C, Thorsen AM, Liljedahl M, Holmqvist LW, von Koch L. Changes in perceived health between one and five years after stroke: a randomized controlled trial of early supported discharge with continued rehabilitation at home versus conventional rehabilitation. J Neurol Sci. 2010;294(1-2):86-8.

189. Gottberg K, Einarsson U, Ytterberg C, de Pedro Cuesta J, Fredrikson S, von Koch L, et al. Health-related quality of life in a population-based sample of people with multiple sclerosis in Stockholm County. Mult Scler. 2006;12(5):605-12.

Karolinska Institutet

Arkitektkopia AB, Bromma, 2018