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# Pain in patients with motor neuron disease: Variation of pain and association with disease severity, health-related quality of life and depression – A longitudinal study

Sören Spörndly-Nees, PH.D.[1], Birgitta Jakobsson Larsson, PH.D.[2], Lena Zetterberg, PH.D.[1], Ylva Åkerblom, PH.D.[1], Dag Nyholm, PH.D.[3] and Pernilla Åsenlöf PH.D.[1]

[1]Department of Women's and Children's Health, Physiotherapy and Behavioral Medicine, Uppsala University, Uppsala, Sweden; [2]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden and [3]Department of Medical Sciences, Neurology, Uppsala University, Uppsala, Sweden

## Original Article

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**Corresponding author:** Sören Spörndly-Nees; Email: soren.sporndly-nees@neuro.uu.se

## Abstract

**Objectives.** To describe levels of pain over time during disease progression in individual patients and for a total sample of patients with motor neuron disease (MND), respectively, and to examine associations between pain, disease severity, health-related quality of life (HRQOL), and depression.

**Methods.** A prospective cohort study was conducted on 68 patients with MND, including data collected on five occasions over a period of 2 years. Pain was assessed using the Brief Pain Inventory – Short Form. Depression was assessed using the Amyotrophic Lateral Sclerosis (ALS)-Depression-Inventory (ADI-12). Disability progression was measured using the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised Version (ALSFRS-R). HRQOL was assessed using the Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5).

**Results.** Participants reported great individual variation over time. The median level of pain was 4 (min 0 and max 10). Higher levels of pain during the last 24 h were associated with higher depression scores (ADI-12), poorer quality of life (ALSAQ-5), and lower reporting of fine and gross motor skills (ALSFRS-R). Baseline pain levels did not predict future values of depression and function. Individuals reporting average pain >3 experienced more hopelessness toward the future and reported higher depression scores compared with participants reporting average pain <3.

**Significance of results.** Great within-individual variation of pain intensity was reported. Pain intensity was associated with depression, function and HRQOL cross-sectionally, but it did not have a strong prognostic value for future depression, function, or HRQOL. Patients with MND should be offered frequent assessment of pain and depressive symptoms in person-centered care, allowing for individualization of treatment.

## Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that affects the motor neurons, leading to loss of strength in the extremities, problems eating and speaking, and problems with respiration. ALS is the most common of the motor neuron diseases (MND). There is no known cure for ALS and the mean survival period is 3–5 years from the disease onset (Tiryaki and Horak 2014). Younger age at symptom onset as well as duration of symptoms correlate to longer survival (Kollewe et al. 2008). Besides the symptoms related to loss of motor neuron function, patients with MND, such as ALS, are at risk of increased prevalence of pain (Tiryaki and Horak 2014), lower quality of life (QOL), and depression (Heidari et al. 2021).

The fatal outcome and the rapid progression of the disease result in caregivers focusing on palliative treatment to help patients with ALS cope with the disabling disease and provide the best possible quality of life (Karam et al. 2016). Recently, individual quality of life (IQOL) was reported as good (Jakobsson Larsson et al. 2017), and no association with pain was found in cross-sectional findings of patients with MND, possibly explained by patients' ability to cope with their situation (Åkerblom et al. 2021).

Individual quality of life differs from health-related quality of life (HRQOL), by allowing the individual to select areas of their own choice of importance for their HRQOL (Neudert et al. 2004). However, when measuring HRQOL, the result may be different. The HRQOL in patients with MND is influenced by several factors; moreover, associations with progression

of the disease (Prell et al. 2019), pain, and depression symptoms (Sandstedt et al. 2016) are reported.

In a review on the pooled prevalence of pain in people with ALS, as many as 60% had pain (Hurwitz et al. 2021); furthermore, when studied prospectively, pain intensity did not change over time (Wigand et al. 2021). Studies on the associations between HRQOL and pain in MND point to conflicting results; two studies reported no correlation (Ganzini et al. 1999; Lopes et al. 2018). Nevertheless, Pagnini et al. (2012) found that higher pain intensity was associated with worse HRQOL. The results were similar in another study until adjustment for depression, which highlights the need to take depression into account when discussing HRQOL (Pizzimenti et al. 2013). A recent review established that depression is prevalent in 34% of the people with ALS (Heidari et al. 2021) but, in a recent longitudinal study, Wigand et al. (2021) found no conclusive evidence of the association between pain and depressive symptoms. Given the prevalence of both pain and depression in MND, and the inconclusive evidence from previous studies concerning associations with QOL, further studies on this association are warranted (Heidari et al. 2021).

Therefore, the aim of this study was to describe the reported levels of pain over time during disease progression in individual patients and for a total sample of people with MND. Another aim was to examine the association between pain, disease severity, HRQOL, and depression.

## Materials and methods

The study was a prospective cohort study, including data collection on five occasions over a period of 2 years. Patients were included in the study from September 2015 and the last follow-up was conducted in September 2019. The study was performed in agreement with the Declaration of Helsinki and approved by the Regional Ethics Committee in Uppsala, Sweden (Approval No. 2015/293). The patients confirmed participation by signing an informed consent form.

### Settings and participants

Data were collected from four multi-disciplinary teams in Sweden, specialized in MND care. Fifteen health professionals with an extensive experience of treating patients with MND were involved in the data collection at the four sites.

Patients were considered eligible if over 18 years of age, had a MND diagnosis according to El Escorial Criteria (Ludolph et al. 2015), and scheduled for routine visits at any of the four multidisciplinary MND teams. Patients were thus included at different states of their MND. Patients having a severe impact on cognitive function, difficulties understanding or expressing themselves in Swedish, and patients with another neurological disease affecting the symptoms of MND were excluded. In addition, patients with Kennedy's disease were excluded due to the sensory impact of the disease possibly affecting the perception of pain (Querin et al. 2017).

### Outcomes and measures

*Pain* was measured with the Short Form of Brief Pain Inventory (BPI-SF) (Cleeland and Ryan 1994). The BPI-SF measures the presence of pain, pain severity, body regions affected, treatments for pain, and pain interference in different activities (Cleeland and Ryan 1994). In the present study, two subscales were used: presence of pain and pain severity during the past 24 h. Presence of pain was indicated with "yes/no." Severity of pain was rated on four 11-point numeric rating scales (NRS) for worst, least, and average pain intensity during the past 24 h, and for current pain. The anchors were labeled: 0 = "no pain" and 10 = "worst imaginable pain" (Cleeland 2009). An average of 0–3 is considered no or mild, 4–6 as moderate, and 7–10 as severe pain (Hoffman et al. 2010). The measure is considered to be valid for several painful conditions (Celik et al. 2017; de Andres Ares et al. 2015; Naegeli et al. 2015) and has been widely used to evaluate pain in neuromuscular disorders, including ALS (Chiò et al. 2012; Hanisch et al. 2015; Hoffman et al. 2005; Stephens et al. 2015; Wallace et al. 2014). The internal consistency is high with Cronbach's $\alpha$ 0.84–0.93 in participants with non-cancer pain, systemic lupus erythematosus, and musculoskeletal pain (Celik et al. 2017; de Andres Ares et al. 2015; Naegeli et al. 2015). In the present study, the Cronbach's $\alpha$ was 0.93.

*Depression* was assessed using the ALS-Depression-Inventory (ADI-12). Patients were asked to state how much they agreed with each statement on a 4-point Likert-scale with regard to the last 2 weeks. Scores range from 0 (best possible) to 48 (worst possible) with scores >23 identifying all patients with any depressive disorder and the corresponding specificity is of 60%. The internal consistency is high (Cronbach's $\alpha = 0.91$) and the ADI-12 is correlated to the Beck Depression-Inventory (Pearson correlation coefficient = 0.81) (Hammer et al. 2008). The Cronbach's $\alpha$ was 0.93 in the present study.

*Disability progression* was measured using the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised Version (ALSFRS-R) (Cedarbaum et al. 1999). This functional rating scale includes four subscales measuring bulbar, fine motor, gross motor, and respiratory function. Each subscale includes three items ranging from 0 (totally lost) to 4 (normal function), resulting in a total score of 12 for each of the subscales. Lower scores indicate a higher level of dysfunction (Cedarbaum et al. 1999). The internal consistency was previously reported as high, Cronbach's $\alpha$ 0.73 (Cedarbaum et al. 1999), and the corresponding number was 0.86 in the present study. The construct validity of the total score correlates with HRQOL measured with the Sickness Impact Profile, $r_s = -0.72$ and with pulmonary function (forced vital capacity %) $r_s = 0.41$ (Cedarbaum et al. 1999).

*Health-Related Quality of Life* was assessed using the Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5). The patients were asked to state how much difficulties they had experienced during the last 2 weeks on a 5-point Likert-scale; total scores range from 0 to 20 (20 indicating the best health status). The five items include: physical function in the lower extremity, physical function in the upper extremities, eating and drinking, communication, and psychological well-being. The ALSAQ-5 was reported with a valid measure of the original 40 items ALSAQ version (Jenkinson and Fitzpatrick 2001). The Cronbach's $\alpha$ was 0.66 in the present study.

### Demographic data

Demographic data were collected during the visits. It included gender, age, family situation, level of education, occupational status, time since first perceived disease symptoms, self-reported comorbidity, and experience of chronic pain before the onset of MND.

### Procedure

An information letter was sent to the patients ahead of their scheduled visit to the MND team, and oral information about the

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**Table 1.** Participants' characteristics at baseline

| | All patients ($N = 68$) |
|---|---|
| Gender, *n* (%) | |
| Female | 24 (35.3) |
| Male | 44 (64.7) |
| Age, all patients, m (SD) | 60.3 (11.8) |
| Family situation, *n* (%) | |
| Married/cohabitant | 39 (57.4%) |
| Partner and children | 15 (22.1%) |
| Single parent | 3 (4.4%) |
| Single | 11 (16.2%) |
| Education, *n* (%) | |
| Elementary school | 15 (22.1%) |
| High school | 24 (35.3%) |
| University | 29 (42.6%) |
| Occupational status, *n* (%) | |
| Working full-time | 6 (8.8%) |
| Working part-time | 3 (4.4%) |
| Working part-time and sickness benefit part-time | 6 (8.8%) |
| Sickness benefit full-time | 20 (29.4%) |
| Sickness benefit part-time | 2 (2.9%) |
| Retired | 29 (42.6%) |
| Unemployed | 1 (1.5%) |
| Other | 1 (1.5%) |
| Diagnosis, *n* (%) | |
| ALS[a] yes | 42 (61.8%) |
| MND[b] yes | 26 (38.2%) |
| Time since first symptom of disease | |
| Years, mean (SD) | 4.2 (5.7) |
| Self-reported comorbidity | |
| Yes | 31 (45.6%) |
| No | 37 (54.4%) |
| Pain, BPI-SF, $n = 68$[c] | |
| Pain during past 24 h, *n* = yes (%) | 41 (68.3%) |
| Worst level of pain past 24 h, md (min, max) | 4 (0, 10) |
| Average pain, md (min, max) | 3 (0, 10) |
| Chronic pain before onset of MND ($n = 67$), *n* (%) | |
| Yes | 31 (46.3) |
| No | 36 (53.7) |
| ALSAQ-5, total score, md (min, max)[d] | 8.5 (0, 20) |
| ALSFRS, bulbar function, md (min, max)[e] | 10 (0, 12) |
| ALSFRS, fine and gross motor function, md (min, max) | 14.5 (0, 20) |
| ALSFRS, respiratory function, md (min, max) | 12 (1, 12) |
| ADI-12, total score, md (min, max)[f] | 21.5 (12, 44) |

[a]ALS = amyotrophic lateral sclerosis, with both upper and lower motor neuron signs.
[b]MND = motor neuron disease with lower motor neuron signs and symptoms.
[c]BPI-SF = Brief Pain Inventory – Short Form.
[d]ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
[e]ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised.
[f]ADI-12 = Amyotrophic Lateral Sclerosis (ALS)-Depression-Inventory.

study was provided during the visit. After the patients had given their informed consent, data were collected during the visit to the clinic. To reduce the length of the clinical visit, the participants completed the BPI-SF (Cleeland and Ryan 1994) at home.

### Data management and analysis

Descriptive statistic was presented in number and percentage for categorical data, mean, and standard deviation for continuous data, and the median was presented with minimum (min) and maximum (max) values for ordinal data.

For evaluation of time lived with MND symptoms, sub-cohorts were generated based on time since the first perceived symptoms. The participants were divided into three sub-cohorts: 0–24 months, 24.1–60 months, and >60 months from symptom onset.

When comparing two groups, Mann–Whitney's *U*-test was used to test for significance. When comparing more than two groups, Kruskal–Wallis test was performed to test if at least one group differed from the other. To test the significance of associations, a Spearman's rank correlation coefficient was calculated. The number included in each analysis is presented in Tables 1–4. The level of significance was set at $p \leq 0.05$. All statistics were performed in R version 4.1.0 (Vienna, Austria).

## Results

### Participants' characteristics

In total, 68 participants were included in the study and 46 participants (67.6%) did not participate in the last assessment; the drop-outs were due to participants being too ill or having passed away. The majority of the participants are men; most lived with a partner (79.5%) and were either retired or received sickness benefits full-time (72%). The detailed characteristics of the participants are presented in Table 1.

### Individual variation of pain over time

The participants reported 4 (min 0 and max 10) in the median level of worst pain during the last 24 h at baseline. To illustrate the variation of self-reported pain throughout the study period, Figure 1 shows the worst pain scores during the last 24 h for each individual and as an average for each of the three sub-cohorts. No clear patterns in the course of pain were seen throughout the study. In some individuals, pain intensity appeared rather stable, whereas in others, the pain fluctuated between high and low levels.

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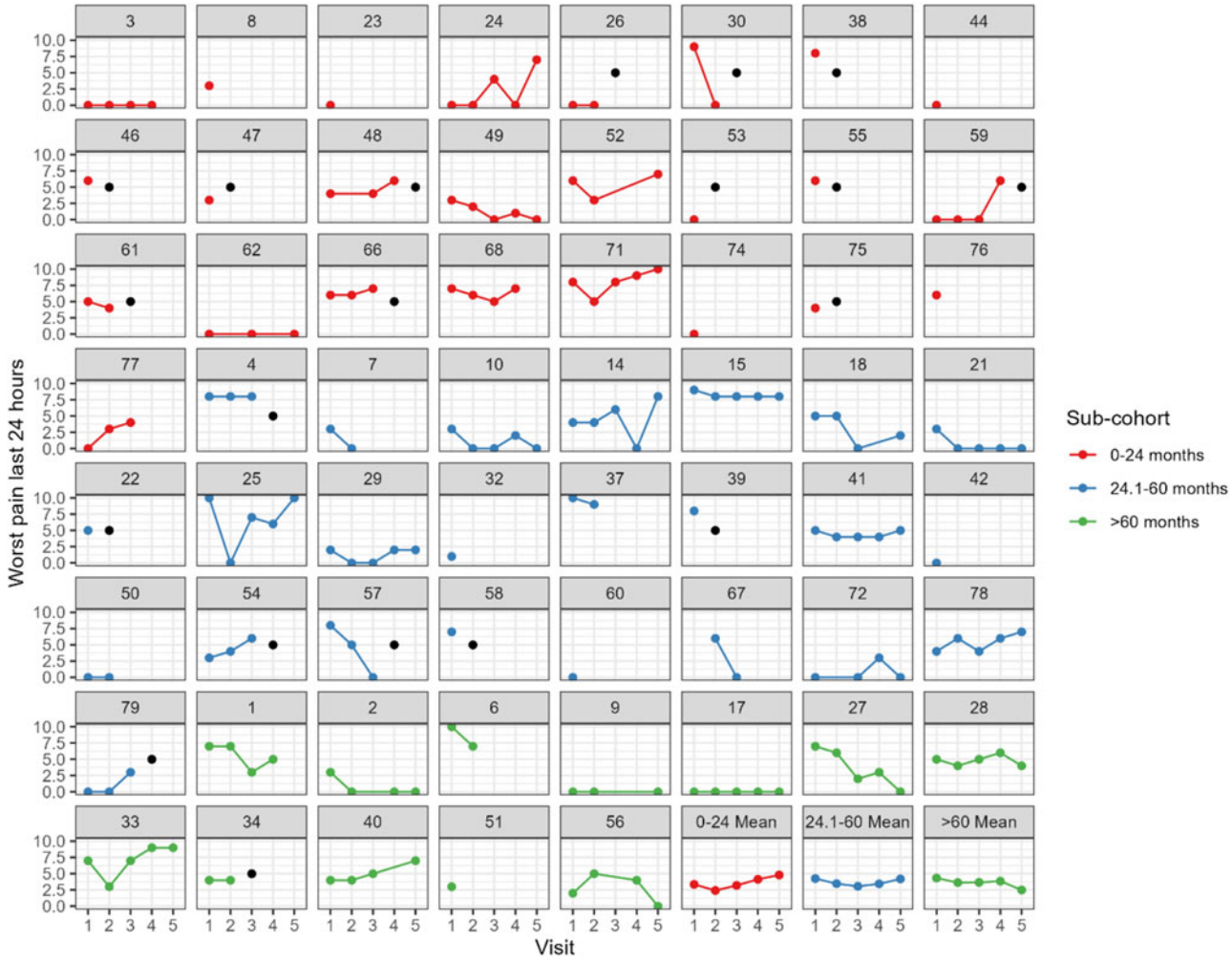


**Figure 1.** Line plots for each individual for the variable BPI worst pain during the last 24 h. The last three-line plots show the average for the three sub-cohorts.

**Table 2.** Spearman rank correlations between baseline pain (BPI average and worst pain during the last 24 h) and depression (ADI-12), function (ALSFRS-R) and quality of life ALSAQ at the five visits

| | BPI[a] average | | | | | BPI worst pain during the last 24 h | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit (n) | 1st visit, *n* (60) | 2nd visit, *n* (40) | 3rd visit, *n* (31) | 4th visit, *n* (23) | 5th visit, *n* (23) | 1st visit, *n* (60) | 2nd visit, *n* (40) | 3rd visit, *n* (31) | 4th visit, *n* (23) | 5th visit, *n* (23) |
| *ADI-12[b] total score* | **0.36*** | [c] | [c] | [c] | 0.22 | **0.34*** | [c] | [c] | [c] | 0.22 |
| *ALSFRS-R[d] – bulbar function* | 0.05 | −0.07 | −0.04 | −0.29 | 0.13 | −0.09 | −0.18 | −0.2 | −0.22 | 0.06 |
| *ALSFRS-R – fine and gross motor skills* | −0.16 | 0.06 | −0.12 | 0.08 | 0.04 | **−0.35*** | 0.01 | −0.27 | 0.02 | 0.05 |
| *ALSFRS-R – respiration function* | −0.10 | −0.17 | 0.02 | −0.03 | −0.19 | −0.23 | −0.08 | −0.14 | −0.09 | −0.25 |
| *ALSAQ[e] – total score* | **0.34*** | 0.21 | 0.17 | 0.39 | 0.16 | **0.37*** | 0.22 | **0.41*** | 0.36 | 0.05 |

[a]BPI-SF = Brief Pain Inventory Short Form.
[b]ADI-12 = Amyotrophic Lateral Sclerosis (ALS)-Depression-Inventory.
[c]ADI-12 was only assessed at the 1st and 5th visit.
[d]ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised.
[e]ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire.
*and bold values are significant at the 5% level).

## *Association and prognostic value of pain for future depression, function, or HRQOL*

The prognostic values of pain on future depression, function, or HRQOL; associations between baseline values of BPI average pain and BPI worst pain during the last 24 h; and depression, function, and HRQOL are presented in Table 2.

At the baseline visit, higher levels of pain during the last 24 h were associated with higher depression scores (ADI-12), a

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**Table 3.** Comparison between individuals with pain less than 3 versus pain 3 or more using Mann–Whitney's *U*-test

| Variables | Average pain BPI $< 3$[a], $N = 28$ (47%) | Average pain BPI $\geq 3$[a], $N = 32$ (53%) | *p*-Value |
|---|---|---|---|
| Age | 60.82 (12.14) | 58.84 (11.51) | 0.45 |
| ALSAQ-5[b] | | | |
| Difficulties getting up | 2.14 (1.35) | 2.53 (1.32) | 0.25 |
| Difficulties using arms and ands | 1.93 (1.56) | 2.56 (1.32) | 0.13 |
| Difficulties eating solid food | 0.82 (1.19) | 1.44 (1.54) | 0.13 |
| Difficulties communicating | 1.54 (1.55) | 1.44 (1.61) | 0.69 |
| Hopelessness toward future | **1.21 (1.03)** | **2.16 (1.19)** | **<0.01*** |
| *Total score* | 7.81 (4.70) | 10.12 (4.47) | 0.07 |
| Time since first symptom of disease (years) | 4.06 (3.83) | 4.72 (7.49) | 0.76 |
| ALSFRS-R[c] | | | |
| 1. Bulbar function | 9.18 (3.12) | 9.31 (3.35) | 0.66 |
| 2. Fine motor function | 5.41 (2.76) | 5.37 (2.24) | 0.62 |
| 3. Gross motor function | 7.64 (3.22) | 7.16 (3.47) | 0.64 |
| 4. Respiratory function | 10.25 (3.24) | 10.19 (2.79) | 0.73 |
| ADI-12 total score[d] | **20.31 (6.81)** | **25.22 (8.30)** | **0.01*** |

[a]BPI-SF = Brief Pain Inventory – Short Form (pain severity rated from 0 = "no pain" and 10 = "worst imaginable pain").
[b]ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire (scores range from 0 to 20 (20 indicating the best health status)).
[c]ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised. Each subscale includes three items ranging from 0 (totally lost) to 4 (normal function), making a total score of 12 for each of the subscales. Lower scores indicate a higher level of dysfunction.
[d]ADI-12 = Amyotrophic Lateral Sclerosis (ALS)-Depression-Inventory; ADI-12 (scores range from 0 (best possible) to 48 (worst possible)).
*and bold values are significant at the 5% level.

poorer quality of life (ALSAQ-5), and lower reporting of fine and gross motor skills (ALSFRS-R). The baseline level of pain, however, did not predict the future values of depression, function, or HRQOL.

### *Pain intensity*

The comparisons of quality of life (ALSAQ-5), time since the first symptom of disease, function (ALSFRS-R), and depression (ADI-12) in patients experiencing lower and higher levels of pain are reported in Table 3. Age, time lived with symptoms, and the total score on quality of life did not differ between the participants reporting lower or higher levels of pain. However, individuals reporting average pain >3, to a larger degree, experienced hopelessness toward the future and reported a higher depression score compared with participants reporting average pain <3.

### *Time lived with motor neuron disease symptoms*

The time lived with MND symptoms ahead of study inclusion is illustrated in Figure 2. Participants were assessed on five occasions at the most during the study. The proportion of patients with ALS in sub-groups 1–3 were 68%, 65%, and 33%, respectively. There were large variations in the number of total follow-up visits, based on the time since the first symptoms. Nearly, half (48.1%) of the first sub-cohort (0–24 months) died during the study period compared with 27.6% in the second sub-cohort (24.1–60 months) and 8.3% in the third sub-cohort, which also had the longest time (>60 months) from the first symptoms to study inclusion.

### *Time in study*

Participants who participated in their 5th visit were younger, had lived for a longer time since they first experienced symptoms, and reported a lower score in the ALSQ-5, indicating a higher quality of life. Participants attending the 5th visit reported lower on the ADI-12, indicating a lower presence of depression on a group level. There was no difference between the groups in pain or disease severity, as reported in the ALSFRS-R (see Table 4).

## Discussion

To the best of our knowledge, this is one of a few prospective studies following a cohort of patients with MND over a longer time. Data were collected on up to five occasions during a period of 2 years, providing a unique opportunity for identification of how pain varies over time and the associations between pain and HRQOL, function, and depression.

At baseline, pain was present in 68.3% of the study participants, which is at the higher end of previously reported data on prevalence (Hurwitz et al. 2021). The intensity of worst pain experienced during the last 24 h was at a moderate level (median 4), and a mild level was reported regarding average pain (median 3) (Hoffman et al. 2010). These findings are comparable to those reported in a review by Hurwitz et al. (2021).

The three sub-cohorts, based on time since the first symptoms, were relatively stable regarding the mean levels of worst pain during the last 24 h throughout the study. This is in accordance with the longitudinal findings by Wigand et al. (2021). Interestingly, when observing the individuals in our study, a large variance was found, i.e., some individuals reported no pain (NRS = 0) during one visit and high levels of pain (NRS = 8) on another visit or vice versa. These findings corroborate the results of our previous qualitative study, where we found patients experienced that pain fluctuated over time and that it was very hard to predict, even on a day-to-day basis (Åkerblom et al. 2020). Taken together, these studies underline the importance of having tailored assessments and treatment, as the level of pain varies both within and between individuals (Åkerblom et al. 2020; Chiò et al. 2012).

In contrast to one study (Ganzini et al. 1999), but in line with Pagnini et al. (2012), the pain reported in this cohort was associated with poor HRQOL at baseline. The association remained similar during all visits; however, it was only significant at the 1st and 3rd visit for worst pain during the last 24 h. Moreover, higher levels of pain were significantly associated with more symptoms of depression at baseline, but the association was not significant at the follow-up. Both HRQOL and symptoms of depression were moderately correlated with pain at baseline, but the strength of the association weakened and lost significance at the later assessments.

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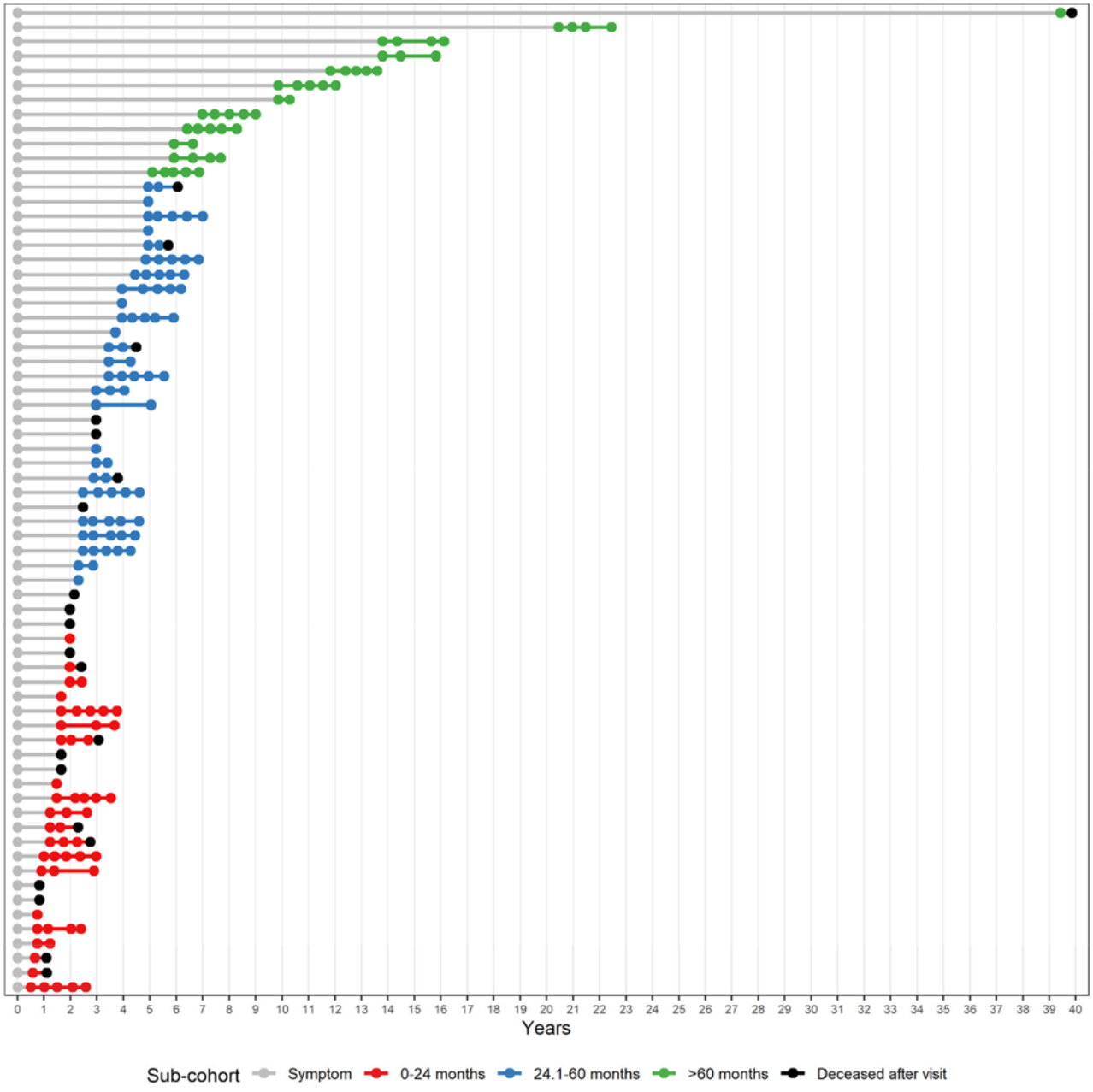


**Figure 2.** Follow-up visits and time from first symptom, standardized to first symptom. The individuals were categorized into three sub-cohorts, based on their time from first symptom at the first visit. The three sub-cohorts are: 0–24: between 0 and 24 months from first symptom at first visit; 24.1–60: between 24.1 and 60 months from first symptom at first visit; >60: over 60 months from first symptom at first visit. A black dot symbolizes death after visit.

This may be an expression of patients adapting to their life situation, referred to as a response shift (Sprangers and Schwartz 1999) due to a redefinition of internal standards and values. The loss of significance may also be due to the lower number of participants at the later assessments, which makes significant correlations less likely. Hence, our findings highlight that pain is not a predictor of future depression, function, and HRQOL on a group level; nonetheless, the results should be interpreted with caution due to the decreased power over time and the high within-individual variation.

In the present study, 32.3% of the patients died during the study period. In the sub-cohort of patients having had symptoms from 0 to 24 months before inclusion, the mortality was higher (48.1%). This may be an expression of a larger proportion of patients with a rapid disease progression. Time from the first symptoms was not associated with the average intensity of pain, indicating that the duration of the disease is not a predictor of pain intensity.

## Methodological considerations

From disease onset, the mean survival period is short, and high mortality would be expected in prospective studies with MND patients. Analysis of those taking part in the 5th and last visit in the study adds information on the characteristics of individuals

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**Table 4.** Comparison of baseline values for the 26 individuals who came to the 5th follow-up visit against the 42 individuals who did not have a 5th visit. Mann–Whitney's *U*-test is used as the significance test

| Variables | 5th visit average | Not 5th visit average | *p*-Value |
|---|---|---|---|
| Age | 55.92 (12.75) | 63.00 (10.41) | **0.03*** |
| BPI average[a] | 2.72 (2.62) | 2.87 (2.41) | 0.74 |
| BPI worst pain during last 24 h | 3.88 (3.02) | 3.91 (3.37) | 0.98 |
| Time since first symptom of disease (years) | 5.45 (4.93) | 3.50 (6.04) | **0.01*** |
| ALSAQ-5[b] | | | |
| Difficulties getting up | 2.20 (1.35) | 2.46 (1.34) | 0.48 |
| Difficulties using arms and hands | 1.88 (1.39) | 2.54 (1.46) | 0.06 |
| Difficulties eating solid food | 0.56 (0.92) | 1.57 (1.56) | **0.01*** |
| Difficulties communicating | 1.04 (1.40) | 1.80 (1.62) | **0.05*** |
| Hopelessness toward future | 1.08 (1.04) | 2.17 (1.12) | <**0.01*** |
| *Total score* | 6.76 (4.06) | 10.85 (4.38) | <**0.01*** |
| ALSFRS-R[c] | | | |
| 1. Bulbar function | 10.19 (2.32) | 8.69 (3.63) | 0.09 |
| 2. Fine motor function | 5.73 (2.41) | 5.21 (2.46) | 0.39 |
| 3. Gross motor function | 7.88 (3.40) | 7.02 (3.19) | 0.19 |
| 4. Respiratory function | 9.50 (3.57) | 10.71 (2.44) | 0.20 |
| ADI-12 total score[d] | 20.84 (7.84) | 24.67 (7.82) | **0.03*** |

[a]BPI-SF = Brief Pain Inventory Short Form (pain severity rated from 0 = "no pain" and 10 = "worst imaginable pain").
[b]ALSAQ-5 = Amyotrophic Lateral Sclerosis Assessment Questionnaire (scores range from 0 to 20 (20 indicating the best health status)).
[c]ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised. Each subscale includes three items ranging from 0 (totally lost) to 4 (normal function), making a total score of 12 for each of the subscales. Lower scores indicate a higher level of dysfunction.
[d]ADI-12 = Amyotrophic Lateral Sclerosis (ALS)-Depression-Inventory; ADI-12 (scores range from 0 (best possible) to 48 (worst possible)).
*and bold values are significant at the 5% level.

surviving the study period and being able to participate in the whole study. Those who participated in the 5th visit were younger, had lived longer with disease symptoms, had better HRQOL, and significantly fewer depression symptoms at baseline. Participants taking part in the 5th visit may experience a slower progression of the disease, which indicates that these individuals belong to another phenotype of MND (Grad et al. 2017).

MND are rare in the general population (Barceló et al. 2021) and, as expected, inclusion of a large number of participants was a challenge. We included participants from multi-disciplinary MND teams in specialized care from different geographic locations to increase the number of participants and the generalizability to patients with MND in Sweden. This approach allowed us to collect baseline data from a reasonable number of patients.

The fast progression of the disease makes it challenging to prospectively follow patients with MND. During a 2-year follow-up period, the number of participants may be expected to decrease due to increased disease severity or death. However, to study the disease over time, a prospective design is needed, which is a major strength of this study. The prospective design allowed for analyses of variation of pain for each individual throughout the five assessments over the two-year study period, which gave valuable data on within-individual variation. Moreover, analysis of the prognostic value of pain intensity was also possible. The high number of drop-outs was an expected limitation, and the lack of significant associations at the follow-up may in part be due to the decreased power throughout the study.

The information on time since first MND symptoms was based on self-report and might therefore be subjected to recall bias. Nevertheless, this approach was deemed to be an appropriate indication of disease onset.

The instruments used to measure depression, disability progression, and HRQOL were all disease specific questionnaires. This is a considerable strength compared to generic instruments, as MND specific instruments are adjusted to the non-curative and fast progressive nature of the disease (Jenkinson et al. 1999). The internal consistency was good for ADI-12, ALSFRS-R, and BPI. The internal consistency of ALSAQ-5 was lower in this study, which may hamper the reliability of the instrument; thus, caution should be taken when interpreting the results.

## Conclusion and clinical implications

This longitudinal study, following patients with MND on several occasions over two years, found great within-individual variation of pain intensity.

Pain intensity was associated with depression and HRQOL cross-sectionally, but it did not appear to have a strong prognostic value for future depression, function, or HRQOL.

In accordance with these and our previous qualitative findings, patients with MND should be offered frequent assessments of pain and depressive symptoms in a person-centered care approach, allowing for individualization of adequate pain management.

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## References

**Åkerblom Y, Jakobsson Larsson B, Zetterberg L, *et al.*** (2020) The multiple faces of pain in motor neuron disease: A qualitative study to inform pain assessment and pain management. *Disability and Rehabilitation* **42**(15), 2123–2132. doi:10.1080/09638288.2018.1555615

**Åkerblom Y, Zetterberg L, Larsson BJ, *et al.*** (2021) Pain, disease severity and associations with individual quality of life in patients with motor neuron diseases. *BMC Palliative Care* **20**(1), 154. doi:10.1186/s12904-021-00848-6

**Barceló MA, Povedano M, Vázquez-Costa JF, *et al.*** (2021) Estimation of the prevalence and incidence of motor neuron diseases in two Spanish regions: Catalonia and Valencia. *Scientific Reports* **11**(1), 6207. doi:10.1038/s41598-021-85395-z

**Cedarbaum JM, Stambler N, Malta E, *et al.*** (1999) The ALSFRS-R: A revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *Journal of the Neurological Sciences* **169**(1–2), 13–21. doi: 10.1016/s0022-510x(99)00210-5

**Celik EC, Yalcinkaya EY, Atamaz F**, ***et al.*** (2017) Validity and reliability of a Turkish Brief Pain Inventory Short Form when used to evaluate musculoskeletal pain. *Journal of Back and Musculoskeletal Rehabilitation* **30**(2), 229–233. doi:10.3233/bmr-160738

**Chiò A, Canosa A, Gallo S**, ***et al.*** (2012) Pain in amyotrophic lateral sclerosis: A population-based controlled study. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies* **19**(4), 551–555. doi:10.1111/j.1468-1331.2011.03540.x

**Cleeland CS** (2009) The brief pain inventory: User guide. https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html (accessed 21 August 2017).

**Cleeland CS and Ryan KM** (1994) Pain assessment: Global use of the Brief Pain Inventory. *Annals of the Academy of Medicine of Singapore* **23**(2), 129–138.

**de Andres Ares J, Cruces Prado LM, Canos Verdecho MA**, ***et al.*** (2015) Validation of the short form of the Brief Pain Inventory (BPI-SF) in Spanish Patients with non-cancer-related pain. *Pain Practice: The Official Journal of World Institute of Pain* **15**(7), 643–653. doi:10.1111/papr.12219

**Ganzini L, Johnston WS and Hoffman WF** (1999) Correlates of suffering in amyotrophic lateral sclerosis. *Neurology* **52**(7), 1434–1440. doi:10.1212/wnl.52.7.1434

**Grad LI, Rouleau GA, Ravits J**, ***et al.*** (2017) Clinical spectrum of amyotrophic lateral sclerosis (ALS). *Cold Spring Harbor Perspectives in Medicine* **7**(8), a024117. doi:10.1101/cshperspect.a024117

**Hammer EM, Häcker S, Hautzinger M**, ***et al.*** (2008) Validity of the ALS-Depression-Inventory (ADI-12) – A new screening instrument for depressive disorders in patients with amyotrophic lateral sclerosis. *Journal of Affective Disorders* **109**(1–2), 213–219. doi:10.1016/j.jad.2007.11.012

**Hanisch F, Skudlarek A, Berndt J**, ***et al.*** (2015) Characteristics of pain in amyotrophic lateral sclerosis. *Brain and Behavior* **5**(3), e00296. doi:10.1002/brb3.296

**Heidari ME, Nadali J, Parouhan A**, ***et al.*** (2021) Prevalence of depression among amyotrophic lateral sclerosis (ALS) patients: A systematic review and meta-analysis. *Journal of Affective Disorders* **287**, 182–190. doi:10.1016/j.jad.2021.03.015

**Hoffman AJ, Jensen MP, Abresch RT**, ***et al.*** (2005) Chronic pain in persons with neuromuscular disease. *Physical Medicine and Rehabilitation Clinics of North America* **16**(4), 1099–1112, xii. doi:10.1016/j.pmr.2005.08.015

**Hoffman DL, Sadosky A, Dukes EM**, ***et al.*** (2010) How do changes in pain severity levels correspond to changes in health status and function in patients with painful diabetic peripheral neuropathy? *Pain* **149**(2), 194–201. doi:10.1016/j.pain.2009.09.017

**Hurwitz N, Radakovic R, Boyce E**, ***et al.*** (2021) Prevalence of pain in amyotrophic lateral sclerosis: A systematic review and meta-analysis. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* **22**(7–8), 449–458. doi:10.1080/21678421.2021.1892765

**Jakobsson Larsson B, Ozanne AG, Nordin K**, ***et al.*** (2017) A prospective study of quality of life in amyotrophic lateral sclerosis patients. *Acta Neurologica Scandinavica* **136**(6), 631–638. doi:10.1111/ane.12774

**Jenkinson C and Fitzpatrick R** (2001) Reduced item set for the amyotrophic lateral sclerosis assessment questionnaire: Development and validation of the ALSAQ-5. *Journal of Neurology, Neurosurgery, and Psychiatry* **70**(1), 70–73. doi:10.1136/jnnp.70.1.70

**Jenkinson C, Fitzpatrick R, Brennan C**, ***et al.*** (1999) Development and validation of a short measure of health status for individuals with amyotrophic lateral sclerosis/motor neurone disease: The ALSAQ-40. *Journal of Neurology* **246 Suppl 3**, Iii16–Iii21. doi:10.1007/bf03161085

**Karam CY, Paganoni S, Joyce N**, ***et al.*** (2016) Palliative care issues in amyotrophic lateral sclerosis: An evidenced-based review. *The American Journal of Hospice & Palliative Care* **33**(1), 84–92. doi:10.1177/1049909114548719

**Kollewe K, Mauss U, Krampfl K**, ***et al.*** (2008) ALSFRS-R score and its ratio: A useful predictor for ALS-progression. *Journal of the Neurological Sciences* **275**(1), 69–73. doi:10.1016/j.jns.2008.07.016

**Lopes LCG, Galhardoni R, Silva V**, ***et al.*** (2018) Beyond weakness: Characterization of pain, sensory profile and conditioned pain modulation in patients with motor neuron disease: A controlled study. *European Journal of Pain* **22**(1), 72–83. doi:10.1002/ejp.1091

**Ludolph A, Drory V, Hardiman O**, ***et al.*** (2015) A revision of the El Escorial criteria – 2015. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* **16**(5–6), 291–292. doi:10.3109/21678421.2015.1049183

**Naegeli AN, Tomaszewski EL and Al Sawah S** (2015) Psychometric validation of the Brief Pain Inventory-Short Form in patients with systemic lupus erythematosus in the United States. *Lupus* **24**(13), 1377–1383. doi:10.1177/0961203315588972

**Neudert C, Wasner M and Borasio GD** (2004) Individual quality of life is not correlated with health-related quality of life or physical function in patients with amyotrophic lateral sclerosis. *Journal of Palliative Medicine* **7**(4), 551–557. doi:10.1089/jpm.2004.7.551

**Pagnini F, Lunetta C, Banfi P**, ***et al.*** (2012) Pain in amyotrophic lateral sclerosis: A psychological perspective. *Neurological Sciences* **33**(5), 1193–1196. doi:10.1007/s10072-011-0888-6

**Pizzimenti A, Aragona M, Onesti E**, ***et al.*** (2013) Depression, pain and quality of life in patients with amyotrophic lateral sclerosis: A cross-sectional study. *Functional Neurology* **28**(2), 115–119. doi:10.11138/FNeur/2013.28.2.115

**Prell T, Gaur N, Stubendorff B**, ***et al.*** (2019) Disease progression impacts health-related quality of life in amyotrophic lateral sclerosis. *Journal of the Neurological Sciences* **397**, 92–95. doi:10.1016/j.jns.2018.12.035

**Querin G, Sorarù G and Pradat PF** (2017) Kennedy disease (X-linked recessive bulbospinal neuronopathy): A comprehensive review from pathophysiology to therapy. *Revue Neurologique* **173**(5), 326–337. doi:10.1016/j.neurol.2017.03.019

**Sandstedt P, Johansson S, Ytterberg C**, ***et al.*** (2016) Predictors of health-related quality of life in people with amyotrophic lateral sclerosis. *Journal of the Neurological Sciences* **370**, 269–273. doi:10.1016/j.jns.2016.09.034

**Sprangers MA and Schwartz CE** (1999) Integrating response shift into health-related quality of life research: A theoretical model. *Social Science & Medicine* **48**(11), 1507–1515. doi:10.1016/s0277-9536(99)00045-3

**Stephens HE, Lehman E, Raheja D**, ***et al.*** (2015) Pain in amyotrophic lateral sclerosis: Patient and physician perspectives and practices. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* **17**(1–2), 21–29. doi:10.3109/21678421.2015.1074701

**Tiryaki E and Horak HA** (2014) ALS and other motor neuron diseases. *Continuum (Minneap Minn)* **20**(5 Peripheral Nervous System Disorders), 1185–1207. doi:10.1212/01.CON.0000455886.14298.a4

**Wallace VC, Ellis CM, Burman R**, ***et al.*** (2014) The evaluation of pain in amyotrophic lateral sclerosis: A case controlled observational study. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* **15**(7–8), 520–527. doi:10.3109/21678421.2014.951944

**Wigand B, Schlichte I, Schreiber S**, ***et al.*** (2021) Characteristics of pain and the burden it causes in patients with amyotrophic lateral sclerosis – A longitudinal study. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* **23**(3–4), 284–291. doi:10.1080/21678421.2021.1962354