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# Long-term follow-up, quality of life, and survival of patients with Lambert-Eaton myasthenic syndrome

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## Abstract

### Objective

To study survival and to characterize long-term functional impairments and health-related quality of life (HRQOL) of patients with Lambert-Eaton myasthenic syndrome (LEMS).

### Methods

In this observational study, survival of patients with LEMS, separately for nontumor (NT) and small cell lung cancer (SCLC), was compared to that of the Dutch general population and patients with SCLC. Disease course in patients with LEMS was recorded retrospectively. Several scales for functional impairments and health-related quality of life were assessed.

### Results

We included 150 patients with LEMS. Survival was similar to that of the general population in 65 patients with NT-LEMS. Tumor survival was significantly longer in 81 patients with SCLC-LEMS compared to patients with non-LEMS SCLC (overall median survival 17 vs 7.0 months, $p < 0.0001$). At diagnosis, 39 (62%) of 63 patients with complete follow-up data were independent for activities of daily living, improving to 85% at the 1-year follow-up. The physical HRQOL composite score (55.9) was significantly lower than in the general population (76.3, $p < 0.0001$) and comparable to that of patients with myasthenia gravis (60.5). The mental HRQOL composite score was 71.8 in patients with LEMS, comparable to that of the general population (77.9, $p = 0.19$) and patients with myasthenia gravis (70.3).

### Conclusions

This study shows that patients with NT-LEMS have normal survival. Patients with SCLC-LEMS have an improved tumor survival, even after correction for tumor stage. A majority of patients with LEMS report a stable disease course and remain or become independent for self-care after treatment.

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## Glossary

**CI** = confidence interval; **DELTA-P** = Dutch-English LEMS Tumour Association Prediction; **HRQOL** = health-related quality of life; **KPS** = Karnofsky Performance Scale; **LEMS** = Lambert-Eaton myasthenic syndrome; **MCS** = Mental Composite Score; **MG** = myasthenia gravis; **mRS** = modified Rankin Scale; **PCS** = Physical Composite Score; **SCLC** = small cell lung cancer; **SF-36** = Short Form-36; **VGCC** = voltage-gated calcium channel.

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder characterized by fluctuating muscle weakness, loss of tendon reflexes, and autonomic dysfunction.[1,2] Muscle weakness usually starts in the proximal leg muscles,[1,3] which can severely limit mobility. Symptoms usually progress over the first months and can often be controlled by symptomatic and immunosuppressive treatment.[4–6]

After diagnosis, symptoms can vary between long-lasting remission on treatment, frequent fluctuations, and permanent disability. Distributions of symptoms and signs have been reported in several studies.[1,3,7–9] Long-term follow-up of muscle strength scores, EMG, and voltage-gated calcium channel (VGCC) antibody results has been reported in 47 patients.[10] Functional impairments of patients with LEMS over the disease course have been described in 12 patients only.[11]

Associated tumors are found in 50% to 60% of patients with LEMS, almost invariably small cell lung cancer (SCLC).[1,3,7,12] Limited data suggest some improvement of symptoms in patients with LEMS with SCLC (SCLC-LEMS) after treatment of the tumor.[13] Previous studies have shown a profound improved tumor survival in SCLC-LEMS,[14–18] but no data exist on the quality of life of this period of improved survival. Hardly any data are available determining survival and quality of life of patients with LEMS without associated tumors.[1]

In this observational study, we aimed to characterize functional impairments over the disease course and the quality of life of patients with LEMS. We studied survival of all patients with LEMS with and without associated tumors.

# Methods

## Patient population

From July 1, 1998, to October 1, 2015, data from all consecutive Dutch patients with LEMS were collected prospectively, as described before.[3,19] Leiden University Medical Center has a tertiary neuromuscular outpatient clinic and is the nationwide referral center for LEMS in the Netherlands. Patients were also identified through diagnosis registration databases and neuromuscular databases in university centers up to 2003. Afterward, we approached treating neurologists of all Dutch patients with positive results for VGCC antibodies (assay performed in Leiden and Rotterdam for all Dutch hospitals). This resulted in a small number of patients added retrospectively after a positive VGCC assay and verification of diagnosis (n = 7). One patient with LEMS who lacked most required data was excluded from this study.

The diagnosis of LEMS was based on characteristic clinical features, supported by either the presence of antibodies to VGCC or abnormal decrement and 60% increment on repetitive nerve stimulation.[2,20] Increment testing was performed immediately after 10 to 30 seconds of voluntary contraction.

## Survival

In the survival analysis, we separated the patients with LEMS with and without associated SCLC, excluding non-SCLC from the analysis (n = 3), as well as 1 patient with SCLC without a known date of tumor diagnosis. Patients with LEMS without associated tumor were compared to the general Dutch population as published by the Central Statistics office of the Netherlands, matching patients with LEMS for age and year at LEMS diagnosis and sex[21] (Statline.cbs.nl[22]). Survival from diagnosis of tumors in patients with LEMS with associated SCLC was compared to survival in all patients with SCLC in the Netherlands from 1998 to 2012, as registered in the Netherlands Cancer Registry Netherlands Cancer Registry operated by Netherlands Comprehensive Cancer Organisation.[23] As a secondary outcome measure, both patients with SCLC-LEMS and controls with SCLC were compared post hoc according to tumor stage (limited or extensive disease). Among patients with SCLC-LEMS, patients with and those without bulbar involvement or loss of weight within 3 months from onset were compared to show whether these variables predicted survival. Survival of these patients was also calculated according to patients' Dutch-English LEMS Tumour Association Prediction (DELTA-P) scores.[24] In patients with follow-up data, medical events leading up to death were studied to determine their potential relation with LEMS.

## Functional impairments

Disease course in patients with LEMS was recorded retrospectively with a semistructured interview in all available patients alive in 2014 to 2015 in combination with medical records. We used the modified Rankin Scale (mRS) and Karnofsky Performance Scale (KPS) to grade functional impairment. For the mRS, a structured interview was performed.[25,26] For a limited number of patients (10 of 63), mRS and KPS scores were collected solely from medical records. In all of these patients, extensive follow-up data were available to derive functional limitations.

Treatment modalities, subjective response, and devices to assist mobility were recorded for all patients. Exacerbations

were recorded, as defined by a subjective decrease in strength reported by patients supported by medical records and exacerbations requiring emergency treatment with either IV immunoglobulin or plasmapheresis as a more robust but less frequent criterion. Maximum disease severity was also recorded as reported by patients and supported by medical records.

### Health-related quality of life

Health-related quality of life (HRQOL) was assessed with the Short Form-36 (SF-36), a self-administered validated questionnaire that was mailed to all known living patients with LEMS in March 2012. Nonresponders were reminded twice. Control cohorts were a population-based cohort of 464 patients with myasthenia gravis (MG) in the Netherlands collected at the same time[27] and published normative data in the Dutch general population.[28]

The SF-36 is organized into 8 domains, with a score ranging from 0 (worst HRQOL) to 100 (best HRQOL). The 8 domains are physical functioning, role physical (role limitations due to physical problems), bodily pain, general health evaluation, vitality, social functioning, role emotional (role limitations due to emotional problems), and mental health. These domains produce a Physical Composite Score (PCS) and Mental Composite Score (MCS).[29]

The impact of baseline demographic and disease-related factors on both PCS and MCS quality of life was first assessed by univariate analysis. The predictors studies were chosen on the basis of expected baseline contributors to quality of life and likely clinical predicting factors. They were age at onset (>50 or <50 years), sex, partner, state of employment, presence of an associated tumor, presence of other autoimmune disease,[30] pattern of muscle weakness, medication status, and mRS score. A second multivariate analysis was performed to determine which of these factors independently predicted HRQOL.

### Statistics

Descriptive measures were presented as mean ± SD if appropriate or as median with interquartile range. Baseline variables between patients with LEMS with and without associated lung cancer were compared by use of *t* tests for linear and Fisher exact tests for categorical variables. Survival analysis was calculated with Kaplan-Meier plots and log-rank tests for nominal variables and log-rank test for trend for ordinal DELTA-P scores. HRQOL scores for all domains and composite scores were compared between LEMS, MG, and normative data in the Dutch general population with a 1-way between-group analysis of variance followed by post hoc comparison with the Tukey multiple-comparison test to test all pairwise comparisons. All individual predicting variables for PCS and MCS were first analyzed with a *t* test or 1-way analysis of variance for categorical variables and linear regression for mRS scores. Variables were included in a multivariate model only in case of a value of $p < 0.20$ in the univariate analysis.[31] For missing values (2.4% of data) in this model, a 10-fold multiple imputation was performed. After missing data imputation, a generalized linear model was performed to determine which of these variables independently predicted HRQOL. Bonferroni correction for multiple comparisons was used, correcting for the number of categories for each variable. Data analysis was performed with SPSS version 23.0 (SPSS Institute Inc, Chicago, IL) and GraphPad Prism 6 (GraphPad, La Jolla, CA).

### Standard protocol approvals, registrations, and patient consents

The study was approved by the Medical Ethics Committee of the Leiden University Medical Center. All patients included for follow-up of functional impairments and quality of life provided written informed consent.

### Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

## Results

We included 150 patients with LEMS, of whom 85 (59%) had an associated lung cancer (flowchart for inclusion available in figure e-1 from Dryad, doi.org/10.5061/dryad.g0t911k). Median time from onset to diagnosis was 18 months in patients without and 4 months in patients with an associated SCLC. Median time from LEMS diagnosis to detection of associated lung cancer was 0 months. A delay beyond 2 years was found in 2 patients (35 and 41 months). The first patient repeatedly avoided screening, while the latter was screened in 1988 according to standards of care that are currently considered insufficient. Baseline characteristics are shown in table 1 for the total LEMS population and subgroups in whom functional impairments and HRQOL were assessed.

### Survival

In the 65 patients with LEMS without an associated tumor, life expectancy was similar to the average life expectancy in the Netherlands adjusted for sex, age, and year of diagnosis (log-rank test $p = 0.63$, hazard ratio [log-rank test] 1.16, 95% confidence interval [CI] 0.59–2.27, figure 1; survival percentages are available in table e-1 from Dryad, doi.org/10.5061/dryad.g0t911k). In 81 patients with LEMS with an associated SCLC, tumor survival was significantly longer compared to patients with SCLC without LEMS (median survival 17 vs 7.0 months, respectively, $p < 0.0001$). According to tumor stage, patients with SCLC-LEMS had a longer tumor survival both in limited (median survival 19 vs 12.1 months, $p = 0.0015$) and extensive (median survival 13 vs 4.9 months, $p < 0.0001$, figure 2 and table e-2 available from Dryad, doi.org/10.5061/dryad.g0t911k) disease. Data were similar after additional correction for sex, age, and year of tumor diagnosis (data not shown). Early bulbar muscle involvement, loss of weight, and DELTA-P scores did not significantly affect survival in patients with SCLC-LEMS ($p = 0.41$, 0.58, and 0.063, respectively).

**Table 1** Baseline characteristics for all patients with LEMS

| | NT-LEMS | PNS-LEMS | *p* Value |
|---|---|---|---|
| **All patients (n = 150), n (%)** | 65 (43) | 85 (57) | NA |
| **Median age at onset (IQR; range), y** | 51 (41–62; 13–80) | 63 (56–68; 38–77) | <0.0001 |
| **Female sex, n (%)** | 35 (54) | 34 (40) | 0.064 |
| **Associated lung cancer, n (%)** | NA | 82 SCLC (96); 3 NSCLC (4) | NA |
| **Presence of autonomic symptoms, n (%)** | 57/63 (90) | 57/65 (88) | 0.78 |
| **Presence of VGCC antibodies, n (%)** | 55/64 (86) | 77/82 | 0.16 |
| **Repetitive nerve stimulation** | | | |
| **Abnormal decrement, n (%)** | 63/64 (98) | 73/74 (99) | >0.99 |
| **Abnormal increment (>60%), n (%)** | 61/64 (95) | 68/74 (92) | 0.50 |
| **Median delay onset–diagnosis (IQR; range), mo** | 18 (8–39; 1–265) | 4 (2–9; 1–40) | <0.0001 |
| **Median delay LEMS to tumor diagnosis (IQR; range), mo** | NA | 0 (0–1; −40 to 41) | NA |
| **Median survival (IQR; range), mo[a]** | Not yet reached | 17 (8–37; 1–209) | <0.0001 |
| **Immunosuppression, n (%)** | 31/64 (48) | 28/85 (33) | 0.064 |
| **Chemotherapy, n (%)** | NA | 74/84 (88.1) | NA |

| **Long-term follow-up (n = 63)** | **NT-LEMS (n = 41)** | **SCLC-LEMS (n = 22)** | ***p* Value** |
|---|---|---|---|
| **Median age at onset (IQR; range), y** | 51 (41–60; 19–80) | 65 (59–67; 50–76) | <0.0001 |
| **Female sex, n (%)** | 23 (56) | 12 (55) | 1.00 |
| **Maximum mRS score, n (%)** | | | |
| **5** | 2 (5) | 4 (18) | |
| **4** | 6 (15) | 9 (41) | |
| **3** | 16 (39) | 6 (27) | |
| **2** | 16 (39) | 3 (14) | |
| **1** | 1 (2) | 0 (0) | |
| **Median time from onset to maximum severity (IQR; range), mo** | 12 (6–60; 0–444) | 4 (2–10; 1–28) | |
| **Median time from diagnosis to maximum severity (IQR; range), mo** | −1 (−4 to 5; −253 to 354) | 0 (−1 to 2; −4 to 24) | |
| **Symptomatic therapy, n (%)** | 40 (98) | 22 (100) | >0.99 |
| **Immunosuppression, n (%)** | 21 (51) | 10 (45) | 0.79 |
| **Chemotherapy, n (%)** | NA | 17 (77) | NA |
| **Exacerbation frequency, n/patient-y (% of patients)** | 1/6.9 (61) | 1/3.2 (41) | NA |
| **Emergency treatment frequency (IVIG/PLEX), n/patient-y (% of patients)** | 1/20.0 (29) | 1/6.7 (23) | NA |

| **HRQOL (n = 42)** | **NT-LEMS (n = 36)** | **SCLC-LEMS (n = 6)** | ***p* Value** |
|---|---|---|---|
| **Median age at onset (IQR; range), y** | 53 (39–62; 19–71) | 56 (51–69; 49–73) | 0.11 |
| **Female sex, n (%)** | 20/36 (56) | 4/6 (67) | 0.69 |
| **Mean HRQOL composite scores** | | | |
| **PCS** | 56.8 | 51.0 | 0.58 |
| **MCS** | 71.4 | 74.3 | 0.77 |

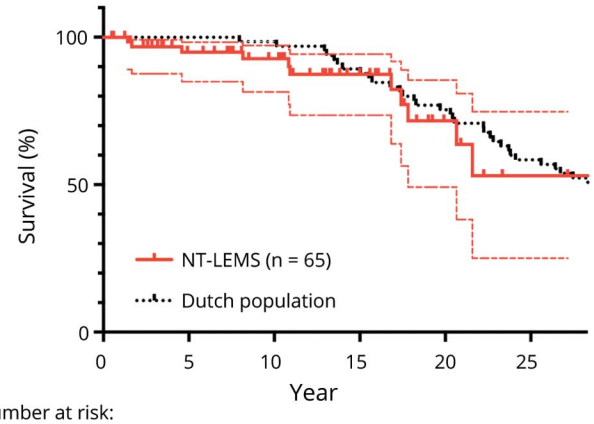
Abbreviations: HRQOL = health-related quality of life; IQR = interquartile range; IVIG = intravenous immunoglobulin; MCS = Mental Component Score; mRS = modified Rankin Scale; NSCLC = non–small cell lung cancer; NT-LEMS = Lambert-Eaton myasthenic syndrome without associated tumor; PCS = Physical Component Score; PLEX = plasma exchange; PNS-LEMS = Lambert-Eaton myasthenic syndrome with associated lung cancer; SCLC = small cell lung cancer; VGCC = voltage-gated calcium channels.
[a] Median survival for SCLC was 17 (IQR 8–37; range 1–209) months; 1 of 3 patients with NSCLC was alive at 24 months, while the other 2 died at 13 and 25 months.

In contrast to the group-wise survival analysis, individually, LEMS likely contributed to death in 3 VGCC-positive patients. Two patients with SCLC-LEMS had respiratory insufficiency due to LEMS. The first had very limited response to aggressive treatment and died of abdominal sepsis while in the intensive care unit. The second died as a result of sudden respiratory deterioration just after a recent intensive care unit stay for respiratory muscle weakness. The third patient, with probably unrelated rectal carcinoma, experienced respiratory insufficiency shortly before his death. He had previously been admitted to the intensive care unit for respiratory muscle weakness but was not analyzed again for his dyspnea in a palliative setting. In all 3 patients, respiratory muscle weakness was likely a relevant contributing factor, although probably not the sole cause of death.

## Functional impairments

Detailed follow-up data for functional impairments were available for 63 patients (41 with LEMS without tumor and 22 with SCLC-LEMS). Median follow-up was 130 months for patients with LEMS without and 12 months for patients with an associated SCLC. At diagnosis, 39 of 63 patients (62%) were independent for self-care (KPS score ≥70), improving to 85% at the 1-year follow-up (figure 3 shows overall KPS and mRS distribution). Patients with lung cancer reported more functional impairments at any point in the disease course (figure 4, A and B). Maximal disease severity was reached at a median of 1 month before diagnosis, while 30% deteriorated beyond diagnosis. In the 32 patients with LEMS with at least 5 years of follow-up, 27 patients (84%) had reached their worst mRS score in or before the first year after diagnosis. Patient-reported maximal disease severity in this group was reached in the first 2 years in 75% of patients.

**Figure 1** Survival of NT-LEMS compared to matched Dutch life expectancy

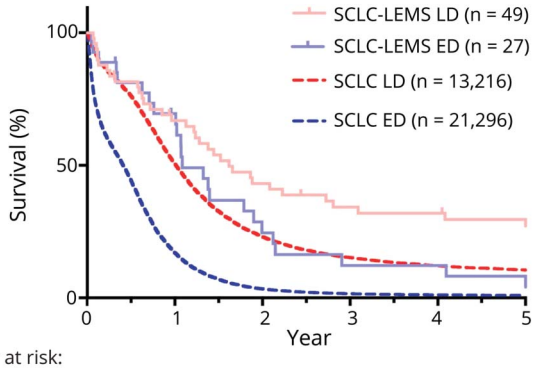



Number at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| NT-LEMS | 65 | 51 | 41 | 23 | 10 | 4 |

Kaplan-Meier curve showing survival of patients with Lambert-Eaton myasthenic syndrome without an associated tumor (NT-LEMS) compared to the average life expectancy in the Netherlands after adjustment for sex, age, and year of diagnosis. Dotted thin lines represent 95% confidence interval, and small vertical lines represent censored data for the patients with LEMS.

**Figure 2** Survival of SCLC-LEMS compared to all Dutch patients with SCLC, LD or ED




Number at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| SCLC–LEMS | LD | 49 | 32 | 17 | 16 | 15 | 14 |
| SCLC–LEMS | ED | 27 | 17 | 7 | 4 | 4 | 3 |
| SCLC | LD | 13,216 | 6,666 | 2,887 | 1,767 | 1,315 | 1,039 |
| SCLC | ED | 21,296 | 3,617 | 671 | 272 | 186 | 136 |

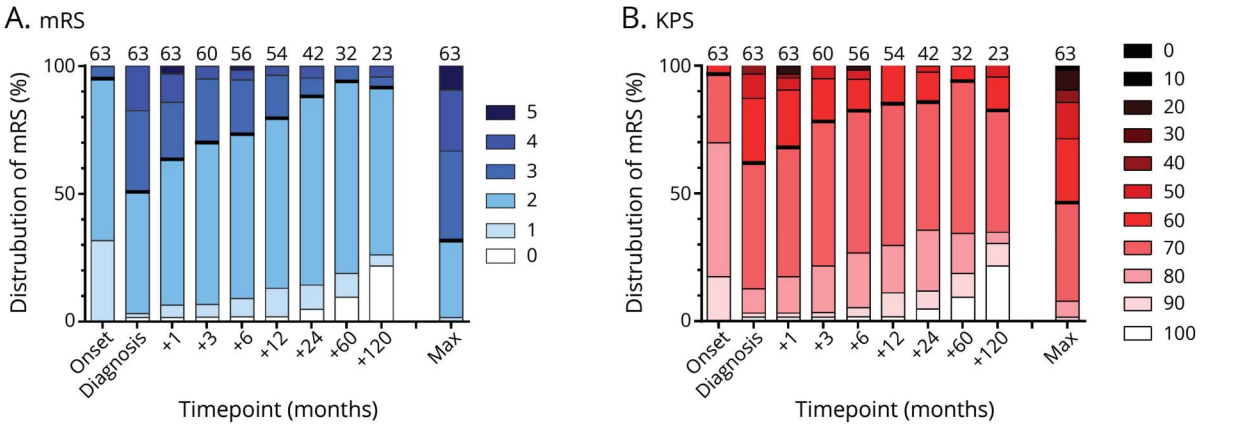
Kaplan-Meier curve showing tumor survival of patients with Lambert-Eaton myasthenic syndrome with an associated small cell lung cancer (SCLC-LEMS) (1998–2015) compared to the average life expectancy of patients with SCLC in the Netherlands (1998–2012) divided according to tumor stage. Small vertical lines represent censored data for the patients with LEMS. ED = extensive disease; LD = limited disease.

During disease course, 73% of patients used any device to assist mobility. Fifty-two percent used a wheelchair, while only 6% were fully wheelchair dependent at any point in disease course. Most patients required a wheelchair for only a limited period of time.

Symptomatic treatment consisted of 3,4-diaminopyridine in 95% of patients and pyridostigmine in 68%. Of patients treated with 3,4-diaminopyridine and pyridostigmine, 88% noticed a subjective improvement in symptoms due to 3,4-diaminopyridine and 67% due to pyridostigmine. Immunosuppressive treatment was started in 49%, of which the most common therapies were either prednisone combined with azathioprine (29%) or prednisone alone (14%). The frequency of both immunosuppressive and emergency treatments showed no significant differences between patients with LEMS with and without SCLC (data not shown). Positive treatment effect, as shown by an improvement in mRS scores after diagnosis, was heterogeneous but generally reached in 6 to 12 months (figure 4, C and D). Patients treated with immunosuppressive drugs reported more functional impairments at diagnosis compared to those treated symptomatically but had a comparable mRS score distribution 2 and 5 years after diagnosis.

Exacerbations reported by patients occurred in 54% of patients. These self-reported exacerbations overall occurred once in every 5.7 patient-years. Exacerbations requiring emergency treatment with either or plasmapheresis were less frequent, occurring in 27% of patients, overall once in every 16 patient-years of follow-up. Nine patients with SCLC-LEMS had follow-up data available after tumor recurrence; of

**Figure 3** Distribution of functional impairments during the disease course




Distribution of (A) modified Rankin Scale (mRS) and (B) Karnofsky Performance Scale (KPS) scores at onset of symptoms; diagnosis; 1, 3, 6, 12, 24, 60, and 120 months after diagnosis; and maximal (max) disease severity. At diagnosis, 62% of patients were independent for self-care (KPS score ≥70), increasing to 68% 1 month later and 85% 1 year later. At maximum disease severity, 46% of patients were independent for self-care. Number of patients available at top of bar for each time point.

them, only 2 had a simultaneous worsening of LEMS. One of these patients, however, had concurrent pancreatitis, and the other had experienced 2 previous LEMS exacerbations without tumor recurrence. Five patients went into full remission and were able to stop all treatment at a median of 4 years after diagnosis; they remained in remission without any symptoms or treatment on long-term follow-up (median 12 years). One of these patients was treated for SCLC and one with immunosuppressants. Two other patients were treated only symptomatically, and the last patient with a short disease course received no treatment at all, suggesting that even spontaneous remission without immunomodulating therapy is possible.

Two patients in the SCLC-LEMS group had paraneoplastic cerebellar degeneration as a second paraneoplastic disease. This had relevant effects on physical limitations, but these patients ultimately had an mRS score time course comparable to that of other patients.

### Health-related quality of life

Forty-four of 67 (66%, 6 with SCLC) patients with LEMS alive and included at the time responded to our SF-36 questionnaire. Two questionnaires were excluded due to incomplete data. Patients with LEMS scored lower on the physical HRQOL than the general Dutch population (PCS 55.9 [95% CI 48.9–62.9] vs 76.3 [95% CI 75.0–77.5], respectively, $p < 0.0001$), reflected in lower scores in 3 of 4 related domains (physical functioning, role physical, general health, figure 5; scores for all domains are available in table e-3 available from Dryad, doi.org/10.5061/dryad.g0t911k). HRQOL scores were comparable for the MCS (71.8 [95% CI 65.4–78.3] vs 77.9 [95% CI 76.8–79.0], $p = 0.19$) but lower for the vitality and social functioning domains (table e-3 available from Dryad, doi.org/10.5061/dryad.g0t911k). Between LEMS and MG, the composite scores and most of the domain subscores were comparable except for lower scores for patients with LEMS in the physical functioning subdomain (45.8 vs 62.2 in MG, $p = 0.0001$), which is dominated by questions involving leg strength.

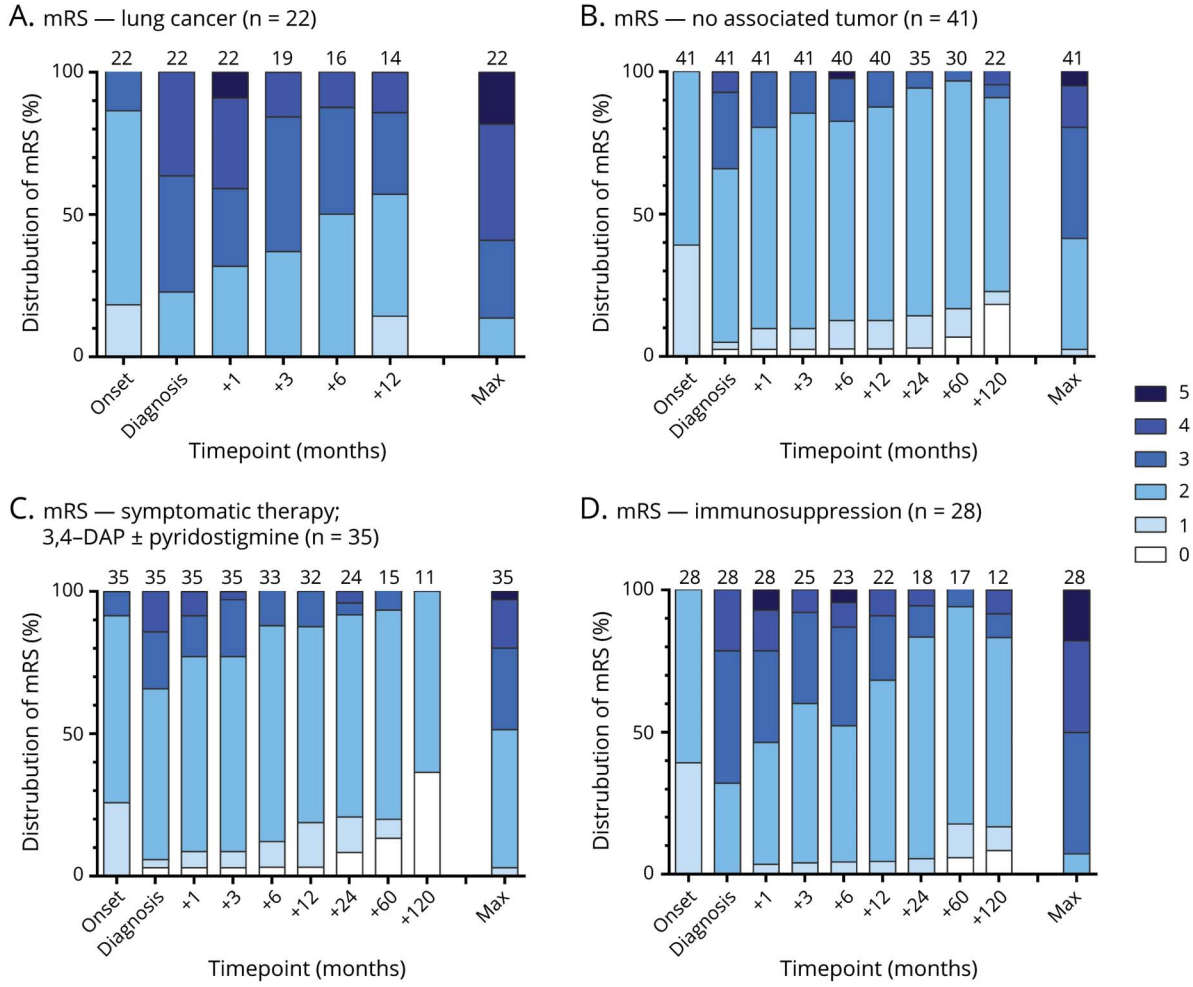
Univariate analysis of potential predicting variables for physical and mental HRQOL composite scores showed employment status, pattern of muscle weakness, and mRS scores to be significantly associated with PCS (table 1). State of employment and whether patients had a partner were associated with MCS. A multivariate analysis aiming to detect independent predictors for quality of life (table 1) showed having a partner and employment status to be independently associated with higher PCS and MCS. In addition, a higher HRQOL was linked to a more limited pattern of muscle weakness for the PCS and male sex for the MCS. The mRS score did not affect either PCS or MCS in this multivariate model.

## Discussion

This study shows that patients with LEMS without an associated tumor have a normal survival, confirms that patients with SCLC-LEMS have an improved tumor survival compared to patients with SCLC without LEMS, and shows that patients with LEMS can have a relatively well-controlled life with mainly physical limitations and normal mental quality of life.

In contrast to patients with MG, we show that survival in patients with LEMS without an associated tumor was similar to the average life expectancy in the Netherlands.[32–34] The increased mortality in MG was at least partially related to an increase in respiratory disease as a cause of death,[35] likely related to respiratory muscle weakness, which can occur in

**Figure 4** Distribution of functional impairments during the disease course for subgroups



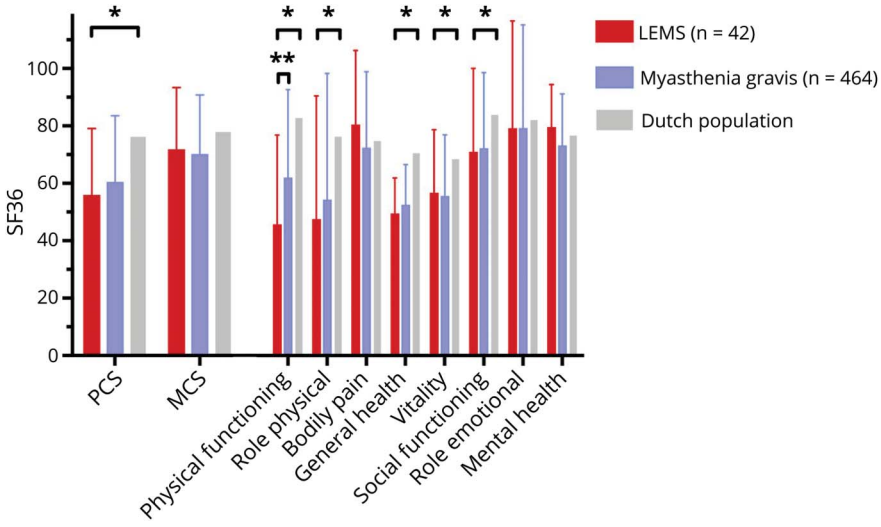

Distribution of modified Rankin Scale (mRS) scores for patients (A) with and (B) without associated lung cancer and those treated (C) purely symptomatically and (D) with immunosuppressants as well. Data presented at onset of symptoms, diagnosis, 1 to 120 months after diagnosis, and at maximal (max) disease severity. Number of patients available at top of bar for each time point. DAP = 3,4-diaminopyridine.

both MG and LEMS but might be less frequent in patients with LEMS given the lack of an increase in mortality.

Our study shows that tumor survival is increased in all patients with SCLC-LEMS with both limited and extensive disease. Median survival is doubled in patients with SCLC-LEMS with extensive disease compared to patients with SCLC without LEMS, and overall 5-year survival is increased from 4.4% to 21%. Survival in patients with SCLC without LEMS (limited disease) is comparable to that of patients with SCLC-LEMS with extensive disease. Several previous smaller studies have reported this improved survival,[14,15,36] including a recent prospective cohort study of patients with SCLC with and without LEMS.[17] Our study shows that this improved survival cannot merely be attributed to tumor stage (patients with SCLC-LEMS are more frequently found while still having limited disease). There will be an inevitable lead-time bias due to earlier diagnosis of SCLC because of neuromuscular symptoms, but this cannot fully explain the survival difference. This additional improvement in survival supports a biochemical or immunologic cause such as an antitumor immune response.

We show that the majority of patients with LEMS have a relatively stable disease course after diagnosis and treatment. Most patients either remain or become independent for self-care over time after appropriate treatment. Because disease severity directly affects treatment decisions, especially whether to add immunosuppressive treatment, we could not compare the effect of individual treatments. We did note that patients treated symptomatically improve sooner after diagnosis than those treated with immunosuppressive drugs (probably a confounder by indication), but both groups ultimately reach a relatively stable level of limitations ≈2 years after diagnosis. Maximum disease severity has already been reached before diagnosis in a majority of patients and within the first 2 years in ≈80%, the latter of which is very similar to that in MG.[34,37] Patients with LEMS with associated lung cancer report more functional impairments over the entire

**Figure 5** Health-related quality of life in LEMS compared to MG and the Dutch general population




All scores range from 0 to 100. PCS = Physical Composite Score; MCS = Mental Composite Score; SF-36 = Short Form-36. *A significant difference between patients with Lambert-Eaton myasthenic syndrome (LEMS) and the Dutch general population. **A significant difference between LEMS and myasthenia gravis (MG).

disease course. Both LEMS symptoms, which can be more progressive in SCLC-LEMS,[3,16,24] and lung cancer and related treatment are likely to contribute to disability in this group. Patients with SCLC-LEMS also seem to have a higher exacerbation rate, although this should be interpreted with caution because follow-up in this group is shorter and exacerbations seem more likely to occur in the first years after diagnosis. It should be noted, however, that most of these patients still become independent for activities of daily life after treatment and seem to have overall HRQOL comparable to that of patients with LEMS without an associated tumor (table 1). This supports the notion that low performance scores due to muscle weakness in SCLC-LEMS should not be a reason to refrain from tumor treatment, especially because tumor treatment can improve symptoms in paraneoplastic disease.[13]

In patients with LEMS with associated lung cancer, LEMS symptoms usually precede tumor diagnosis. However, after initial treatment and improvement of both diseases, frequently no exacerbation of LEMS occurs on tumor progression as a (repeated) warning. This could mean either that tumor progression does not elicit such a strong immune response as the initial tumor presentation or that an exacerbation of LEMS would require more time to develop, as is the case before the start of the disease.

The reduced HRQOL in patients with LEMS was comparable to that in patients with MG and related mostly to physical limitations. General demographic factors seemed to predict variation in HRQOL that was at least as strong as disease-specific variables in our population, especially for mental health. Several previous studies in MG have reported reduced HRQOL in patients with MG for most domains of the SF-36.[27,38–40] Our study showed female sex, generalized disease, and lack of employment to be associated with reduced HRQOL, comparable to results in 2 large MG studies.[27,41] In contrast to the pattern of muscle weakness, the mRS score as a marker for disease severity did not independently predict HRQOL. This could be related to the limited number of patients, limited overall variation in mRS scores, or confounding by also including the pattern of weakness in the model.

The largest previous study concerning disease course in LEMS (n = 47) focused on muscle strength scores and EMG and antibody results. In contrast, we report patient-oriented outcomes, including functional impairments and quality of life.[10] This previous study[10] also reported a variable prognosis, with sustained clinical remission in 43% of patients and about a quarter of patients remaining (at least partially) wheelchair dependent at follow-up. In this cohort, both treatment with immunosuppressants and sustained clinical remission occurred more frequently compared to our study. Although this might suggest an association between the two, we consider it more likely a difference in definition of clinical remission, because many patients in our study still report a decrease in their level of work and social activities even after substantial or apparent full clinical improvement without major objective weakness at the outpatient clinic. A smaller study of 12 patients with LEMS reported lifestyle limitations comparable to our cohort, with restrictions in activities of daily living in 75% of patients, poor reported health status, and low HRQOL scores as measured by EQ-5D utility scores.[11] Previous follow-up of 16 patients with SCLC-LEMS reported sustained improvement of LEMS after tumor treatment.[13] Our study confirms that patients with SCLC-LEMS can improve and regain independence for self-care, but these patients still experience limitations in daily life.

Limitations of our study include a relatively small sample size inherent to the rarity of this disease, the partly retrospective nature of the study, and the use of different subpopulations for

disease course and HRQOL. The limited number of deaths in our study precludes a certain conclusion that survival is normal in patients with LEMS without associated tumor. Lacking sufficient EMG or laboratory parameters for comparison, we specifically focused on patient-oriented outcomes because they represent patients' limitations best. Functional impairments could have been influenced by comorbidity, but this effect is group-wise minimal in that only 2 of 22 patients with SCLC-LEMS had another paraneoplastic neurologic disease (cerebellar degeneration). In addition, in the few patients with relevant comorbidity, the level of physical functioning appeared to be determined mainly by LEMS.

This study provides detailed information on long-term prognosis and limitations in LEMS. This can guide expectations of doctors and patients and be of potential relevance for treatment choices. Although LEMS is usually a chronic disease with long-term physical limitations and reduced quality of life, appropriate treatment results in a relevant decrease in functional impairments for most patients.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## Disclosures

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## Publication history

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## Appendix Authors

| Name | Location | Role | Contribution |
|---|---|---|---|
| **Alexander F. Lipka, MD** | Leiden University Medical Center, Groene Hart Hospital, the Netherlands | Author | Study design, data acquisition, data analysis and interpretation, drafting and revising manuscript |
| **Marion I. Boldingh, MD, PhD** | Oslo University Hospital, Norway | Author | Study design, data acquisition, data analysis and interpretation, revising manuscript |
| **Erik W. van Zwet, PhD** | Leiden University Medical Center, the Netherlands | Author | Data analysis and interpretation, revising manuscript |
| **Marco W.J. Schreurs, PhD** | Erasmus University Medical Center, Rotterdam, the Netherlands | Author | Data acquisition, revising manuscript |
| **Jan BM Kuks MD, PhD** | University Medical Center Groningen, the Netherlands | Author | Data acquisition, revising manuscript |
| **Chantal M. Tallaksen, MD, PhD** | Oslo University Hospital, Norway | Author | Study design, revising manuscript |
| **Maarten J. Titulaer, MD, PhD** | Erasmus University Medical Center, Rotterdam, the Netherlands | Author | Study design, data acquisition, data analysis and interpretation, revising manuscript |
| **Jan J.G.M. Verschuuren, MD, PhD** | Leiden University Medical Center, the Netherlands | Author | Study design, interpretation of data, revising manuscript |

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# Disputes & Debates: Editors' Choice



## Editors' Note: One-Stage, Limited-Resection Epilepsy Surgery for Bottom-of-Sulcus Dysplasia

In "One-Stage, Limited-Resection Epilepsy Surgery for Bottom-of-Sulcus Dysplasia," Macdonald-Laurs et al. described the performance of corticectomy guided by MRI and electrocorticography (ECoG) in 38 patients with bottom-of-sulcus dysplasia (BOSD). They found that at a median of 6 years postop, 87% of patients were seizure free and noted that their outcomes are similar to those reported in a small series of patients with BOSD who underwent stereotactic thermocoagulation (STC) and laser interstitial thermal therapy (LITT). Hu et al. reported that based on their recent LITT trial, in which they found that 6 of 7 (86%) patients with BOSD were seizure-free 6 months postop, they recommend minimally invasive procedures for BOSD. Harvey et al. agreed with the use of STC or LITT for BOSD in locations that are not easily accessible via a small craniotomy. However, these procedures preclude the use of ECoG to determine epileptogenicity, histopathologic confirmation, and genetic testing of the tissues. In addition, STC and LITT pose risk to surrounding normal cortex and are not widely available. The authors all agree that there is a need for additional long-term outcome data using different treatment strategies in larger cohorts of patients with BOSD.

Ariane Lewis, MD, and Steven Galetta, MD
*Neurology*® 2021;97:1051. doi:10.1212/WNL.0000000000012922

## Reader Response: One-Stage, Limited-Resection Epilepsy Surgery for Bottom-of-Sulcus Dysplasia

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*Neurology*® 2021;97:1051-1052. doi:10.1212/WNL.0000000000012924

Dr. Macdonald-Laurs et al. reported 38 patients with bottom-of-sulcus dysplasia (BOSD), who underwent a limited corticectomy and whose seizure outcomes indicated minor neurologic complications,[1] echoing previous literature.[2,3] Although subtle changes can be found from structural MRIs, combined fluorodeoxyglucose (FDG)-positron emission tomography (FDG-PET) and MRI imaging can produce high sensitivity in detecting these small lesions. Because these lesions are well confined, sulcus-centered resections could be considered for better function protection, while also guaranteeing the seizure outcome.[4]

The authors implied the outcome of conventional open surgery is similar to that of laser interstitial thermal therapy (LITT). In our recent LITT clinical trial, a subcohort of 7 patients with BOSD were included—6 achieved an Engel IA outcome and 1 an Engel IB outcome, postoperatively, with a mean follow-up of 6 months. In addition, patients were willing to consent to LITT, given its minimally invasive nature. Considering BOSD is mostly located outside the temporal lobe, the traditional viewpoint that extratemporal surgeries are less effective than temporal lobe ones may not apply to this condition.[5] The existing research stems from all

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retrospective studies—as such, multicenter collaborations could yield high class evidence that may profoundly change the treatment strategies for BOSDs.


1. Macdonald-Laurs E, Maixner WJ, Bailey CA, et al. One-stage, limited-resection epilepsy surgery for bottom-of-sulcus dysplasia. *Neurology*. 2021;97(2):e178-e190.
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## Author Response: One-Stage, Limited-Resection Epilepsy Surgery for Bottom-of-Sulcus Dysplasia

A. Simon Harvey (Melbourne) and Emma Macdonald-Laurs (Melbourne)
*Neurology*® 2021;97:1052. doi:10.1212/WNL.0000000000012923

We thank Dr. Hu et al. for their encouraging comments on our article.[1] Both our groups advocate minimal, targeted resections of bottom-of-sulcus dysplasia (BOSD),[1,2] and we further promote omitting intracranial EEG monitoring in MRI-positive cases. As noted in references 41–45 in our article, laser interstitial thermal therapy (LITT) and stereotactic thermocoagulation (STC) are reported in BOSD, further minimize surgical intervention, and are appropriate for BOSD on the medial and basal cerebral surfaces—occurrences which are not as easily accessed with a small craniotomy as BOSD on the cerebral convexity. STC is typically undertaken in patients who undergo previous stereo-EEG with an electrode directly sited in an MRI-positive BOSD. The potential disadvantages of LITT and STC are the lack of confirmation of epileptogenicity with electrocorticography, a pathologic diagnosis from histopathology, and identification of genetic variants from deep sequencing of tissue.

It is important to consider that limiting thermal injury to the dysplastic cortex of the BOSD and avoiding injury to the surrounding normal cortex or white matter tracts is sometimes challenging with LITT and STC. In addition, many neurosurgical centers around the world, especially pediatric centers, do not have LITT or STC capabilities such that targeted small resections are their best option. We eagerly await publications from Dr Hu's group and others reporting large numbers of patients with BOSD undergoing LITT and STC with long follow-up periods, given the potential for temporary seizure remissions, and MRI figures highlighting the preoperative dysplastic and postoperative thermal lesions.


1. Macdonald-Laurs E, Maixner WJ, Bailey CA, et al. One-stage, limited-resection epilepsy surgery for bottom-of-sulcus dysplasia. *Neurology*. 2021;97(2):e178-e190.
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Author disclosures are available upon request (journal@neurology.org).

CORRECTION

# Long-term Follow-up, Quality of Life, and Survival of Patients With Lambert-Eaton Myasthenic Syndrome

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In the article "Long-term Follow-up, Quality of Life, and Survival of Patients With Lambert-Eaton Myasthenic Syndrome" by Lipka et al.,[1] table 2 was previously missing from the paper and is shown below. Further, the references to "table 1" in the last paragraph of the Results section, on page e516, should read "table 2." The authors regret the errors.

## Reference

1. Lipka A, Boldingh M, van Zwet E, et al. Long-term follow-up, quality of life, and survival of patients with Lambert-Eaton myasthenic syndrome. *Neurology*. 2020;94(5):e511-e520.

**Table 2** Predictors of Quality of Life in Patients With LEMS

| **Univariate analysis** | | | | | |
|---|---|---|---|---|---|
| | **No. of patients** | **PCS (95% CI)** | ***p*** | **MCS** | ***p*** |
| **Age** | | | 0.78 | | 0.96 |
| **<50** | 19 | 57.1 (46–68) | | 72.0 (61–82) | |
| **≥50** | 23 | 55.0 (45–64) | | 71.6 (63–81) | |
| **Sex** | | | 0.22 | | 0.18 |
| **Female** | 23 | 51.9 (42–62) | | 67.7 (58–78) | |
| **Male** | 19 | 60.8 (50–72) | | 76.7 (68–86) | |
| **Partner** | | | 0.079 | | 0.018* |
| **Yes** | 34 | 60.0 (51–67) | | 75.6 (69–82) | |
| **No** | 8 | 43.0 (22–64) | | 55.8 (35–76) | |
| **Employment** | | | 0.035* | | 0.042* |
| **Employed** | 10 | 71.8 (56–88) | | 85.8 (81–91) | |
| **Housekeeping** | 4 | 53.4 (22–85) | | 58.1 (28–115) | |
| **Disability** | 9 | 41.6 (32–52) | | 71.0 (45–71) | |
| **Retired** | 19 | 54.9 (43–67) | | 71.7 (59–83) | |
| **Associated tumor** | | | 0.58 | | 0.77 |
| **No tumor** | 36 | 56.8 (49–64) | | 71.4 (65–78) | |
| **SCLC** | 6 | 51.0 (19–83) | | 74.3 (42–107) | |
| **Other autoimmune disease** | | | 0.57 | | 0.54 |
| **Yes** | 11 | 59.4 (44–75) | | 68.4 (52–85) | |
| **No** | 31 | 54.7 (46–63) | | 73.0 (65–81) | |
| **Muscle weakness** | | | <0.0001* | | 0.14 |
| **No weakness** | 9 | 83.3 (71–95) | | 84.5 (69–100) | |
| **Limited to legs only** | 6 | 57.2 (28–87) | | 69.1 (42–96) | |
| **Generalised** | 27 | 46.6 (40–53) | | 68.2 (60–76) | |

Continued

**Table 2** Predictors of Quality of Life in Patients With LEMS *(Continued)*

| Univariate analysis | | | | | |
|---|---|---|---|---|---|
| | **No. of patients** | **PCS (95% CI)** | ***p*** | **MCS** | ***p*** |
| **Medication** | | | 0.39 | | 0.21 |
| **None** | 6 | 66.3 (35–98) | | 79.6 (52–107) | |
| **Symptomatic** | 23 | 54.9 (47–63) | | 74.1 (67–81) | |
| **Immunosuppression** | 10 | 51.0 (35–67) | | 63.0 (46–80) | |
| **Modified Rankin Scale** | | | 0.008* | | 0.085 |
| **Correlation coefficient (r)** | | | −0.44 | | −0.29 |
| **0** | 2 | 68.6 (−234 to 372) | | 62.9 (−306 to 432) | |
| **1** | 2 | 77.8 (−30 to 185) | | 85.4 (17–153) | |
| **2** | 25 | 52.2 (45–60) | | 72.3 (65–79) | |
| **3** | 6 | 44.3 (18–71) | | 59.6 (30–89) | |
| **4** | 1 | 8.8 (n/a) | | 18.3 (n/a) | |
| **Multivariate analysis** | | | | | |
| | **No. of patients** | **PCS** | ***p*** | **MCS** | ***p*** |
| **Sex** | | | n/a | | 0.031* |
| **Female** | 23 | | | 67.7 | |
| **Male** | 19 | | | 76.7 | |
| **Partner** | | | 0.018* | | 0.015* |
| **Yes** | 34 | 60.0 | | 75.6 | |
| **No** | 8 | 43.0 | | 55.8 | |
| **Employment** | | | 0.036* | | 0.012* |
| **Employed** | 10 | 71.8 | | 85.8 | |
| **Housekeeping** | 4 | 53.4 | | 58.1 | |
| **Disability** | 9 | 41.6 | | 71.0 | |
| **Retired** | 19 | 54.9 | | 71.7 | |
| **Muscle weakness** | | | <0.001* | | n.s.[a] |
| **No weakness** | 9 | 88.3 | | 84.5 | |
| **Limited to legs only** | 6 | 57.2 | | 69.1 | |
| **Generalised** | 27 | 46.6 | | 68.2 | |
| **Modified Rankin Scale** | | | 0.25 | | 0.31 |
| **0** | 2 | 68.6 | | 62.9 | |
| **1** | 2 | 77.8 | | 85.4 | |
| **2** | 25 | 52.2 | | 72.4 | |
| **3** | 6 | 44.3 | | 59.6 | |
| **4** | 1 | 8.8 | | 18.3 | |

* Represents $p < 0.05$ for comparison.
[a] Bonferroni correction (of post-hoc pooled parameter estimates of the generalized linear model) results in a *p*-value > 1.
CI = confidence interval; MCS = mental composite score; PCS = physical composite score; SCLC = small cell lung cancer.