Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis

Development and Evaluation of a Clinical Staging System for Amyotrophic Lateral Sclerosis

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Body, tables/figures (no limit)

ABSTRACT

Background

Staging of disease severity is useful for prognosis, decision-making and resource planning. However, no commonly-used, validated staging system exists for amyotrophic lateral sclerosis (ALS). We purposed to develop an ALS staging system (ALS Milano Torino Staging) that captures the observed progressive loss of independence and function.

Methods

We utilized data from the Quality of Care in ALS (QOC) study and clinical trial of lithium carbonate in amyotrophic lateral sclerosis (LiTALS study). Clinical milestones in ALS progression were defined by loss of independence in 4 key domains on the ALS Functional Rating Scale (ALSFRS): swallowing, walking/self-care, communicating, and breathing, determined by thresholds in specific ALSFRS item scores. Stages were defined as: Stage 0 - functional involvement but no loss of independence on any domain; Stages 1-4 -number of domains in which independence was lost; Stage 5 - death. Staging criteria were applied to patients enrolled in a 12-month follow-up QOC study to assess disease progression and correlates with function (ALSFRS), quality of life (Short Form-36) and health service costs. We evaluated between-stage transition probabilities utilizing the 15-month follow-up LiTALS study.

Results

Following 12 months in the QOC study (*N*=130), ? 83 (63.8%) of participants progressed to higher stages of disease compared with their baseline stage. Functional (ALSFRS) and quality of life measures were inversely related to disease stage. Health service costs were directly related to increasing disease stages from 0 to 4 (P<0.001). In the 15-month LiTALS study, probabilities for transitioning from a given stage at baseline were usually greatest for the next highest stage.

Conclusions

The proposed ALS Milano Torino Staging system correlated well with assessments of function, quality of life and health service costs. Probabilities of transition between stages were consistent with the well-defined progression of ALS. Further studies are warranted to validate this system and determine its potential utility.

Background

Amyotrophic lateral sclerosis (ALS) is an idiopathic neurodegenerative disease that affects motor neurons, typically leading to death within 3 years of symptom onset [1]. ALS is characterized by a progressive loss of functions such as speech, swallowing, mobility and respiration. Functional rating scales such as the ALS Functional Rating Scale (ALSFRS) [2] and ALSFRS–Revised (ALSFRS-R) [3] are useful to measure functional decline and have been used to evaluate treatment effects on function in clinical trials (e.g., refs [4-8]). However, the ALSFRS/ALSFRS-R may not fully capture the functional characteristics of later stage ALS progression [9,10] and there is no agreed-upon threshold at which a change in ALSFRS/ALSFRS-R score is viewed as an important transition point in functional status.

Definition of discrete stages of disease progression based on such clinical milestones can be a useful tool for prognosis, therapeutic decision-making, assessment of quality of care and resource allocation [11]. A staging system also allows patients and caregivers to understand their disease and its clinical course better. In the case of ALS, a valid staging system should correlate with ALS disease progression and demarcate meaningful differences in quality of life (QOL) and economic burden. Although staging systems for ALS have been proposed [12,13], currently, there is no commonly used system. The lack of a validated staging system for ALS makes it difficult to quantify the degree of clinical, socioeconomic, or QOL impact of a therapeutic intervention.

We sought to develop an ALS staging system that captures the observed progressive loss of independence and function, and to apply it to the evaluation of patients' clinical outcomes, QOL, and costs in ALS.

Methods

Patients and measures

4

We utilized data from the Quality of Care in ALS (QOC) study [14], a prospective study of consecutively enrolled patients (aged ≥18 and ≤80 years) from 11 Italian ALS centers (2001 to 2002) were to develop and evaluate the proposed ALS staging system. Patients were included in the QOC study if they met El Escorial revised criteria for definite, probable or probable laboratory-supported sporadic ALS)[15]. Ethical approvals were obtained from Institutional Review Boards at each participating study center. Exclusion criteria included participation in ongoing clinical trials, familial ALS, ALS plus syndrome, ALS frontotemporal degeneration, and serious medical conditions requiring care (eg, cancer, ischemic heart disease, chronic obstructive pulmonary disease, and renal insufficiency).

Patients were evaluated at study entry, 4-, 8- and 12-month follow-up visits for 1 year between mid-2001 to mid-2002. At each study visit, patients were evaluated for functional status using the 10-item ALSFRS, health-related QOL (HRQOL) using the Medical Outcome Study 36-Item Short-Form General Health Survey (SF-36), and overall individual QOL using the Schedule for Evaluation of Individual QOL–Direct Weighting (SEIQOL-DW). Both SF-36 and SEIQoL-DW have been validated for the Italian population and these normative data were used as a comparison[16].

Direct health service costs were obtained from ad hoc forms filled at each study visit. Patients were requested to complete a daily diary including all uses of health system provisions. All direct costs were analyzed including hospital admissions, nursing care admissions, day hospital visits, clinic visits, diagnostic examinations, pharmacological treatments, nurse caring, rehabilitation interventions, psychological support, visits by the general practitioner, provisions of aids for mobility and communication. Indirect costs were not considered. The cost of each service was obtained from the official costs for the year 2001-2003 provided by the Italian National Health System.

We examined between-stage transition using data from an interventional clinical trial of lithium carbonate in amyotrophic lateral sclerosis (LiTALS study; EudraCT

number 2008–001094-15) for which detailed methods have been published previously [17]. Briefly, 171 patients (aged ≥18 and ≤75 years) from Italian ALS study centers were enrolled in a 15-month trial comparing postulated therapeutic (n=87) and subtherapeutic (n=84) levels of lithium carbonate (2008 to 2009). Patients with mild to moderate disease (ALS onset ≤36 months; ALSFRS-R scores: swallowing, ≥3; cutting food and walking, ≥2; respiratory capacity, ≥3) and were allowed to take riluzole if they had been on a stable dose for at least 2 months. The ALSFRS-R was performed at randomization and follow-up months 1, 3, 6, 9, 12 and 15. The study was terminated early due to lack of efficacy and occurrence of adverse events.

Definition of ALS Milano-Torino Staging in the QOC study

Critical milestones in ALS progression were defined by loss of independent function in 4 key domains that are included in both the ALSFRS and ALSFRS-R: walking/self-care, swallowing, communicating, and breathing (**Table 1**). Impairment in each domain was determined by thresholds in the specific ALSFRS 10-item scale scores. Values of 0 (below threshold) or 1 (above threshold) were assigned and the stages were determined as the sum of those values across the 4 domains. Stages were defined as: stage 0, functional involvement but no loss of independence on any domain; stages 1 to 4, number of domains in which independence was lost; and stage 5, death (**Table 1**). Transition probabilities were calculated by a Markov model [18]. The staging system was given the name ALS Milano-Torino Staging (ALS-MITOS).

Statistical analysis

ALS MiToS stage was calculated for each participant visit in the QOC and LiTALS study. We examined the distribution of ALS stage at 12 months by baseline ALS stage using descriptive statistics. The distribution of ALSFRS score at each observed stage during follow-up was evaluated.

Cost data were analyzed using analysis of variance. Trends in cost data and SF-36 comparisons were evaluated using the Kruskal-Wallis test.

Results

In the initial analysis from the QOC study, a total of 130 patients (56 females, 74 males) met the inclusion criteria (**Figure 1A**). The mean age of ALS onset was 57 years, with an average time of 2.5 years since symptom onset (**Table 2**). Most patients (64%) were diagnosed with definite ALS, followed by probable laboratory-supported ALS (22%), and probable ALS (14%). The majority (66%) of patients had spinal ALS onset. At baseline, the mean ALSFRS score was 24.5 (SD=9.7); 55% of the patients were unable to move or required adaptive aids, 21.5% could not communicate by speech, 24.6% had enteral feeding and 21% needed ventilatory assistance. Adjuvant therapies (physical and speech therapy) were used at baseline by 67% and 20% of patients respectively. Some adaptive aides were also being used, including wheelchairs (28.5%) and walkers (14%). The remainder of the palliative care milestones had not yet been reached by most patients. For example, at baseline, fewer than 10% of patients had recourse to paid home care or psychosocial care resources, had prepared for end-of-life car, or had used ameliorative or life-extending (percutaneous gastrostomy tube, non-invasive ventilation or tracheotomy) technologies. Eighty percent of patients used riluzole, 40% used creatine or vitamin E, whereas use of psychopharmaceuticals, anticholinergic to control drooling and antispasticity drugs was rare. Finally, 2% of the cohort had used the emergency room and none was in hospice at baseline. A spouse was the primary care giver for 72% of patients and spent a median of 13 h/day caring for the patient. Thirty-two patients received home health care services, of which 60% were private.

In the LiTALS study, 171 patients (71 females, 100 males) also had an average age of onset of 57 years, and most (75%) had spinal ALS onset (**Figure 1B, Table 2**). A more complete description of the study population has been published previously [17]. Briefly, the mean age of

ALS onset was 57 years and most patients had spinal ALS onset (75%). At baseline, the mean ALSFRS-R score was 36.9.

In the analysis of progression by baseline stage in the QOC study, most patients at baseline were in stage 0 (48.7%) or stage 1 (27.7%); 11.8% were in stage 2, 3.4% were in stage 3, and 8.4% were in stage 4. At 12 months, 63.8% (83) patients within each of the stages at baseline had progressed to more advanced stages of disease (**Figure 2A**). In total, 18.1% of patients were in stage 0, 22.08% were in stage 1, 16.5% were in stage 2, 5.5% were in stage 3, 7.9% were in stage 4, and 29.1% were in stage 5 (death). ALSFRS scores for each stage for all patients progressively decreased from stage 0 to stage 4 (**Figure 2B**).

In the QOC study, only 3 patients did not complete the SF-36 questionnaire. At the domain level, the proportion of missing replies ranged from 2% to 4%. The HRQOL in ALS patients was consistently lower than that of published Italian norms of across all domains of the SF-36 and decreased with increasing stages (**Figure 3A**). The SF-36 physical and mental health composite scores (mean ± s.d.) were 30.5 ± 10.3 and 43.3 ± 12.3 respectively at baseline and decreased with increasing stages (**Figure 3**). The Italian National Health Service mean total costs per patient per year increased with progress to each consecutive stage (**Figure 4**).

In the analysis of progression by baseline stage in the LiTALS study, all patients at baseline were in stage 0 (80.3%) or stage 1 (19.7%) (**Figure 5**), reflecting the study enrollment criterion of ALS onset within 36 months. In total, 22.4% were in stage 0, 35.5% were in stage 1, 10.5% were in stage 2, 5.3% were in stage 3 and 26.3% were in stage 5 (death). As also observed in the QOC study population, ALSFRS-R scores for each stage for all patients in the LiTALS study progressively decreased from stage 0 to stage 4; mean (SE) for stages 0 to 4, respectively: 38.6 (0.21), 29.0 (0.31), 20.3 (0.74), 14.8 (1.16), 10.8 (0.48).

Based on the LiTALS study data, probabilities for transition between stages were calculated. As shown in **Figure 6**, probabilities for transition from a given stage were usually highest for the next highest stage compared with any other higher or lower stage. For stages 0, 1, 3 and 4, the

highest probabilities were evident for transitions to the next highest stage. Patients in stage 0 and stage 1 had lower probabilities of 'skipping' intervening steps and only stages 1 and 2 were associated with any probability of reversion to a previous stage. However, patients in stage 2 were equally likely to progress to stage 3 or revert to stage 1. The probability of death showed stepwise increases with increasing stage up to stage 2, remained relatively constant between stages 2 and 3, then increased to 1.0 at stage 4.

Discussion

We have shown that the proposed ALS-MITOS staging system, based on the validated ALSFRS/ALSFRS-R, identified relevant stages of disease in these patients. This approach partitions individuals with ALS into the relevant stages through which they progress according to the number of important life functions lost. The distribution of patients across these stages and the probabilities of transition between stages were consistent with sequential disease progression with increasing stage. In the QOC study, the QOL and health care costs of patients with ALS also were correlated with the ALS-MITOS clinical stage.

A strength of this staging system is the fact that it is based on the ALSFRS/ ALSFRS-R, which is a tool already familiar to most ALS clinicians and one that is widely used in clinical trials. Thus, this staging system can be readily incorporated as an endpoint in clinical trials to allow investigators to evaluate treatment impact on different ALS stages without a requirement for additional assessments.

The use of ALSFRS items as the basis of this system should facilitate further retrospective validation studies using existing databases that collected functional data using that scale. Furthermore, this system may enhance physicians' ability to have a meaningful discussion with patients and caregivers about what to expect as the disease progresses. In addition, resource needs evolve with progression of disease, as earlier stages require diagnostics, intermediate

stages may involve various specialties and later stages require palliative care [19]. Thus, a validated staging system should help with resource planning.

Although these initial analyses may support the validity of the ALS-MITOS staging system, it is important to point out the limitations of this study. For example, it was not possible to determine the amount of time spent in the baseline stage prior to study entry because stages were not assessed retrospectively. The small sample size limited an assessment of changes in the stage distribution from baseline to later assessment time points and may be too small to reach any definite conclusions. Stage transitions and the relationship between this staging system and clinical outcomes such as mortality could not be evaluated owing to the short follow-up time and small sample size. The initial staging assessment may have been impacted by the long time from symptom onset to study entry (2.5 years in the initial study). Finally, because patients with frontotemporal degeneration were excluded, and this system does not capture the impact of cognition, an important aspect of ALS, it is not clear how cognitive impairment might affect staging of disease.

The potential limitations of the ALS-MITOS system are likely be more than compensated by its utility because it is based on a well-validated and widely used rating scale. Thus, it has the potential to provide meaningful information to clinicians and patients. Furthermore, it can be readily applied to existing datasets to further establish its validity. Further investigation of transitions through stages and associated changes in costs and QOL would add to our understanding of the utility of this proposed system.

Conclusions

The results of this study are sufficiently compelling to warrant further evaluations of the ALS-MITOS system of staging.

List of abbreviations used

ALS, amyotrophic lateral sclerosis; ALS-MITOS, Amyotrophic Lateral Sclerosis Milano-Torino Staging; ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; HRQOL, health-related quality of life; LiTALS, Lithium carbonate in Amyotrophic Lateral Sclerosis study; QOC; Quality of Care in Amyotrophic Lateral Sclerosis study; QOL, quality of life

Competing interests

Adriano Chiò serves on a scientific advisory board for Biogen Idec and Cytokinetics. Edward Hammond served as a consultant to Biogen Idec. The other authors report no other conflicts of interest.

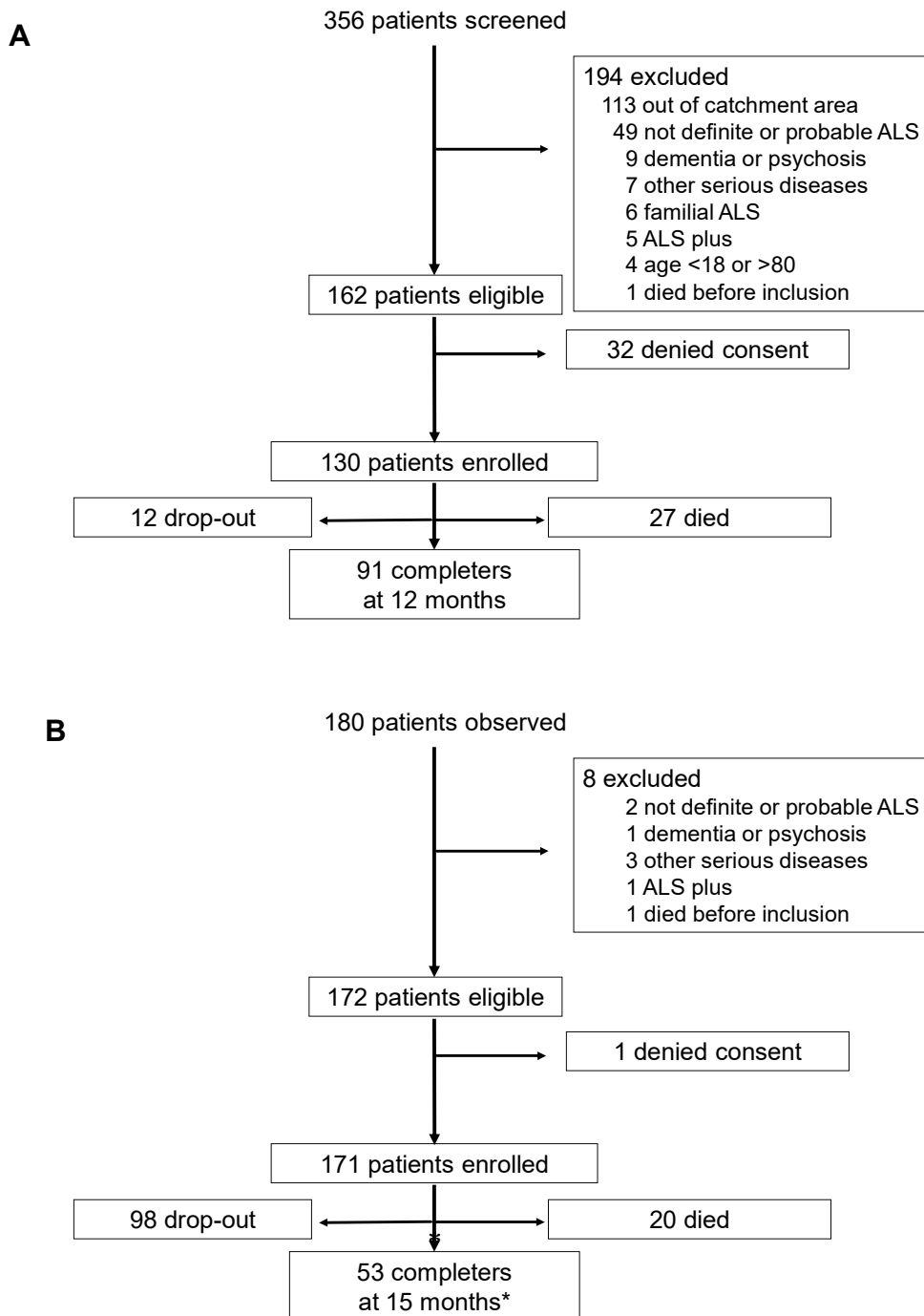All authors reviewed drafts and approved the final version of this manuscript for submission to BMC Neurology.

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Figure 1: (**A**) Patient disposition in the Italian study of the Quality of Care in ALS; (**B**) patient disposition in the Lithium Carbonate in ALS study

A

356 patients screened

194 excluded
113 out of catchment area
49 not definite or probable ALS
9 dementia or psychosis
7 other serious diseases
6 familial ALS
5 ALS plus
4 age <18 or >80
1 died before inclusion

162 patients eligible

32 denied consent

130 patients enrolled

12 drop-out   27 died

91 completers
at 12 months

B

180 patients observed

8 excluded
2 not definite or probable ALS
1 dementia or psychosis
3 other serious diseases
1 ALS plus
1 died before inclusion

172 patients eligible

1 denied consent

171 patients enrolled

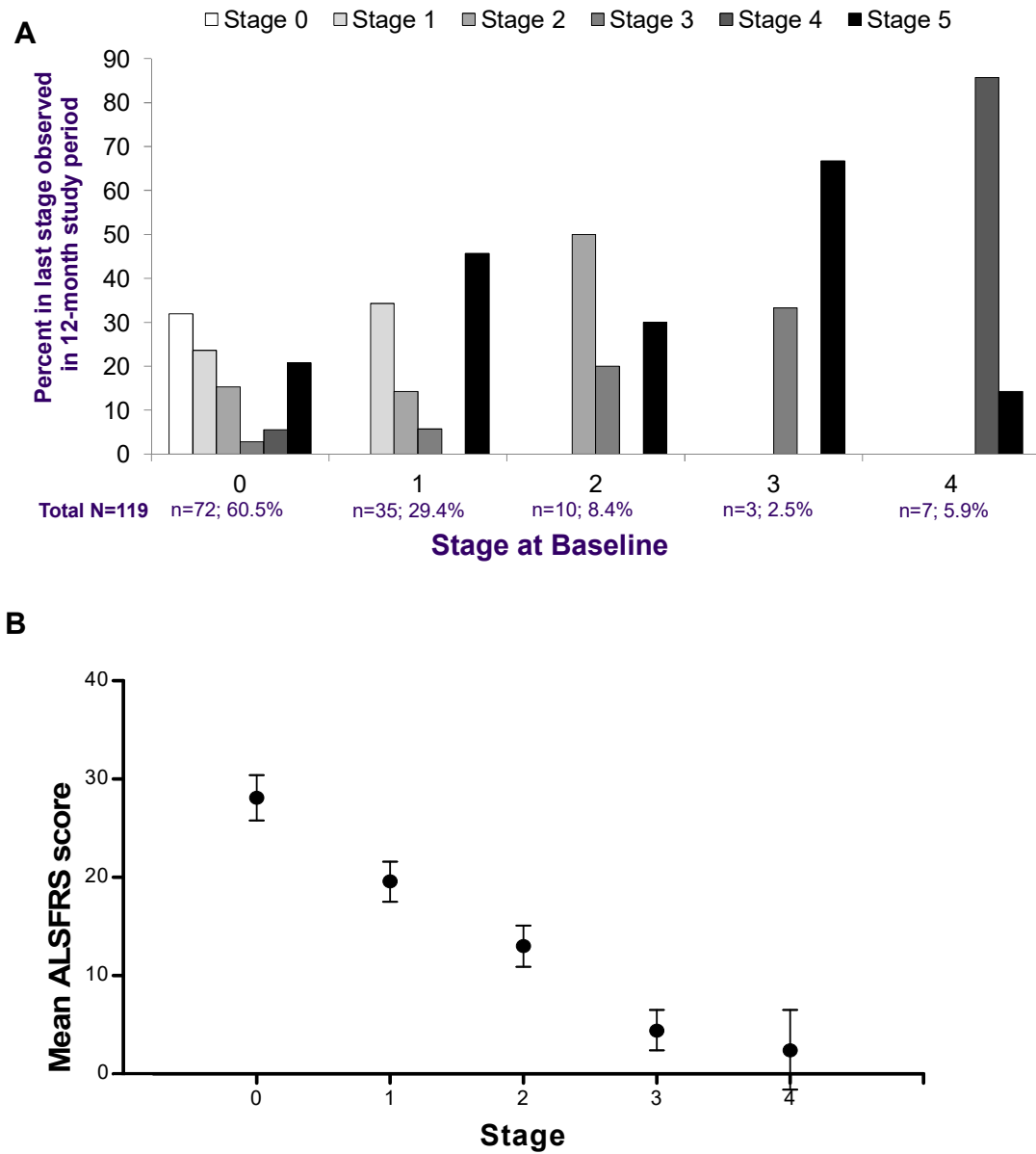98 drop-out   20 died

53 completers
at 15 months*

*Includes patients enrolled but not completed at study termination

ALS, amyotrophic lateral sclerosis; LiTALS, Lithium Carbonate in ALS study

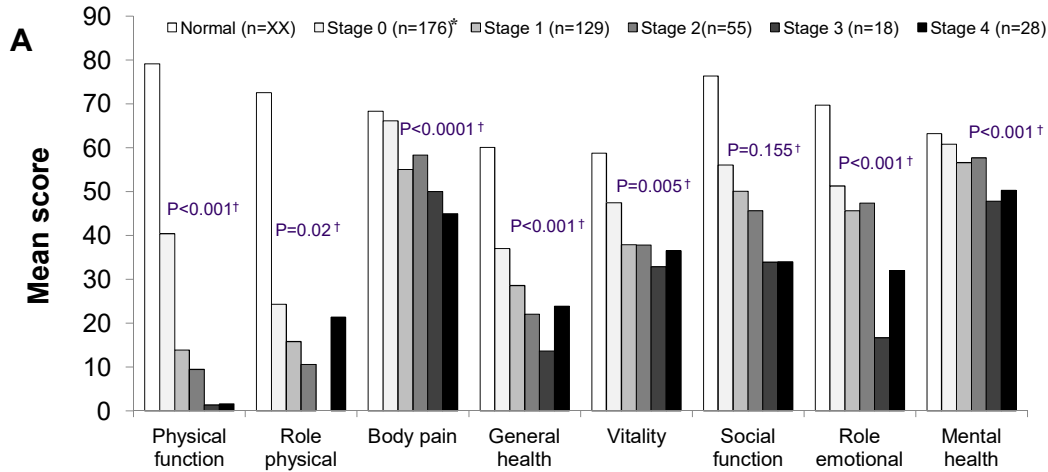**Figure 2.** (**A**) ALS stage at 12 months by baseline stage; (**B**) mean (± 95% confidence interval)

ALSFRS* score by stage for all patients in the QOC study

ALS, amyotrophic lateral sclerosis; ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating
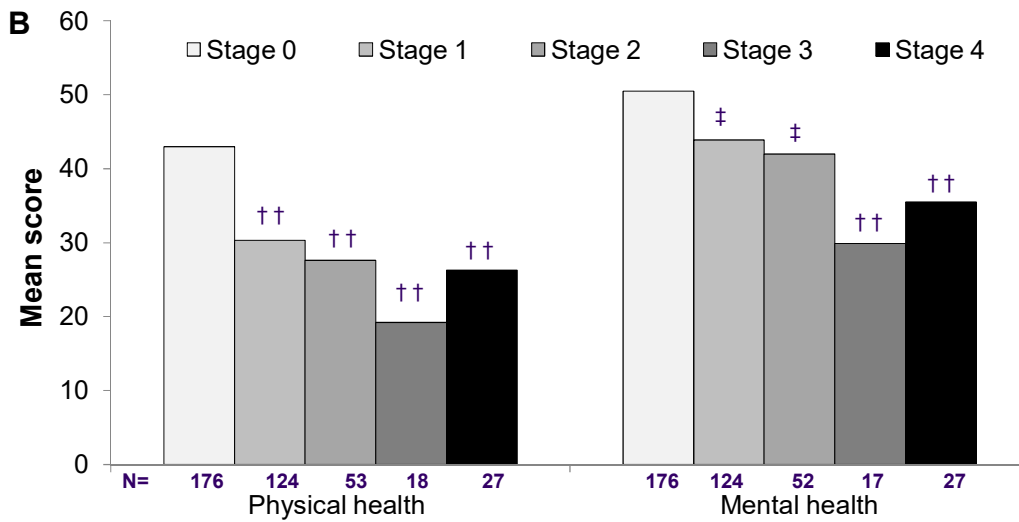Scale; QOC, Quality of Care in ALS
*The 10-item ALSFRS scale was used.

Figure 3. (**A**) SF-36 domain by ALS stage for all patients in the QOC study at baseline and normal controls; (**B**) composite scores by ALS stage for all patients in the QOC study at baseline

A

□Normal (n=XX) □Stage 0 (n=176)* ▤Stage 1 (n=129) ▦Stage 2(n=55) ▨Stage 3 (n=18) ■Stage 4 (n=28)

P<0.001† (Physical function)
P=0.02† (Role physical)
P<0.0001† (Body pain)
P<0.001† (General health)
P=0.005† (Vitality)
P=0.155† (Social function)
P<0.001† (Role emotional)
P<0.001† (Mental health)

SF-36 Domain

† P-value for trend, stages 0–4, Kruskal-Wallis test; * n=patient visits; numbers differ owing to the number of missing values in different domains

B

□Stage 0 ▤Stage 1 ▦Stage 2 ▨Stage 3 ■Stage 4

N=   176   124   53   18   27   176   124   52   17   27
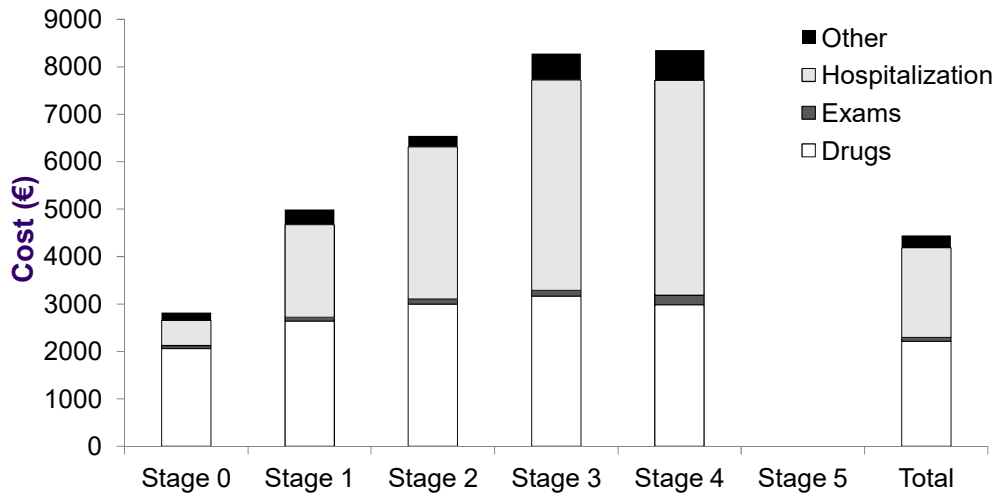   Physical health   Mental health

SF-36 Composite

†† **P<0.001 compared with Stage 0;** ‡ **P<0.01 compared with stage 0**

ALS, amyotrophic lateral sclerosis; QOC, Quality of Care in ALS

Figure 4. ALS costs over the one-year study period by ALS-MITOS stage* in the Quality of Care in ALS study
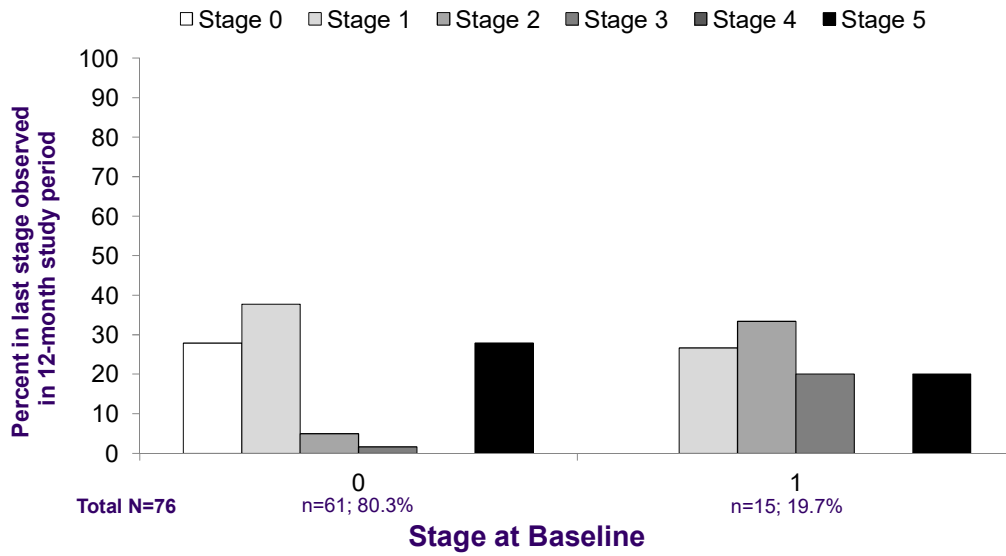

ALS, amyotrophic lateral sclerosis; ALS-MITOS, Amyotrophic Lateral Sclerosis Milano-Torino Staging
*Includes each stage for all patients

Costs per stages 4 months NHS - ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
Drugs 4 months NHS	Between Groups	56685991	6	9447665,086	16,298	,000
	Within Groups	2,97E+08	513	579667,980		
	Total	3,54E+08	519			
Exams 4 months NHS	Between Groups	158777,6	6	26462,939	5,469	,000
	Within Groups	2482432	513	4839,049		
	Total	2641210	519			
Hospitalisation 4 months NHS	Between Groups	1,42E+08	6	23657610,17	2,860	,009
	Within Groups	4,24E+09	513	8271587,711		
	Total	4,39E+09	519			
Treatments 4 months NHS	Between Groups	2006867	6	334477,824	7,883	,000
	Within Groups	21765915	513	42428,684		
	Total	23772782	519			

Figure 5. (**A**) ALS stage at 12 months by baseline stage in the LiTALS study

ALS, amyotrophic lateral sclerosis; LiTALS, Lithium carbonate in Amyotrophic Lateral Sclerosis study

Figure 6. Probability of transition between ALS-MITOS stages in the LiTALS study
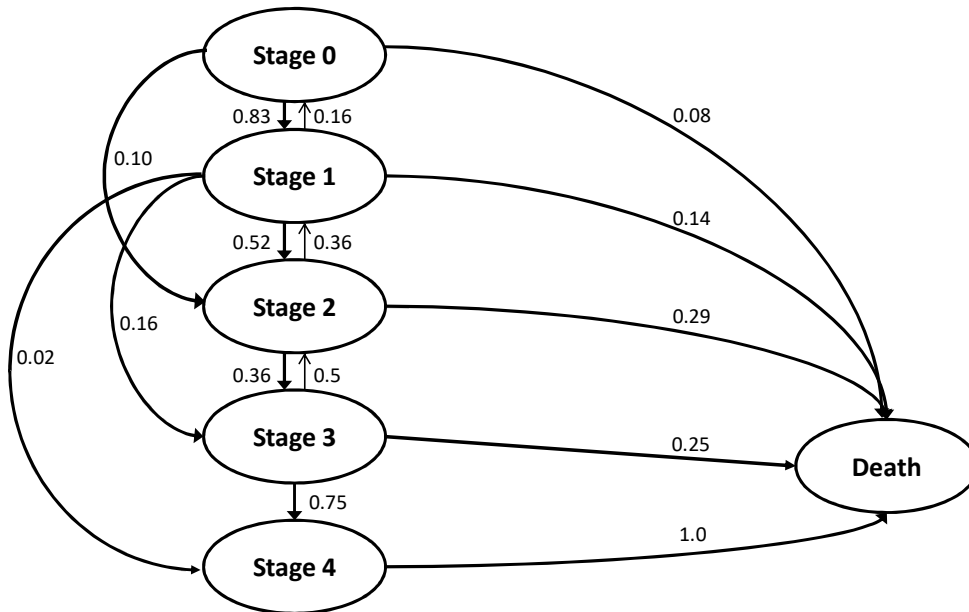
ALS-MITOS, Amyotrophic Lateral Sclerosis Milano-Torino Staging; LiTALS, Lithium carbonate in amyotrophic lateral sclerosis

Table 1. Functional domains and stages

ALSFRS domain	Item	Score	Functional score[a]
Movement (Walking/Self-care)[b]	8 Walking	4 Normal	0
		3 Early ambulation difficulties	
		2 Walks with assistance	
		1 Nonambulatory functional movement only	1
	OR	0 No purposeful leg movement	
	6 Dressing and hygiene	4 Normal function	0
		3 Independent and complete self-care with effort or decreased efficiency	
		2 Intermittent assistance or substitute methods	
		1 Needs attendant for self-care	1
		0 Total dependence	
Swallowing	3 Swallowing	4 Normal eating habits	0
		3 Early eating problems; occasional choking	
		2 Dietary consistency changes	
		1 Needs supplemental tube feeding	1
		0 NPO (exclusively parenteral or enteral feeding)	
Communicating[b]	1 Speech	4 Normal speech processes	0
		3 Detectable speech with disturbances	

		2 Intelligible with repeating	
	AND	1 Speech combined with nonvocal communication	1
		0 Loss of useful speech	
	4 Handwriting	4 Normal	0
		3 Slow or sloppy; all words are legible	
		2 Not all words are legible	
		1 Able to grip pen but unable to write	1
		0 Unable to grip pen	
Breathing[b]	10 Dyspnea	4 None	0
		3 Occurs when walking	
		2 Occurs with one or more of the following: eating, bathing, dressing	
		1 Occurs at rest, difficulty breathing when either sitting or lying	1
		0 Significant difficulty, considering using mechanical respiratory support	
	OR		
	12 Respiratory insufficiency	4 None	0
		3 Intermittent use of NIPPV	
		2 Continuous use of NIPPV during the night	1
		1 Continuous use of NIPPV during the night and day	
		0 Unable to grip pen	

ALS-MITOS	
Stage	**Functional domains lost**
0	None
1	1 domain
2	2 domains
3	3 domains
4	4 domains
5	Death

ALFSRS-r, Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; ALS-MITOS, Amyotrophic Lateral Sclerosis Milano-Torino Staging; NIPPV, nasal intermittent positive pressure ventilation; NPO, nothing by mouth
[a]Staging determined by the sum of functional score of 1 for each domain
[b]Where 2 items were used, scoring was based on either or both item scores as indicated

TABLE 2: Baseline Characteristics

Characteristic	QOC study N=130	LiTALS study N=171
Mean age, y (range)	60 (27-80)	58 (27-76)
Male, n (%)	74 (56.9)	71 (41.5)
Mean age at ALS onset, y (range)	57 (25-78)	57 (26-76)
Time since ALS onset, y (range)	2.5 (0.3-13.3)	1.5 (0.1 – 5.0)
ALS onset type, n (%)		
Spinal	86 (66)	129 (75)
Bulbar	38 (29)	42 (25)
Both	6 (5)	0
Mean ALSFRS-R score at entry (range)	24.5 (0-40)*	36.9 (15-48)[†]

*ALSFRS score

[†]ALSFRS-R score

ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; LiTALS, Lithium carbonate in ALS; QOC, Quality of care in ALS.