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REVIEW

Prognostic factors for the course of functional status of patients with ALS: a systematic review

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Abstract The progressive course of amyotrophic lateral sclerosis (ALS) results in an ever-changing spectrum of the care needs of patients with ALS. Knowledge of prognostic factors for the functional course of ALS may enhance clinical prediction and improve the timing of appropriate interventions. Our objective was to systematically review the evidence regarding prognostic factors for the rate of functional decline of patients with ALS, assessed with versions of the ALS Functional Rating Scale (ALSFRS). Two reviewers independently assessed the methodological quality of the thirteen included studies using the Quality in Prognosis Studies (QUIPS) tool. The overall quality of evidence for each prognostic factor was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering risk of bias, imprecision, inconsistency, indirectness, and publication bias. The quality of evidence for the prognostic value of age at onset, site of onset, time from symptom onset to diagnosis, and ALSFRS-Revised baseline score was low, mainly due to the limited data and inconsistency of results in the small number of studies included. The prognostic value of initial rate of disease progression, age at diagnosis, forced vital capacity, frontotemporal dementia, body mass index, and comorbidity remains unclear. We conclude that the current evidence on prognostic factors for functional decline in ALS is insufficient to allow the development of a prediction tool that can support clinical decisions. Given the limited data, future prognostic studies may need to focus on factors that have a predictive value for a decline in ALSFRS(-R) domain scores, preferably based on internationally collected and shared data.

Keywords Amyotrophic lateral sclerosis · Patient counseling · Disease progression · Prognosis

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease showing signs of both upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction, resulting in increasing muscle weakness in one or more body regions [1]. Due to different rates of degeneration and progression of loss of motor neurons in brain, brainstem, and spinal cord, clinical manifestations may vary widely between patients [2]. Adding to the heterogeneity in motor impairments, varying degrees of cognitive impairment and behavioral dysfunction are present in patients with ALS [3].

The heterogeneity of the ALS syndrome poses a challenge to multidisciplinary, neuro-palliative, rehabilitation management [4]. Because of the progressive course, the care needs form a broad and ever-changing spectrum. The timing of appropriate interventions is important and requires accurate prediction of the individual course of the disease. In clinical practice, individual prognostication with regard to disability progression and the timing of

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supportive interventions are largely based on the clinician's cumulated experience. Despite attempts to construct prognostic algorithms for survival, prognostic tools for the functional course in ALS are lacking [5, 6]. Evidence on prognostic factors for disability progression may enhance clinical prediction and guide clinical decision making, including patient counseling and treatment selection [7, 8].

The aim of our study is to identify factors from the literature that have a predictive value for the course of the functional status of patients with ALS.

Methods

Literature selection

We searched the literature up to March 2014 to identify prognostic studies of the functional status in ALS. Two of the researchers (AB and HC) identified relevant articles by searching the computerized bibliographic databases EMBASE (1980–March 2014), CINAHL (1982–March 2014), PsycINFO (1995–March 2014), MEDLINE (1965–March 2013), and Web of Science (1988–March 2014).

A sensitive search strategy was built on the subjoined components: (1) patients with ALS (MESH term and text word), (2) prognostic studies (we used a revised version of the Yale University School of Medicine Prognosis and Natural History Filter), and (3) the functional status outcome—a self-compound filter of ALS-related functioning and disability assessment as measured with the ALSFRS/ALSFRS-R/ALSFRS-EX.

We decided to select the ALSFRS(-R) as outcome measure because it is a commonly used, validated, clinically meaningful, reliable, and easy to administer measure of functional status [9–12]. The full search strategy is available on request.

Two reviewers (HC and AB) independently screened the abstracts identified by the search strategy. Relevant publications, potentially eligible for inclusion, were read in full by the two reviewers and in case of disagreement on inclusion, subsequently discussed during a consensus meeting. One researcher (HC) screened the reference lists of each of the selected publications to retrieve relevant publications which had not been identified by the computerized search.

An eligible study aimed to identify prognostic factors (socio-demographic, disease-specific, psychosocial, and comorbid factors) on functional status assessed using (versions of) the ALSFRS in patients with ALS who were classified according to the El Escorial diagnostic criteria [1]. This had to be designed as a longitudinal cohort study, with at least one follow-up measurement. Both prospective and retrospective studies were included. Results were published in English as full length articles between January 1960 and March 2014.

Data extraction

One reviewer (HC) used a standardized form to record information and data regarding study design, sample size, study population, patients' characteristics, treatment, outcome measure(-s), ALSFRS(-R) score(-s) at baseline, loss to follow-up, follow-up duration, prognostic factor(-s) studied and strength of association between prognostic factors and ALSFRS(-R)-outcome.

Methodological quality assessment

There is international consensus on how to appraise the quality of prognostic studies [13, 14]. The Quality in Prognosis Studies (QUIPS) tool is designed for systematic reviews of prognostic studies. We used an adapted QUIPS which contained five categories assessing potential sources of bias conducting prognostic studies—patient selection, study attrition, measurement of prognostic factors, outcome measurement, statistical analysis, and results presentation. We considered the original QUIPS items on confounding not relevant for our study, because included studies were designed to predict a specific outcome based on a combination of several potential prognostic factors. In advance, we determined the key characteristics specific for the source population, the baseline study sample, and the participants who completed the study and those who did not, to assess potential risks of bias in study participation and attrition.

Two reviewers (HC and AB) independently rated the methodological quality of the selected studies. Rating of adequacy of reporting in the included studies was carried out for each separate prompting item of the six categories using yes, partial, no, or unsure. Subsequently, potential bias for each of the six domains was rated: high quality when there was low risk of bias, moderate quality with moderate risk, and low quality when there was high risk of bias. The two reviewers discussed disagreement about whether a criterion was met, and resolved by consensus.

Data synthesis

Due to the expected heterogeneity of selected studies, we performed a qualitative best evidence synthesis. Most important elements of this synthesis were the prognostic factors, the strength of the association and the methodological quality of the studies (QUIPS). We applied the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to judge the quality of evidence across studies and to grade strength of recommendations in

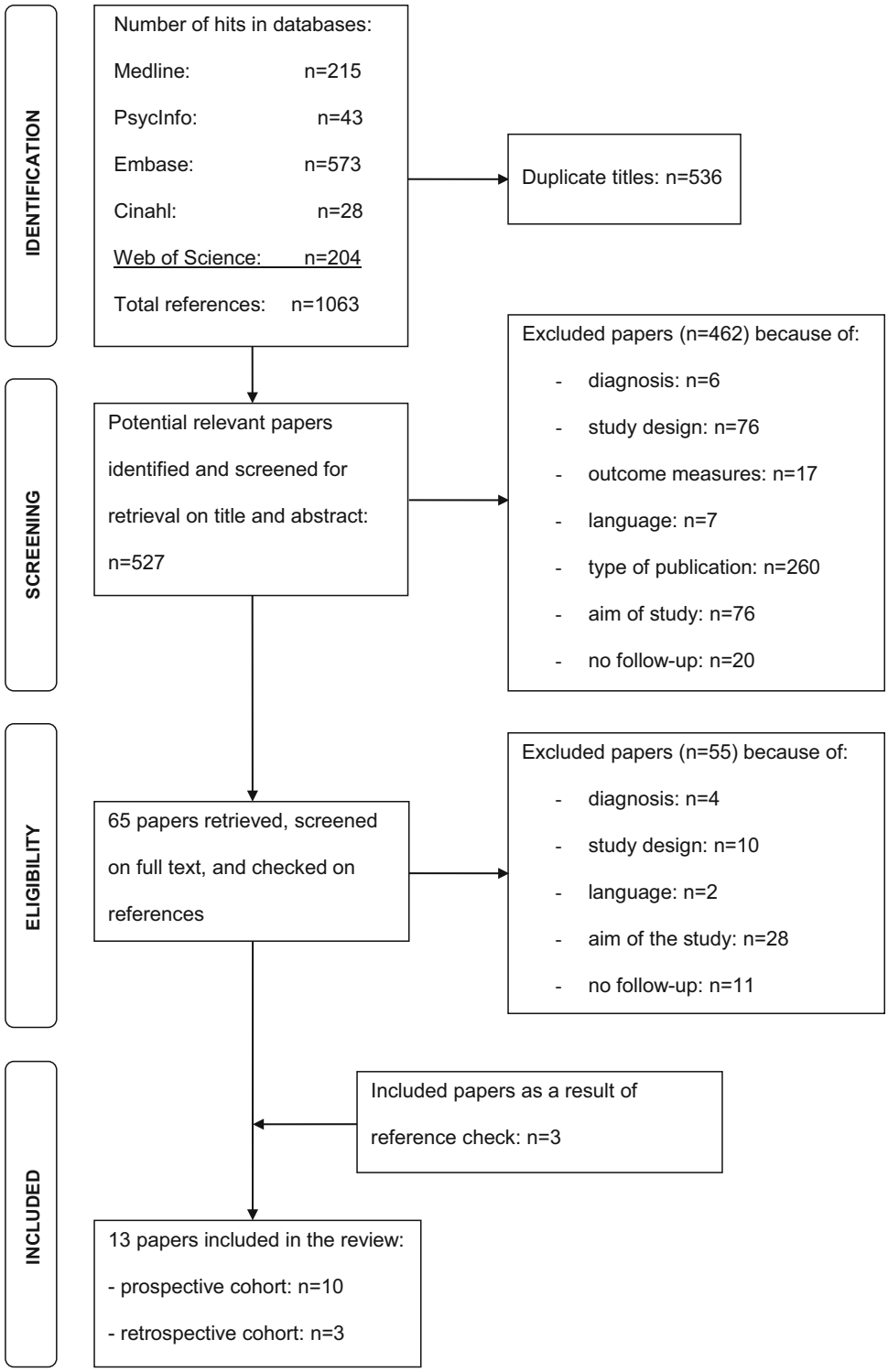

Fig. 1 Flowchart study selection

systematic reviews [14–16]. Two reviewers (HC and AB) judged how the GRADE factors—phase of investigation, study limitations (QUIPS; subgroup analyses), inconsistency, indirectness, imprecision, publication bias, and moderate or large effect size—impacted the overall quality of evidence (BOX). We omitted the factor 'exposure–response gradient' as it was not relevant for the quality of evidence of the prognostic studies we selected. The level of evidence was rated as high, moderate, low, or very low according to the GRADE approach [17].

Box: The GRADE process rating the quality of evidence across studies

(Modified from Huguet et al. 2013 [16]).

Rating is modified downward:

Univariate analysis is applied to identify associations between a number of potential prognostic factors and the ALSFRS(-R).

Study limitations; moderate or low study quality based on the QUIPS 'risk of bias' score [14].

Inconsistency of results; difference in results are not clinically meaningful. Point of effect estimates are on either side of the line of no effect.

Indirectness of evidence; the study sample does not fully represent the review question defined in the systematic review, but only represents a subset of the population of interest.

Publication bias likely; publication bias exists when a prognostic factor has been investigated in a small number of cohort studies.

Within study imprecision; (1) sample size justification is not provided and sample size of each included study <100 patients, and (2) no precision in the estimation of the effect size within each included study is reported [18].

Rating is modified upward:

Moderate or large effect size. For meta-analysis: pooled effect is moderate or large. For narrative summary; moderate or large similar effect is reported by most studies.

Results

Selection of studies

Thirteen publications with a total of 5,341 patients were included in this review (Fig. 1) [19–31].

Study characteristics

The studies were published between April 2006 and March 2014. The search yielded ten prospective cohort studies and three retrospective cohort studies. Four of the prospective studies were clinical trials. In one study, the data were generated from three clinical trials and one observational study [27]. The study characteristics are summarized in Table 1. The number of study patients varied from 31 to 2,452. Seventy-two percent of the total number of patients ($n = 5{,}341$) came from observational studies. Mean (±SD) age of the patients varied between 53.9 (12.5) and 63.4 (10.2) years. One study looked at two groups of patients whose presented median (range) ages were 61 (45–74) and 55 (35–73) years, respectively [29]. Bulbar type of onset varied from 16 to 40 %; this was not specified in two studies [19, 29]. The sample in one study consisted of patients from a population-based ALS register (PRO-ACT; https://nctu.partners.org/ProACT/) [19]. Duration of follow-up varied from 6 months to 5 years. Most studies did not report on co-interventions between baseline and follow-up (e.g., Riluzole use, Percutaneous Endoscopic Gastrostomy (PEG), non-invasive ventilation (NIV), multidisciplinary care). Mean (±SD) baseline ALSFRS(-R) score ranged from 27.0 (6.6) to 42.8 (5.8). Five studies included an inception cohort—the other studies used non-inception cohorts. Six studies presented the ALSFRS as outcome measure for disability accumulation. Three of these studies started patient recruitment prior to the revision of the ALSFRS in 1999 [10]. One study did not report the time period of inclusion [28].

Prognostic factors

Table 2 summarizes the candidate prognostic factors studied in relation to the outcome measures ALSFRS(-R) total score, and analyzed in more than one study ($n = 14$). A description of the candidate prognostic factors studied in relation to the outcome measures ALSFRS(-R) total score and ALSFRS-R bulbar domain score, and analyzed in single studies ($n = 16$), is provided as supplementary material (Appendix 1). The prognostic factors summarized involved socio-demographic characteristics ($n = 11$), clinical characteristics ($n = 12$), environmental factors ($n = 1$), psychosocial factors ($n = 2$), and biological markers of disease progression ($n = 2$). Ten studies used statistical analysis modeling for covariates to estimate the strength of the independent association between prognostic factor and outcome.

Methodological quality of included studies

The results of our risk of bias assessment using the QUIPS tool are summarized in the 'risk of bias table' (Appendix 2). The overall methodological quality of five studies was judged as 'high', five studies scored 'moderate', and three studies 'low' quality. In almost all studies, measurement of prognostic factors and ALSFRS(-R) outcomes were performed in a similar, valid, and reliable way for all participants. These quality domains were classified as 'low' risk of bias. Due to lack of reporting on key characteristics of the source population ('study participation') and of participants loss to follow-up ('study attrition'), bias could not be ruled out. We were, therefore, compelled to classify studies as 'moderate' ($n = 6$) and 'high' risk ($n = 5$) of selection bias. The statistical analysis, model-building process or completeness of reporting were judged to be inadequate in six studies, resulting in 'moderate' to 'high'

Table 1 Characteristics of the included studies ($n = 13$)

Author, year	Study design	Sample size (n), study population	Patients' characteristics	Treatment	Outcome measure(s) and baseline score(s)	Loss to follow-up, n (%)	Follow-up duration (mo)	Prognostic factor(s)
Gomeni [19]	Prospective multicenter cohort	338 PRO-ACT database	Age (years): mean 55.5 (SD 11.6) Male: 65 %	Not reported	ALSFRS-R; mean 38.7 (SD 4.9)	6 (2)	12	Baseline ALSFRS-R; %Change in ALSFRS-R from baseline at week two; %Change in ALSFRS-R from baseline at week four
Clavelou [20]	Prospective multicenter cohort	382 Sixteen outpatient university hospitals	Age (yrs): mean 61.0 (SD 12.4) Male: 55 % Bulbar onset: 23.3 % Mean time to diagnosis: 9.6 mo (SD 8.1) Time since diagnosis ≤6 mo	Riluzole 100 %	ALSFRS; mean 32.82 (SD 4.66); median 34.00; range 10–40	132 (35)	30	Site of onset (bulbar, lower limbs, upper limbs); Gender
Elamin [21]	Prospective cohort	186 Population-based ALS register	Age (yrs): mean 63.4 (SD 10.2) Male: 60 % Bulbar onset: 36 %	Riluzole 82.8 %	ALSFRS-R; total and bulbar domain scores median total: 38	175 (94)	18	Age; Gender; Site of onset (bulbar versus spinal); Baseline ALSFRS-R; Frontotemporal syndrome
Körner [22]	Retrospective cohort	514 ALS outpatient clinic	Age at diagnosis (yrs): mean 58.8 Male: 56 % Bulbar onset: 28 %	Not reported	ALSFRS-R; baseline score not reported	0 (0)	≥6	Comorbidities; Gender; Age at diagnosis; Site of onset (bulbar versus spinal); Time to diagnosis
Reich-Slotky [23]	Prospective multicenter cohort	150 Nineteen outpatient centers	Age (yrs): mean 57.0 (SD 10.9) Male: 57 % Bulbar onset: 16 % BMI: mean 26.2 FVC %: mean 88	Riluzole 72 % Coenzyme Q10: 50 %	ALSFRS-R; mean 35.44 (SD 5.22)	None	9	BMI

Table 1 continued

Author, year	Study design	Sample size (*n*), study population	Patients' characteristics	Treatment	Outcome measure(s) and baseline score(s)	Loss to follow-up, *n* (%)	Follow-up duration (mo)	Prognostic factor(s)
Paganoni [24]	Prospective multicenter cohort	251 Thirty-seven outpatient centers	Age (yrs): mean 53.9 (SD 12.5) Male: 63 % Bulbar onset: 16 % FVC %: mean 87.1 Time since diagnosis (days): mean 294.9 Time since onset (days): mean 672.1 BMI: mean 26.8 VC ≥60 % Disease duration ≤5 yrs	Riluzole 59 %	ALSFRS-R; mean 42.8 (SD 5.8)	103 (59)	8	Uric acid levels; BMI
Gordon [25]	Prospective cohort	2,452 One outpatient hospital	Age at diagnosis (yrs): mean 59.7 (SD 13.2) Male: 57 % Bulbar onset: 28 %	Not reported	ALSFRS-R; baseline score not reported	608 (25)	Mean 32 mo (SD 36)	Age at onset; Site of onset (bulbar versus limb); Baseline ALSFRS-R; Time to diagnosis; Gender; Weight at the first visit; Height
Sorarù [26]	Retrospective cohort	40 One outpatient hospital	UMN-ALS group ($n = 20$): Age at onset (yrs): mean 60 Male: 50 % Bulbar onset: 40 % Time to diagnosis (yrs): mean 2.7 Typical ALS group ($n = 20$): Age at onset (yrs): mean 60 Male: 50 % Bulbar onset: 25 % Time to diagnosis (yrs): mean 1.0	Not reported	ALSFRS-R, total and domain scores Baseline total score: UMN-ALS group: mean 35.5; range 15–40 Typical ALS group: mean 37.7; range 24–45	8 (20)	18	Upper Motor Neuron dominance

Table 1 continued

Author, year	Study design	Sample size (*n*), study population	Patients' characteristics	Treatment	Outcome measure(s) and baseline score(s)	Loss to follow-up, *n* (%)	Follow-up duration (mo)	Prognostic factor(s)
Qureshi [27]	Prospective multicenter cohort	795 Twenty-one outpatient centers	Age (yrs): mean 56.0 (SD 12.2; $n = 596$) Male: 64 % Bulbar onset: 19.5 % %VC: mean 86.3 (SD 17.7)	Topiramate 57 % Creatine 58 % Celecoxib 67 %	ALSFRS; mean 31.2 (SD 5.3)	294 (37)	6–12 (range)	Baseline laboratory parameters
Krampe [28]	Prospective cohort	31 One outpatient clinic	Age (yrs): mean 60.3 (SD 10.4) Age at onset (yrs): mean 58.4 (SD 10.3) Male: 61 % Bulbar/mixed onset: 19/13 % Time to diagnosis (weeks): mean 52.4 (SD = 32.3) FVC %: mean 62.4 (SD 24.5; $n = 20$); range 13–100 Time from onset (yrs): <6yrs	Melatonin 100 % Vitamin E 74 % Riluzole 81 % Amitriptyline 48 % Baclofen 26 % Mg 52 % Vit C 23 % Creatine 13 %	ALSFRS; mean 27.0 (SD 6.6); range 12–38	17 (55)	12	Gender; Age at onset; Years of education; Time since onset; Time from diagnosis to study inclusion; FVC; Personality factors (neuroticism, extraversion, openness, agreeableness, conscientiousness); Depression; FTD and cognitive performance
Rauchway [29]	Retrospective cohort	50 One neurophysiology laboratory	Group I ALSFRS ≤26: $n = 14$ Age at onset (yrs): median 61; Time since onset (mo): median 4; range 2–24 Group II: ALSFRS > 26; $n = 33$ Age at onset (yrs): median 55; Time since onset (mo): median 10; range = 1–24	Not reported	ALSFRS; median (minimum–maximum) Group I; 28 (13–40) Group II; 36 (28–40)	3 (6)	10 (median)	Time from onset of symptoms to initial EDX studies

Table 1 continued

Author, year	Study design	Sample size (*n*), study population	Patients' characteristics	Treatment	Outcome measure(s) and baseline score(s)	Loss to follow-up, *n* (%)	Follow-up duration (mo)	Prognostic factor(s)
Qureshi[30]	Prospective cohort	95 One outpatient hospital	Age (yrs): mean 54.4 (SD = 13.1) Male: 63.2 % Bulbar onset: 24 % Time to diagnosis (yrs): mean 0.9 (SD 0.9)	Not reported	ALSFRS; mean 31.9 (SD 5.7)	None	12	Socio-demographic characteristics: Age; Age at onset; Age at diagnosis; Gender; Years of education; Male veterans; Marital status; Race Clinical examination characteristics: El Escorial criteria; Site of onset (bulbar/limb); Time to diagnosis; Baseline FVC; Baseline ALSFRS; Height; Weight; Familial ALS History of ALS ALS risk factors ($n = 12$ factors) Comorbidity ($n = 12$ factors)
De Carvalho[31]	Prospective cohort	57 One outpatient center	Age (yrs): mean 61.1; range 32–78 Male: 51 % Bulbar onset: 23 % Time since onset (mo): mean 16.4; range 2–63	Not reported	ALSFRS; Group 1: mean 34.7 (SD 1.7); range 32–37 Group 2: mean 33.3 (SD 4.7); range 24–39	24 (42)	6	A ≥8.78 % reduction in ALSFRS score at 3 months

PRO-ACT Pooled Resource Open-Access ALS Clinical Trials database (https://nctu.partners.org/ProACT/), *mo* months, *yrs* years, *SD* standard deviation, *ALSFRS(-R)* Amyotrophic Lateral Sclerosis(-Revised), *BMI* Body Mass Index, *FVC* % percentage forced vital capacity of predicted normal values, *VC* vital capacity, *UMN* upper motor neuron, *Mg* magnesium, *Vit* vitamin, *FTD* frontotemporal dementia, *EDX* electrodiagnostic

Table 2 Prognostic factors related to outcome measures

Prognostic factor	No. of studies (participants)	Significant association reported number of studies (participants)	Statistical analysis	Strength of association	Quality score (based on GRADE if applicable)	Level of evidence Considered judgment
Outcome: Decline in ALSFRS total score or ALSFRS-R total score						
Socio-demographic characteristics						
Age at onset	4 [21], [25], [28], [30] (n = 2,764)	1 [25] (n = 1,844)	[21] Multiple linear regression [25], [28], [30] Mixed effects model	[25] ALSFRS-R = −0.046 (SE = 0.013) points for every age year $p < 0.001$ [21], [28], [30] Not significant	'Low' evidence	There is 'low' evidence that older age at onset is associated with a steeper functional decline
Age at diagnosis	2[22], [30] (n = 609)	1 [22] (n = 514)	[22] Multiple linear analysis (only results from univariate analysis reported) [30] Mixed effects model	[22] Mean ratio[a] = 1.01 (95 % CI = 1.00, 1.02); For every age year the difference in ALSFRS-R decline is 1 % $p = 0.015$ [30] Not significant	'Very low' evidence	There is 'very low' evidence that older age at diagnosis is associated with a worse functional decline
Gender	6 [20], [21], [22], [25], [28], [30] (n = 3,660)	0	[20], [25], [28], [30] Mixed effects model [21] Multiple linear regression [22] Multiple linear analysis (only results from univariate analysis reported)	[20], [21], [22], [25], [28], [30] Not significant	'High' evidence	There is 'high' evidence that gender is not associated with a steeper functional decline
Weight	2 [25], [30] (n = 2,547)	0	[25], [30] Mixed effects model	[25], [30] Not significant	'Moderate' evidence	There is 'moderate' evidence that weight is not associated with functional decline
Height	2 [25], [30] (n = 2,547)	0	[25], [30] Mixed effects model	[25], [30] Not significant	'Moderate' evidence	There is 'moderate' evidence that height is not associated with functional decline
Years of education	2 [28], [30] (n = 126)	0	[28], [30] Mixed effects model	[28], [30] Not significant	'Low' evidence	There is 'low' evidence that years of education is not associated with functional decline

Table 2 continued

Prognostic factor	No. of studies (participants)	Significant association reported number of studies (participants)	Statistical analysis	Strength of association	Quality score (based on GRADE if applicable)	Level of evidence Considered judgment
Clinical characteristics: disease-related and functional factors						
Site of onset	5 [20], [21], [22], [25], [30] (n = 3,629)	3 [22], [25], [30] (n = 3,061)	[20], [25], [30] Mixed effects model [21] Multiple linear regression [22] Multiple linear analysis (only results from univariate analysis reported)	[22] Mean ratio[a] = 1.34 (95 % CI = 1.07, 1.68); Bulbar onset results in a difference in ALSFRS-R decline of 34 % compared to spinal onset $p = 0.012$ [25] Steeper change in ALSFRS-R leg onset versus arm onset Data not reported $p = 0.02$ [25] Steeper change in ALSFRS-R proximal limb onset versus distal limb onset Data not reported $p = 0.004$ [30] The mean change in ALSFRS = −0.02 (SE = ± 0.01) points/month of patients with bulbar onset versus limb onset $p = 0.02$ [20], [21] Bulbar versus limb onset (ALSFRS and ALSFRS-R); not significant	'Low' evidence	There is 'low' evidence that bulbar onset of disease is associated with a worse functional decline compared to limb onset There is 'very low' evidence that: - Leg onset is associated with a steeper decline in functional status compared to arm onset - Proximal limb onset is associated with a steeper decline in functional status compared to distal limb onset
Time from symptom onset to diagnosis	3 [22], [29], [30] (n = 3,111)	3 [22], [29], [30] (n = 656)	[22] Multiple linear analysis (only results from univariate analysis reported) [29] Mann–Whitney U-test [30] Mixed effects model	[22] Mean ratio[a] = 0.99 (95 % CI = 0.98, 0.99); For every month between symptom onset to diagnosis the ALSFRS-R decline decreases with 1 % $p < 0.001$ [29] A shorter interval between symptom onset and diagnosis is associated with a lower ALSFRS score at 6 months follow-up $p = 0.02$ [30] For every year that elapses between symptom onset and diagnosis, the slope of the ALSFRS score declines by 0.12 points (SE = 0.036) per month $p = 0.001$	'Low' evidence	There is 'low' evidence that a longer time between symptom onset and diagnosis is associated with a milder functional decline

Table 2 continued

Prognostic factor	No. of studies (participants)	Significant association reported number of studies (participants)	Statistical analysis	Strength of association	Quality score (based on GRADE if applicable)	Level of evidence Considered judgment
Initial rate of disease progression	2 [19], [31] ($n = 395$)	2 [19], [31] ($n = 395$)	[19] Stepwise logistic regression [31] Mann–Whitney *U*-test	[19] %change ALSFRS-R score at week 2 was an independent prognostic factor of slow disease progression at 6 months [odds ratio = 0.0156 (95 % CI = 0.0057, 0.0424), $p < 0.0001$] and 12 months [odds ratio = 0.1637 (95 % CI = 0.0945, 0.2833), $p < 0.0001$] [19] %change ALSFRS-R score at week 4 was an independent prognostic factor of slow disease progression at 6 months [odds ratio = 0.0797 (95 % CI = 0.0451, 0.1406), $p < 0.0001$] and 12 months [odds ratio = 0.3073 (95 % CI = 0.2290, 0.4123), $p < 0.0001$] [31] A cutoff point of 8.78 % reduction in ALSFRS score in 3 months (the 80th percentile and 2 SD's above the mean) identifies patients with a rapid disease progression. $p < 0.01$	'Very low' evidence	There is 'very low' evidence that a higher percentage change in ALSFRS(-R) score at diagnosis is associated with a faster functional decline
Comorbidities	2[22], [30] ($n = 609$)	1 [22] ($n = 514$)	[22] Multivariate analysis (adjusted for age at diagnosis, region of onset, time from first symptom to diagnosis) [30] Mixed effects model	[22] Parkinson's disease; mean ratio[a] = 0.46 (95 % CI = 0.22, 0.98). Patients with symptoms of Parkinson's disease have a milder ALSFRS-R decline of 46 % $p = 0.04$ [12] not significant	'Very low' evidence	There is 'very low' evidence that 'comorbidity Parkinson's disease ALS' is associated with a slower functional decline compared to ALS with no comorbidity
Respiratory status; FVC	3 [23], [28], [30] ($n = 276$)	1 [23] ($n = 150$)	[23] Univariate regression [28], [30] Mixed effects model	[23] FVC was significantly associated with the ALSFRS-R decline (data not reported) $p = 0.01$ [28], [30] Not significant	'Very low' evidence	There is 'very low' evidence that a lower FVC is associated with a worse functional decline

Table 2 continued

Prognostic factor	No. of studies (participants)	Significant association reported number of studies (participants)	Statistical analysis	Strength of association	Quality score (based on GRADE if applicable)	Level of evidence Considered judgment
Nutritional status; BMI	2 [23], [24] ($n = 401$)	1 [23] ($n = 150$)	[23] Multivariate regression model (adjusted for age at inclusion and FVC) [24] Mixed effects model	[23] BMI was significantly associated with ALSFRS-R reduction over time, with a minimal ALSFRS-R score decline at BMI of 30 (data not reported) $p < 0.01$ BMI < 30; $\beta = -0.48$ (SE = 0.22) points ALSFRS-R $p = 0.03$ BMI ≥30 Not significant [24] Not significant	'Very low' evidence	There is 'very low' evidence that a BMI of 30 is associated with a minimal functional decline compared to BMI of <30 or >30, and that a higher BMI score on BMI of <30 is associated with a slower functional decline compared to a lower score
Baseline ALSFRS-R score	4 [19], [21], [25], [30] ($n = 3,071$)	2 [19], [25] ($n = 2,176$)	[19] Stepwise logistic regression [21] Multiple linear regression [25], [30] Mixed effects model	[19] Baseline ALSFRS-R score was an independent prognostic factor of slow disease progression at 6 months; odds ratio = 1.116 (95 % CI = 1.032, 1.207) $p = 0.0047$ [25] β baseline ALSFRS-R = 0.0660 (SE = 0.024) points $p < 0.001$ [21], [30] Not significant	'Low' evidence	There is 'low' evidence that a higher baseline ALSFRS-R total score is associated with a slower functional decline
Frontotemporal syndrome[b]/ extent of FTD and cognitive performance	2 [21], [28] ($n = 217$)	1 [21] ($n = 186$)	[21] Kruskal–Wallis test ($n = 98$) [21] Multiple linear regression ($n = 186$) [28] Mixed effects model	[21] Median ALSFRS-R decline at 12 months is higher in patients with a frontotemporal syndrome. Executive dysfunction, −0.76; no cognitive abnormality 0.42; nonexecutive cognitive impairment, −0.66 points/month $p = 0.025$ [21], [28] Not significant	'Very low' evidence	There is 'very low' evidence that the presence of a frontotemporal syndrome at baseline is associated with a worse functional decline

No. number, *GRADE* Grading of Recommendations Assessment, Development and Evaluation, *ALSFRS (-R)* amyotrophic lateral sclerosis functional rating scale (-Revised), *CI* confidence interval, % percentage, *SE* standard error, *β* beta; regression coefficient, *FVC* forced vital capacity, *BMI* Body Mass Index, *FTD* frontotemporal dementia

[a] Mean ratio; difference in ALSFRS-R score ratio. ALSFRS-R ratio = the deterioration of the score per month

[b] Frontotemporal syndrome = comorbid FTD or executive dysfunction in a patient without dementia

risk of bias. Some of the studies reviewed only presented results from univariate analysis on the prognostic factor(-s) studied, thus causing the data quality assessment to be downgraded [22, 26, 29, 31]. One study could be classified as 'low' risk of bias on all quality domains [23].

Synthesis of evidence

The GRADE qualitative synthesis of evidence for factors analyzed in two or more studies, resulted in a rating of 'low' quality of evidence for site of onset, age at onset, time from symptom onset to diagnosis, and ALSFRS-R score at diagnosis as independent prognostic factor for decline in ALSFRS(-R) total score (Table 3). Based on the GRADE approach, we concluded 'high' evidence for gender, 'moderate' evidence for weight and height, and 'low' evidence for years of education as factors that are not associated with a decline in ALSFRS(-R), and 'very low' evidence for age at diagnosis, initial rate of disease progression, forced vital capacity (FVC), body mass index (BMI), frontotemporal dementia (FTD), and comorbidities as prognostic factor for decline in ALSFRS(-R) total score. Age at onset and age at diagnosis could be considered as interrelated factors, representing the same prognostic variable. However, as the duration of the trajectory of diagnosis might differ within cohorts of patients or between health care systems, we present the prognostic value for each factor separately. We did not conduct sensitivity analyses because of the small number of studies for each prognostic factor.

The evidence according to the GRADE approach for the prognostic value of time from symptom onset to diagnosis, site of onset, ALSFRS-R score at diagnosis, and age at onset is summarized below.

Time from symptom onset to diagnosis

The 'low' quality of evidence according to the GRADE approach for the prognostic value of time from symptom onset to diagnosis was based on three studies. The independent association between longer time from symptom onset to diagnosis and a slower functional decline turned out to be significant in one study [30]. Another study presented a significant association in a univariate analysis [22]. The third study did not present the strength of the association and uncertainty estimation [29]. Imprecision and moderate to 'high' risk of bias within studies forced the quality of evidence to be downgraded to 'low'.

Site of onset

Five studies investigated the prognostic value of site of onset for decline in ALSFRS(-R) total score. Prognostic value of bulbar onset versus limb onset was reported in four studies. Inconsistency due to non-significance in two of these four studies and imprecision of results, resulted in 'low' quality of evidence for greater decline in ALSFRS(-R) total score in bulbar onset ALS.

Baseline ALSFRS-R score

Within the four studies presenting baseline ALSFRS-R score as prognostic factor, we summarized the overall quality of evidence according to the GRADE approach as 'low' mainly due to inconsistent and imprecise findings. Two studies with 'low' risk of bias, showed inconsistent results. One study demonstrated a significant association between a higher baseline ALSFRS-R total score and a slower functional decline [25]. The multiple linear regression model in the other study, using the total ALSFRS-R slope as dependent variable, showed no statistically significant association [21]. We judged the other two studies to be 'moderate' quality or 'low' quality [19, 30].

Age at onset

Four studies investigated the prognostic value of age at onset for a decline in ALSFRS(-R) total score. Only one study presented a significant, independent association between older age at onset and greater decline in ALSFRS-R total score [25]. Inconsistency and imprecision in results, taking into account the small number of studies, resulted in an overall 'low' quality of evidence according to the GRADE approach.

Discussion

Our systematic review summarizes the evidence on prognostic factors for the rate of decline in functional status of (recently) diagnosed patients with ALS. The qualitative synthesis according to the GRADE approach resulted in 'low' evidence for age at onset, site of onset, time from symptom onset to diagnosis, and baseline ALSFRS(-R) score. We graded the evidence for age at diagnosis, initial rate of disease progression, FVC, FTD, BMI, and comorbidity as 'very low', mainly due to the heterogeneity, the limited number, and methodological quality of the selected studies.

In contrast to the limited number of studies reporting prognostic factors predictive for the patients' functioning, a larger number of publications on prognostic factors for survival of patients with ALS are available. In their critical review, Chiò et al. [32] summarized the evidence on prognostic factors related to survival. Although several ALS outcome studies are based on register methodology (longitudinal cohorts, prospective population-based

Table 3 Adapted GRADE table for narrative systematic reviews of prognostic studies

Potential prognostic factors identified	Partici-pants (*n*)	Number of studies	Uni-variate + 0 −	Multivariate + 0 −	Phase	Grade factors						
						Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/ large effect size	Overall quality of evidence
Age at onset	2,156	4 [21, 25, 28, 30]		…3…1	1 [21] 2 [26, 29, 31]	X	X	✔	X	✔	X	'Low'
Age at diagnosis	609	2 [22, 30]	1	…1	1 [22] 2 [30]	X	X	✔	X	X	X	'Very low'
Time from symptom onset to diagnosis	656	3 [22, 29, 30]	……2	……1	1 [23, 30] 2[30]	X	✔	✔	X	✔	✔	'Low'
Site of onset	3,021	5 [21–23, 26, 31]	…1	…2…2	1 [21–23] 2 [25, 30]	X	X	✔	X	✔	X	'Low'
Baseline ALSFRS(-R) score	2,457	4 [19, 21, 25, 30]		1…2…1	1 [21] 2 [25, 30] 3 [19]	X	X	✔	X	✔	X	'Low'
Initial rate of disease progression	389	2 [19, 31]	…1	…1	1 [31] 3 [19]	X	✔	X	X	X	X	'Very low'
FTD	217	2 [21, 28]	……1	…1	1 [21] 2 [28]	X	X	✔	X	X	X	'Very low'
FVC	276	3 [24, 29, 31]	1	…2	2 [24, 29, 31]	X	X	✔	X	X	X	'Very low'
Comorbidities	609	2 [22, 30]		…1…1	1 [22] 2 [30]	X	X	✔	X	X	X	'Very low'
BMI	401	2 [23, 24]		…1…1	2 [24, 25]	X	X	✔	X	X	X	'Very low'

Phase, phase of investigation: phase 1 explanatory study, identifying associations; phase 2 explanatory study, testing independent associations; phase 3 explanatory study, understanding prognostic pathways

For uni- and multivariate analyses: +, number of significant effects with a positive value; 0, number of non-significant effects; −, number of significant effects with a negative value

For GRADE factors: ✔, no serious limitations; X, serious limitations (or not present for moderate/large effect size); unclear, unable to rate item based on available information

For overall quality of evidence: 'Very low', 'Low', 'Moderate', 'High'

GRADE Grading of Recommendations Assessment, Development and Evaluation, *ALSFRS (-R)* Amyotrophic Lateral Sclerosis Functional Rating Scale (-Revised), *FTD* frontotemporal syndrome, *FVC* forced vital capacity, *BMI* Body Mass Index, *Univariate* univariate analyses, *Multivariate* multivariate analyses

registers), the appraisal of the methodological quality of these studies was not conducted. In view of the strong correlation between rate of progression of ALSFRS-R and survival, certain prognostic factors for survival also have prognostic value for functional decline: age at onset, site of onset, diagnostic delay, FVC, BMI, and baseline ALSFRS(-R) [32]. This finding strengthens the relevance of the prognostic factors we found, contrary to our overall quality of evidence judgment of these factors based on the GRADE approach. Nevertheless, it seems reasonable to assume that other prognostic factors for survival will also be associated with functional decline, but these (e.g., El Escorial diagnostic categories, nutritional status, and cognitive functions) have either not yet been studied, or we found no evidence in the identified studies about their prognostic value for the functional course.

We selected the ALSFRS(-R) representing functional status in ALS as the most widely used outcome marker of disease progression in clinical practice and research. Recently, Franchignoni et al. (2013) [33] questioned the metric quality of the subjective ALSFRS-R and demonstrated that the scale as a single (total) score lacks unidimensionality. Treating an ordinal summed rating scale as an interval measure, assuming equal intervals, and subjecting such scale to parametric statistics (as regression analyses) will likely lead to invalid results [23]. This may well be one of the reasons for the low level of evidence we found for the prognostic factors, even for those that are often used by professionals in individual prognostication. Furthermore, most statistical models used in prognostic studies assume a linear decline in functioning during the entire disease trajectory; this assumption is not met for the total raw score of the ALSFRS(-R) in ALS [19, 25]. In contrast to the heterogeneity of the ALSFRS(-R) total score, the domains of the ALSFRS(-R) (bulbar, motor, and respiratory functions) appear unidimensional, and adequately represent the respective constructs [34]. It is surprising that only one study was identified that investigated prognostic factors for ALSFRS-R domains, and even this was limited to one domain (bulbar). It may well be that stronger associations can be found between potential prognostic factors and decline in bulbar, motor, or respiratory functions.

Most likely, ALS disease heterogeneity complicates the development of prognostic models. More knowledge about the genetic and molecular pathophysiological mechanisms is required to allow development of more accurate prediction models [35]. In this context, the identification of genetic subtypes in ALS might be of vital importance. The phenotypic heterogeneity in ALS is evident in view of the clinical manifestation of the region of symptom onset and disease course in ALS [22, 37–39]. Although studies showed differing average rates of disease progression across ALS phenotypes, there was also a clear variation within these phenotypes [39, 40]. Within each subgroup, patients might have a relatively slow or fast disease course. Consequently, prediction of functional deterioration on the basis of the specific phenotype encompasses major uncertainty. Furthermore, there are no clear boundaries between phenotypes [41]. Future analysis of large numbers of patients within phenotypes might elucidate the within-phenotype variation and could identify phenotypes with consistent prognostic patterns [2].

Previous studies made use of prognostic categories for survival in ALS by applying prognostic models or staging systems [5, 42]. As far as we know, there are no studies about the validity and applicability of comparable models and systems for functional status. Further research is warranted to assess the validity of such models and systems and their clinical applicability in individual patient management [43].

This review has strengths and limitations. The robust search in five relevant databases, the use of the QUIPS tool for the appraisal of study quality and the GRADE framework for the quality of prognostic evidence are strengths of our study. It is possible that we have missed studies that are not indexed for these databases, but by checking references of included studies, we presume that no relevant articles were missed. Earlier studies reported negative consequences due to our selection criteria ‘published in English’. We conclude, based on the available English abstracts of the non-included, non-English articles, that it is unlikely that our results are biased because of language restrictions [44, 45].

As we selected studies with the ALSFRS (-R) as outcome measure for functional status, we may have missed prognostic studies with different outcome measures. One study suggested that the examination-based AALSS (Appel ALS Score) provides a better estimate of disease severity in ALS compared to the questionnaire-based ALSFRS [46]. Based on normalized scores of both scales, the ALSFRS underestimated disease severity defined by the AALSS; this increased with disease progression. Both scales, however, showed a significant change with disease progression. We do not expect that including other outcome measures for functional status in the present review would lead to higher levels of evidence for prognostic factors as the ALSFRS(-R) is the most frequently used clinical measure for disability progression in ALS.

The ability to predict the decline in functional status of the individual patient with ALS remains uncertain. This review has highlighted a gap in the current literature about prognostic value of clinical variables for functional decline. Comprehensive data collection—national and international standardized measurements of patient, disease, and intervention variables recorded in daily clinical

practice and entered into large electronic databases—might enhance the possibility of identifying prognostic factors. Furthermore, it is likely that the genetic variation in ALS will be unraveled and genetic subtypes with less clinical heterogeneity will be identified in the years to come. This might enable the development of prediction tools stratified by ALS subtypes with better prognostic performance in individual patients.

Our results endorse the need for well-conducted prospective cohort studies on prognostic factors for the course of the functional status of patients with ALS. These studies should not only focus on socio-demographic and clinical prognostic factors, but also investigate the prognostic importance of psychosocial factors, cognition and comorbidity. Future prognostic studies preferably use an optimal design including selection of inception cohort, multivariate statistical models, registering reliable information about the (multidisciplinary) treatment given and all potential prognostic variables [47].

In conclusion, the current strength of evidence on prognostic factors for functional decline in ALS is insufficient to allow the development of a clinical prediction tool that can support the professionals' judgement of the functional course. Methods for standardized assessment and registration of patients' socio-demographic, clinical and psychosocial characteristics, symptom treatment, and outcome measures preferably may be agreed internationally; data sharing may enable more reliable evidence synthesis of prognostic factors for functional decline in ALS. With the future prospect of improved understanding of ALS genetics, more accurate prognostication may be achieved through the development of prediction tools stratified by genetically defined subtypes of ALS.

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