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Prognostic factors in ALS: A critical review

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Abstract

We have performed a systematic review to summarize current knowledge concerning factors related to survival in ALS and to evaluate the implications of these data for clinical trials design. The median survival time from onset to death ranges from 20 to 48 months, but 10–20% of ALS patients have a survival longer than 10 years. Older age and bulbar onset are consistently reported to have a worse outcome. There are conflicting data on gender, diagnostic delay and El Escorial criteria. The rate of symptom progression was revealed to be an independent prognostic factor. Psychosocial factors, FTD, nutritional status, and respiratory function are also related to ALS outcome. The effect of enteral nutrition on survival is still unclear, while NIPPV has been found to improve survival. There are no well established biological markers of progression, although some are likely to emerge in the near future. These findings have relevant implications for the design of future trials. Randomization, besides the type of onset, should take into account age, respiratory status at entry, and a measure of disease progression pre-entry. Alternative trial designs can include the use of natural history controls, the so-called minimization method for treatment allocation, and the futility approach.

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by a progressive degeneration of upper and lower motor neurons leading to limb paralysis, dysphagia, dysarthria, and respiratory failure. The cause of the disease is unknown and there is no effective cure. Although it is generally reported that the mean survival of patients from symptom onset is 3–5 years (1), ALS has a considerable variability in outcome and its prognostic factors are not satisfactorily defined. A better understanding of factors influencing ALS outcome would guide physicians and patients in scheduling therapeutic interventions (2) and is particularly relevant to clinical trials design (3).

The design of clinical trials to test compounds for therapeutic benefit in ALS relies on accurate information on disease outcome and prognostic factors (4). A priori knowledge of pattern of survival would allow effective stratification, decrease the number of patients that

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need to be enrolled to achieve adequate study power, and, consequently, decrease the cost of ALS trials. Unequal distribution of patients with different outcomes between the treatment groups has complicated the interpretation of the results of at least three trials (branch chain amino acids, IGF-1) (5-7). These failures indicate that the current method of case stratification (i.e. bulbar onset versus spinal onset) may be inadequate. Another more subtle bias in clinical trials is the inclusion of long-surviving (i.e. prevalent) patients.

The purpose of this review is to summarize current knowledge concerning factors related to survival in ALS, to evaluate the strength of evidence supporting each factor, and to assess the implications of these data for clinical trial design.

Methodological considerations

Search strategy and selection criteria

Papers published between 1960 and August 2008 were identified by PubMed literature searches using the terms “amyotrophic lateral sclerosis”, “motor neuron disease”, “progressive muscular atrophy”, “progressive bulbar palsy”, “survival”, “outcome”, “prognosis”, and “prognostic factor”, Additional publications were identified using the world wide web, from the references of these papers and from the authors’ own files. Only articles in English were considered.

Classification of outcome studies

Outcome studies can be classified into three broad categories: 1) studies based on series from ALS referral (tertiary) centres; 2) studies based on the placebo arm of pharmacological trials; and 3) studies based on epidemiological series. Moreover, each study can be defined as prospective or retrospective, according to the type of observation over time.

(1) Studies based on referral centres series (Table I) are typically based on large cohorts of patients, collect high quality data on clinical factors, and have a high level of diagnostic accuracy. However, referral centre studies are prone to patient selection bias due to the retrospective nature of these studies, referral bias that is inherent to a tertiary referral centre, and a relatively high loss to follow-up (8-15).

(2) Studies based on the placebo arm of pharmacological trials (5,16) (Table I) are generally prospective, well conducted, and have a good standardization of examined prognostic factors, a high level of diagnostic accuracy and include a relatively homogeneous population. However, this population is likely to have unique characteristics, representing a highly selected group of ALS patients, generally younger and more motivated than the general ALS population (1,17), fulfilling the criteria for ‘probable’ and ‘definite’ ALS by the El Escorial criteria (18) and with minimal respiratory involvement. Trial protocols typically exclude patients with conditions such as renal or liver failure and a variety of other chronic conditions, as well as fast progressors, thus further limiting the usefulness of these data for prognostic purposes in the clinical setting.

(3) Prognostic surveys performed on population-based series rely on unselected populations, and therefore are likely to provide a better assessment of prognostic factors. However, the majority of epidemiologically-based studies are retrospective and small in size (19-22) (Table II). Retrospective design has several pitfalls: 1) it does not allow certain prognostic factors, such as symptoms progression rate to be assessed; 2) it is less accurate with regard to certainty of disease diagnosis, since it is usually based on the retrospective revision of clinical data; and 3) there is a risk of missing specific subsets of patients not captured by the study design.

Recently, outcome studies based on prospective population-based registers using multiple sources of information to ensure complete case ascertainment within a defined geographical area have been published (23-27) (Table III). These studies represent an advancement of the classical epidemiological studies and are considered the best available methodological design for the study of rare disorders. They have the advantage of allowing the application of uniform and definite diagnostic criteria and permit the assessment of prognostic factors in a standardized manner. Most importantly, the completeness of case ascertainment permits the analysis of the full clinical spectrum of the ALS population, in particular the old or very old cases, as demonstrated by the older mean age of onset observed in the registry cohorts compared to that of both retrospective epidemiological series and referral series. The drawbacks of epidemiological registries are the costs of a prospective follow-up and the complexity in organization and coordination.

Overall survival

The median survival from onset to death in ALS is reported to vary from 20 to 48 months with ALS referral centres reporting longer survival times (8,9,11,13,28,29). This wide range narrows when considering population-based studies, which are more likely to reflect the experience of the general ALS population (20–36 months) (22-27). All studies report that 5 to 10% of ALS patients survive for more than 10 years.

Specific prognostic factors

Demographic factors

Age: The vast majority of studies has found that age is a strong prognostic factor in ALS, with decreasing survival time correlating with increasing age of symptom onset (9,11,12,14,20,25-27,31,32). Patients with symptom onset before 40 years of age have longer survival, often exceeding 10 years (14,26). It is noteworthy that over 80% of patients less than 40 years of age are men (26). Conversely, median survival among patients presenting after 80 years of age is less than two years (31) and males and females are equally represented in this age group.

Gender: Most studies have found that gender has no effect on ALS outcome, despite the higher frequency of bulbar onset disease among older women. Notable exceptions are the two register-based studies from Washington State, U.S.A. and Scotland (23,26) and the two small retrospective studies (33,34) that found a significantly shorter survival among women both in univariate and in multivariate analyses.

Clinical factors

Site of onset: Bulbar onset disease is associated with a worse prognosis than spinal onset (12,14,26,32,35). This finding is not completely explained by the increased frequency of bulbar disease in old age (17,24,25,31,35). In a registry-based study, the presence of bulbar symptoms at the time of diagnosis was an independent prognostic factor (25) indicating that bulbar function at any stage of the illness plays a major role in determining outcome.

Not surprisingly, respiratory onset disease is a strikingly negative prognostic factor (36,37). However, a recent paper indicated that ALS patients with respiratory onset who underwent non-invasive ventilation had a significant improvement of survival compared to those who did not use non-invasive ventilation (38).

Data on differences in prognosis between patients with upper and those with lower limb onset are conflicting. Some studies showed a poorer prognosis with lower limb onset (11,25,32), perhaps due to an increased risk of thromboembolic disease and infections

arising from loss of motility. One study found a poorer outcome in patients with upper limb onset (39).

Patients with incomplete forms of motor neuron disease, such as those with pure lower motor neuron disease (sometimes referred as progressive muscular atrophy, PMA), have a better prognosis than those with 'classic' ALS (27,32).

Diagnostic delay: Several studies, but not all, have found that a longer delay from symptom onset to diagnosis carries a better prognosis (10,12,14,15,26,27,29,35,40-42). Interestingly, in a study comparing a population-based incidence cohort to a referral cohort, the duration of symptoms from onset to diagnosis was significantly related to survival only in the latter cohort (17). In general, the finding of a worse prognosis in patients with a short time delay between onset and diagnosis is likely to indicate a more aggressive disease, which leads the patient to seek medical attention more rapidly and is more readily diagnosed (26).

Family history of ALS: Most studies have not found any differences in outcome between patients with sporadic and those with familial ALS (12,25,43). However, it is now generally accepted that different mutations of Cu/Zn superoxide dismutase (SOD1) have different effects on the age of onset of symptoms (43,44) and on the rate of progression of the disease. For example, A4V mutation is associated with an extremely rapid decline, with a mean survival of 12 months, whereas E21G, G37R, D90A G93C, and I113T mutations determine a more benign course, with a median survival – 80 months) (43,45). In most instances, clinically mild mutations are characterized by a prevalent lower motor neuron disease, with few or no pyramidal signs. Furthermore, some mutations, such as I113T, are characterized by large intra-familial variations both in age of onset and in clinical phenotype (46), indicating the presence of modifying factors that may either be genetic or environmental in nature. A systematic analysis of the different phenotypes of SOD1 mutations is still lacking.

Rate of disease progression: It has long been believed that the loss of motor neurons in ALS is linear, but it is unclear if clinical decline is also linear. The rate of symptom progression has been analysed in relatively few studies. A study analysing a series of 62 patients enrolled in two clinical trials found that linear estimates of rates of disease progression based on isometric myometry and FVC measures were better predictors of patient survival than demographic data (28). These findings were replicated in two additional independent series (47). Similarly, in a prospective study based on a referral centre, ALS outcome was significantly related to the decline of various measures of disease progression (MRC compound score, FVC% and ALSFRS) during the first year of follow-up (39). In a prospective register-based study, the rates of progression of respiratory, lower limb and bulbar impairment during the first six months after diagnosis (measured with FVC, MRC scale and bulbar scale, respectively) were independent prognostic factors in the Cox multivariable model (25). Similar data were found from the analysis of two different series of patients enrolled in the placebo arm of two clinical trials (16,48). In a recent paper on a small series, the progression rate of ALSFRS-R score evaluated at presentation was significantly related to ALS prognosis (49). Lastly, in a paper on a referral ALS series, the rate of progression of ALS-FRS-R, both during the whole disease and the first 100 days after diagnosis, revealed to be strongly related to survival (50).

Also, neurophysiological data support this concept: a study on the decline of motor unit number using MUNE indicated that this parameter is related to prognosis (51). More indirect evidence comes from the parallel decline between ALS-FRS and neurophysiological measurements (52).

These observations, taken together, indicate that each individual ALS patient has an intrinsic 'disease progression rate', and that this rate is maintained during the course of the disease, indirectly confirming the hypothesis of a linear decline of clinical status in ALS. More important, these findings suggest that it could be possible to utilize symptom progression rate as a measure of efficacy in clinical trials of new drugs.

Psychosocial factors—Although often overlooked by clinicians, psychosocial factors seem to play an important role in ALS outcome. A longitudinal study has found that patients with psychological distress (measured with a battery of psychological assessment scales evaluating perceived stress, depression, hopelessness, anger expression, and purpose in life) had a 2.24-fold (95% CI 1.08–4.64) increased risk of dying than patients with psychological well-being (53). A longitudinal assessment of mood and self-esteem on survival showed that lower mood predicted a faster progression and a shorter survival (54). However, it is also possible that this effect is related to the fact that low mood is the consequence of having a more rapidly progressive disease. In an analysis of the effect of quality of life (QoL) on outcome, the physical health summary measure of the SF-36 was found to be independently related to outcome, whereas only a trend was found for the mental health summary measure (26). In the same paper, marital status was also shown to be relevant in the outcome of ALS; patients who lived alone had a significantly worse prognosis than patients who were married.

Despite this, attention must be drawn to one major caveat. There are increasing clinical, pathological and genetic data suggesting that ALS and FTD syndromes form a spectrum of disease (55). It is well recognized that ALS patients with florid FTD have a shortened survival and so it cannot be discounted that the psychological features identified in the above studies are symptomatic of early or mild clinical cognitive impairment (56). It should be noted that none of the studies on QoL and survival rigorously assessed frontal lobe function.

Cognitive functions: In recent years, it has become increasingly evident that 5–10% of ALS patients develop an overt frontotemporal lobar dementia (FTLD), and probably up to half of all patients have a subtle impairment of temporal and frontal lobe cognitive function (57). Despite this, there have been no population-based, longitudinal studies of cognition in ALS. A recent clinic-based study found that patients with ALS-FTLD have a shorter survival than those with normal executive and behavioural function (median survival, 28 months vs. 39 months) (51). This difference is likely to be due, at least in part, to poor compliance of ALS-FTLD patients for non-invasive positive pressure ventilation (NIPPV) and percutaneous endoscopic gastrostomy (PEG). Conversely, mild cognitive impairment may have little or no effect on ALS outcome (58).

Nutritional status: It is generally recognized that malnourishment is a relevant determinant of outcome in ALS. However, surprisingly few studies, if any, have analysed this factor in ALS series. Body Mass Index (BMI) is a generally accepted marker of nutritional status: in a study on 55 ALS patients prospectively followed up, a BMI value 518.5 has been found to be an independent prognostic factor for death both in univariate and in multivariable analysis (59). Similarly, in a prospective study based on patients allocated to the placebo arm of the CNTF trial, weight loss compared to pre-study weight appeared to be significantly related to a worse prognosis (16).

Respiratory status: Respiratory function is generally considered important in ALS. All studies evaluating respiratory status found that a lower predicted forced vital capacity (FVC %) at diagnosis was the single most relevant prognostic factor in ALS (16,25,38,60,61). Per cent predicted vital capacity (VC%) and the slope of decline of VC% have been

significantly correlated with ALS survival (62). Sniff nasal pressure (SNP) has been found to accurately reflect intra-thoracic pressures and to be more significantly associated with respiratory failure than FVC%, but not in bulbar onset patients (63). Upright and supine forced vital capacity, maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were significantly correlated to tracheostomy-free survival in a series of 95 ALS patients (64).

Functional/disability scores: Several disability scores have been proposed for ALS. The ALS functional rating scale (ALSFRS) is the most widely used functional scale for ALS. A recent single-centre study found that ALSFRS-R, a revised form of the original ALSFRS score, was significantly related to outcome, and that the respiratory sub-score was the single most significant component (41). In a small study, the progression rate of the ALSFRS-R, calculated as differential of score from onset to diagnosis/disease duration (in months), resulted to be significantly related to prognosis (49).

Rarely, other disability scores have been used for assessing ALS progression. In one centre study, the Amyotrophic Lateral Sclerosis score was the only significant prognostic factor besides age (65). Similarly, the Appel ALS Score (AALSS) was a significant predictor of ALS prognosis in a Cox multivariable analysis of a series of 831 patients from a tertiary ALS centre (10). This finding was confirmed by a second study performed in the same ALS centre, which found that both a higher baseline AALSS and a higher slope of AALSS from onset to the basal visit were correlated to a shorter survival (29).

El Escorial criteria: The El Escorial criteria (EEC) (66) and their more recent revised form (EEC-R) (18) were developed to provide a structured tool to define the level of confidence of a diagnosis of ALS in individual patients in order to facilitate international collaboration in clinical trials and studies of ALS. According to the presence of lower and upper motor neuron signs and their distribution in four regions, i.e. bulbar, upper limb, thoracic, lower limb, the EEC-R classify patients to different degrees of diagnostic certainty (definite, probable, probable with laboratory confirmation, possible). Although mainly intended for use in research settings, the EEC have also been studied as potential prognostic markers. Most studies (13,15,25,27,39,41,67) but not all (24), have found that a diagnosis of definite ALS at the time of presentation carries a poorer prognosis compared to all other diagnostic levels. However, further analysis of the Irish data confirms that definite ALS carries a significantly worse prognosis than suspected and possible ALS (unpublished data, Orla Hardiman). Since a diagnosis of definite ALS implies muscle weakness and wasting in at least three regions, this finding is likely to indicate that patients with more widespread clinical involvement at the time of diagnosis have a more rapid progression of the disorder. However, it must be noted that the EEC were not originally designed as tools to determine burden of disease, but rather to reflect certainty of diagnosis, and in this context it is perhaps not surprising that the specificity of the criteria as a prognostic indicator is poor.

Therapeutic factors

Therapeutic interventions: After the licensing of riluzole in 1996, several studies, both population-based and from referral centres, have found a positive, independent, effect of this drug on ALS patients outcome (13,25,68,69). Riluzole may improve mortality rate by 23% and 15% at 6 and 12 months, respectively (68,70).

While the insertion of PEG is now widely used as a measure for avoiding starvation and dehydration and improving QoL (71,72), it is still debated whether enteral nutrition has a positive effect on survival. A population-based study has found that PEG is an independent prognostic factor (25). Conversely, one study from Scotland found that PEG did not confer

any survival advantage compared to no gastrostomy (73), but this study reported a 25% one-month mortality after gastrostomy, a figure substantially higher than that found in clinical series (74). Also, different practices in proposing and executing PEG (i.e. early or late after the onset of swallowing difficulties) could play a role.

Although two controlled studies have demonstrated that NIPPV confers a significant advantage to ALS patients in terms of median survival (increase of 205 days) and quality of life (35,75), surprisingly NIPPV has not been widely studied as a prognostic factor. In a population-based study NIPPV did not modify overall survival, but this finding was explained by the low number of patients who underwent this intervention (25). There are indications that early NIPPV increases survival compared to late NIPPV (76).

Interdisciplinary care: A positive effect of being followed by a neurologist versus a non-neurologist has been reported by two population-based studies (20,31). Recently, two registry studies have shown that patients followed by ALS tertiary centres have a better prognosis than patients seen by traditional neurology clinics (77,78), but this finding has not been confirmed by another registry study (79). The positive effect of ALS centres seems to be independent from all other considered prognostic factors (namely age, site of onset, enteral nutrition and NIPPV), and has been therefore explained as a consequence of comprehensive care of patients. However, these results should be considered cautiously, since they were not controlled and were based on a post hoc analysis.

Biological markers

Biological markers of progression: One of the most difficult tasks in ALS is to identify biological markers of disease progression. Contrasting results have been reported for APOE genotypes, with most studies indicating no effect on survival (38,80,81), and a single study on 403 ALS patients demonstrating that APOE plasma levels over 6.3 mg/dl were correlated with a shorter survival time (Cox model, relative risk 1.083, 95% CI 1.019–1.151) (81) The presence of a homozygous deletion SMN2 gene has been found to be over-represented in a series of 110 ALS patients compared with controls (16% vs. 4%) and to carry a shorter median survival time (2.3 vs. 4.2 years) (82); however, this finding was not confirmed by a study on 106 patients with sporadic ALS and 18 with familial ALS (83). Recently, the muscle expression of NOGO A, a protein inhibiting axonal regeneration, has been found to significantly correlate with the severity of clinical disability of a series of 15 ALS patients (84). A lower serum chloride level at study entry has been related to a worse prognosis in a study based on 245 patients of the placebo group of the observational study on 2069 patients, plasma creatinine levels below the normal range resulted to be a strong independent prognostic factor (15), although no convincing explanations for this finding have been proposed. A recent study on 369 ALS patients from a single referral centre found a significant increase of survival among patients with an elevated LDL/HDL ratio (85). Although intriguing, this factor needs confirmation in different populations. A study of magnetic resonance spectroscopic imaging (MRSI) of brain in a small prospective series of patients with ALS showed that patients with a Nacetylaspartate (NAA)/choline (Cho) ratio in the motor cortex lower than 2.11 had a reduced survival of 19.4 months compared with 31.9 of patients with a ratio over 2.11 (86). According to the authors, this observation is suggestive of cerebral degeneration and could represent a sensitive and specific marker both of ALS diagnosis and ALS survival.

Summary of observations: The discrepancies about ALS survival found in the published literature are mostly related to differences in study design. However, when considering only studies based on register methodology (more likely to report the full spectrum of the ALS population), the range of median survival is quite narrow (around 30 months from first

symptom). Interestingly, these studies are also characterized by an older age of onset (62–67 years) than those based on other designs. However, in 10–20% of cases survival exceeds five years and, in 5–10%, 10 years.

Despite the evidence of several publications, it is still impossible to predict with a good approximation the prognosis for an individual patient at the time of his/her diagnosis. However, several prognostic factors are well established.

There is a general consensus that older age and bulbar onset are negatively related to ALS outcome, but the complex relationship between age, female gender and bulbar onset remains to be clarified. Also, the time delay from onset to diagnosis and the El Escorial diagnosis of definite ALS at the time of presentation, seem to have prognostic relevance, since they probably reflect a more rapid progression of the disorder.

Several measures of disease progression have been found to be related to ALS outcome; all these measures have demonstrated linear progression, confirming the hypothesis that the loss of function in ALS has a linear course, paralleling the rate of loss of motor neurons. It remains to be established which is the best measure for estimating the loss of function in ALS, but some studies reported that ALSFRS (or its more recent revision, ALSFRS-R) could be a reliable, easy-to-use and reproducible measure to be included in trials. Several trials are actually using these measures.

Although relatively few studies have been performed on psychosocial factors, these factors seem to have a profound effect on ALS outcome, both influencing the patients' choices on the use of life-supporting interventions, such as PEG and NIPPV (2), and acting on their health behaviour, on the behaviours of family and professional carers and on psychological mechanisms relevant to disease progression (54). Also, the impairment of cognitive functions could have some impact on ALS outcome, but this issue deserves further study with standardized batteries of tests and a clearer definition of the level of cognitive impairment to be included as a cut-point.

Advances in the care of people with ALS, including enteral nutrition and NIPPV, have to some extent modified the course of the disease to the point that it is now no more possible to talk of 'ALS natural history'. These interventions should be considered when planning future pharmacological trials. Even if only few studies have analysed it, multidisciplinary care seems to have a positive and cost-effective effect on ALS outcome, and, most important, this effect seems to be independent of other known prognostic factors. However, the nature of this additional value of multidisciplinary centres remains unclear, and should be further studied.

Today, despite some attractive preliminary findings, we still lack biological markers of ALS progression that can be applied to routine clinical practice and clinical trials. It is likely, however, that future search in this area will give us relevant new prognostic tools.

Implication for clinical trials: Use of El Escorial classification for the enrolment of patients for clinical trials.

In all recent trials, only patients with clinically definite, clinically probable or clinically probable-laboratory supported ALS were eligible for enrolment. However, it has been found that 20–44% of ALS patients are trial ineligible (i.e. they have a clinically possible or suspected ALS) at the time of diagnosis, and 5–10% of patients are still trial ineligible at death (24,87). Moreover, the median time from symptom onset to trial eligibility has been estimated to be 12.9 months (24). This observation questions the use of El Escorial

classification as criteria for trial eligibility, and indicates the need to revise some aspects of this classification.

Patient stratification for placebo-controlled trials: The traditional stratification for clinical trials of ALS patients in bulbar and spinal onset is no longer sufficient and adequate. The factors to be included in stratification should also include age, respiratory status at entry, and a measure of disease progression pre-entry, such as the decline of ALSFRS-R score in a 3–6 month run-in period before recruitment. Moreover, recognizing the effect of PEG and NIPPV on ALS outcome, trial protocols should include guidelines for major interventions and 'best clinical practice' for ALS patients. It is clear that such requirements for the implementation of a clinical trial in ALS can be obtained only in medium-to-large size phase III studies. Another proposed approach is the use of a lead-in period in order to select a more homogeneous group of patients with a rapidly progressive disorder (88). Alternative methods for designing smaller phase II clinical trials should therefore be considered.

Alternative trial designs: Since the use of placebo in such a severe disorder as ALS may be considered unethical, natural history controls have been advocated as an effective means to eliminate placebo in clinical trials in ALS (10,15,48,89). This approach may also reduce the number of patients that need to be recruited. The use of historical controls is quite frequent in oncology, where knowledge of prognostic factors derived from well-designed natural history studies allows accurate matching of cases and historical controls. However, regulatory agencies currently do not accept non-controlled trials for the purpose of registration of new drugs. Thus, clinical trials utilizing natural history controls are appropriate only for phase I and II clinical trials.

An alternative approach to classical randomization, widely accepted in oncology for the implementation of small trials, is minimization, a method ensuring excellent balance between groups for a range of prognostic factors (90). With minimization, the treatment allocated to the next participant enrolled in the trial depends on the characteristics of those participants already enrolled. However, a requirement of this method is to establish 'a priori' all relevant prognostic factors and their respective weight (91).

A different option for phase II trials could be the futility approach, i.e. designing studies to identify which agents are least likely to demonstrate benefits rather than the more typical goal of identifying the most promising agents. In this approach the null hypothesis is that treatment has promise and will therefore produce results exceeding a meaningful threshold (93). This approach considerably reduces the sample size, with a reduction of costs, and, more importantly, makes it possible to perform a large number of trials each with a reduced number of centres. Such a design is being implemented in a study on coenzyme Q10 in ALS (85). Again, however, the design of such studies should rely on the availability of hard endpoints. Therefore, the complete understanding of more relevant factors related to ALS outcome, including therapeutic interventions, remains a major goal of clinical research.

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Table I

Studies of prognosis in ALS: studies based on referral series

Reference	Cases#	Prospective/retrospective	Mean age at onset (years)	Median survival from onset (months)	% 5-year survival from onset	Significant prognostic factors	Comments	Drop-out rate (%)
[94]	668	R	56	36§	39	Age, bulbar (worse)	Highly selected cohort (ALS Foundation)	NS
[32]	768	R	NS	NS	12.8 (ALS) 28.8 (PMA) 4.3 (PBP)	Type on onset; age; protein content of CSF (worse if >61 mg/dl); presence of hyperactive reflexes or Babinski response (worse). Geographical region not significant	Questionnaire to 24 neurological institutes in Japan. Only deceased cases included	
[95]	515	R	50.8	NA	NA	ALS worse than PMA. Older age, bulbar, left limbs (worse)	Only deceased cases	0
[96]	155	R	48	>72§	56 §	Age, diffusion of symptoms at time of diagnosis	PMA only	3
[97]	318	R	56.6	36	29	Bulbar (worse)	Israel national neurological register	NS
[98]	27	R	50.3	24	8	None	FALS only	0
[9]	336	R	57	60 (48 for ALS)	35	Age Type of onset non-significant	Highly selected population	0
[65]	194	P	59	36	32	Age, ALS score, ALS duration		3
[8]	708	R	57 (m), 60 (f) (ALS) 49 (m) 54 (f) (benign ALS)	38	28	Plateau in survival of younger patients	162 more cases excluded due to various reasons	1
[99]	138	P	57.8 (m) 60.7 (w)	43.2 (m) 38.4 (w)	NA	Age	Only deceased patients from a series of 246	0
[60]	167	P	56	NA	48	Age, presence of bulbar symptoms at entry, presence of fasciculations. Prevalent cases better than incident cases (4.7 vs. 2.1 years).	5 ALS centers in U.S.	1
[53]	144	R	55	NA	NA	Effect of distressing psychological factors (COX: OR 2.24 [1.08–4.64])	Patients from 3 ALS centers across U.S.	0
[10]	831	R	55.7	35	37.5	Age, diagnostic delay, slope of Appel score		0

Reference	Cases#	Prospective/retrospective	Mean age at onset (years)	Median survival from onset (months)	% 5-year survival from onset	Significant prognostic factors	Comments	Drop-out rate (%)
[11]	158	R	62.7	25.0–26.9	14.7	COX: upper limbs worse than lower Bulbar worse than spinal Age at onset		NS
[34]	71	R		31.2	25	Gender (women worse), age Bulbar not significant		NS
[5]	90	P	56.8	23 (17 from onset of study + 6 pre-study)	NA	None	Placebo arm of IGF-I trial	NS
[12]	307	R	60	16.8§	NA	Age, bulbar, time from onset to diagnosis	11 additional patients were excluded because they were lost to follow-up FALS not significant	0 (3%)
[28]	62	P	57	38.4	NA	COX: linear estimate of decline in foot dorsiflexion strength, FVC%, grip strength	Patients included in two trials	NS
[16]	245	P	53.1 (surviving) 59.6 (deceased)	NA	NA	Age; bulbar onset; body weight; weight change from prestudy; FVC; pCO2; ALSFRS score; muscle strength megascore	Placebo arm of CNTF trial. Comparison between surviving and deceased patients	0
[40]	105	R	57.1	32		FVC at study entry (<80% worse than FVC ≥80%); bulbar (worse)	The analysis included only the 74 patients for whom FVC was available COX: age, bulbar onset, diagnostic delay (per month), FVC%	30
[39]	155	P	54.2	47	NA	Bulbar onset and >55 years worse COX: age, bulbar, faster progression in the first year of observation	92 other patients were excluded because of missing data	0
[13]	841	R	56	43	NA	Age, referral delay, El Escorial classification	Several variables with missing data	NA
[67]	985	R	NA	39	NA	Mean age of onset lower in long survivors (43 vs. 57)	Analysis of long survivors (>120 months) from a tertiary center database	22
[14]	793	R	56	34.8	24	Diagnostic delay, age, bulbar onset, diagnosis ≥1990 better than before 1990		0
[41]	267	R	61.7	33.6	NA	COX: symptom duration, ALSFRS-R, FVC at baseline	ALS referral center in New York City	3
[15]	1398 671	R	62.5 61.7	26 26	NA NA	COX: Age (≥65, >65), disease duration at diagnosis (<2, >2 years), plasma creatinine, atrophy diffusion, pyramidal	Several variables with missing data, replaced with statistical	0

Reference	Cases#	Prospective/retrospective	Mean age at onset (years)	Median survival from onset (months)	% 5-year survival from onset	Significant prognostic factors	Comments	Drop-out rate (%)
						signs, spasticity, fasciculation, muscle strength (MMT), cough, swallowing, sVC	artifices Patients separated in 2 cohorts	
[56]	81	P	NA	NA	NA	FTLD significantly worse in univariate analysis but not in multivariate. COX: age and bulbar onset significant	FLTD was significantly associated with bulbar onset and older age at onset	0
[100]	123	R	63.3	27	23	Age, lower limb onset (better), area of residence (mountainous areas worse), and work (agricultural workers worse)		0
[29]	1034	R	54.1	41.4	28	COX: FVC < 75% at baseline; age at onset, bulbar onset, duration at diagnosis PEG and NIPPV not significant	A series of three papers concerning the same large series of cases (see also ref. 55 and 91)	0
[61]	1034	R	54.1	41.4	28	Prolonged survival related to younger age, limb site of onset and longer diagnostic delay, lower baseline AALSS, lower AALSS- preslope and higher baseline FVC		0
[101]	1034	R	54.1	41.4	28	Prolonged survival in more recent patients (1984–1998 vs. 1999–2004)		0
[50]	479	R	58	42.8	20	Prolonged survival related to young age at onset (<40), spinal onset, FVC >80 at diagnosis, longer diagnostic delay, ALSFRS-R score-ratio < 1.185	ALSFRS-R score ratio was calculated as ALSFRS-R score at first visit – ALSFRS-R score at last visit/time between first and last visit in months	18.90%

Table II

Studies of prognosis in ALS: studies based on retrospective epidemiological series

Reference	Cases#	Population	P/R	Mean age at onset (years)	Median survival from onset (months)	% 5-year survival from onset	Significant prognostic factors	Comments	Drop-out rate (%)
[102]	118	Y (Funen County, Denmark)	R	57	34	20	Age; bulbar worse, but due to higher age in bulbar onset cases		NS
[103]	128	Y (northern Sweden)	R	59	36	28	Bulbar (worse)	Included both ALS and PMA	0
[104]	220	Y (Torino, Italy)	R	55.5	33	25.1	None	Included both ALS and PMA cases	2%
[19]	44	Y (Rochester, U.S.)	N	67.5	23.8	14	Age; no time period effect (1925–1965 vs. 1965–1984)		0
[105]	72	Y (Ferrara, Italy)	N	59	24 (PBP) 48 (ALS) 72 (PMA)	<10	Bulbar (worse)		0
[33]	62	Y (Cantabria, Spain)	N	60.5	26.6	18	Age, gender (women worse)		
[35]	84	Y (Hordaland County, Norway)	N	61	28	25	24 (PBP), 40 (ALS); age COX: only bulbar vs. spinal (OR 2.93 [1.57–5.47]) Gender, time period (<1984; ≥1984) non-significant		0
[20]	186	Y (2 Danish Counties)	N	64	23	6	Age, bulbar (worse)		0
[21]	148	Y (Norway)	R	60.6	16.5§	18§	Bulbar (worse); age; diagnostic delay FALS not significant		0
[106]	121	Y (Parma, Italy)	R	59.6	30	11.3	Bulbar (worse); age not significant; no time period effect		0
[17]	97 439	Y (epid. cohort, Texas) N (referral cohort)	R P	57.3§ 58.5§	21.3§ 22.3§	4 21	Age, bulbar (worse), FALS (worse), diagnostic delay Older age	Comparison of a referral cohort to an incidence cohort	0 in both cohorts
[107]	58	Y* (Beograd, Yugoslavia)	N	56.2	27.7	NA	Gender (f 38.6, m 22.8); age (<49, 36.3, ≥50, 26.8) Site of onset non-significant	Only the 32 patients deceased during the follow-up were considered for survival analysis	

Reference	Cases#	Population	P/R	Mean age at onset (years)	Median survival from onset (months)	% 5-year survival from onset	Significant prognostic factors	Comments	Drop-out rate (%)
[22]	77	Y (Rochester, U.S.)	R	63	23–24	NA	Age Period (1925–1989; 1991–1998) not significant		0
[108]	133	Y* (Greece)	R	60.3	20.4	22	None		38%

Table III

Studies of prognosis in ALS: studies based on prospective epidemiological series (register methodology)

Reference	Cases#	Population- based	P/R	Mean age at onset (years)	Median survival from onset (months)	% 5-year survival from onset	Significant prognostic factors	Comments	Drop-out rate
[23]	229	Y (Scotland)	P	64.3 (sALS) 55.6 (fALS)	30	28	PMA (better); PBP (worse); Age (<65 vs. > 65); Gender (women worse)		0
[24]	388	Y (Ireland)	P	63.3(M) § 64.4(W) §	NA	17§	No effect of El Escorial criteria on ALS survival		0
[25]	193	Y (Piemonte, Italy)	P	62.8	30.5	24.7	COX: FVC (progression rate), lower limbs (progression rate), PEG, age, bulbar (progression rate), definite ALS (EEC), riluzole		0
[26]	180	Y (Washington State, U.S.)	P	61.3§	32	7§	Gender (women worse), age, bulbar, ALS-SS, residence, no partner, BMI change, scarce physical activity (worse) COX: age, bulbar, SF-36 (physical function), time from onset to diagnosis	No information on PEG, NIPPV	0
[30]	1226	Y (Scotland)	P	65.2 (M) 67.6 (W)	25	11	COX: Date of diagnosis (<1993 better than ≥1994); bulbar (worse); UMN + LMN worse than pure LMN Positive factors: riluzole, longer time onset-diagnosis, to be followed by a neurologist	n.s. gender, fALS not included PEG, NIV Cox final model on 1048 patients	0
[31]	1226	Y (Scotland)	P	NS	20.3 (≥80 yrs) 25.1 (<80 yrs)	NA	Age strong predictor, independent from type of onset	Comparison of patients with age ≥80 vs. <80.	0
[27]	79	Y (Lombardia, Italy)	P	64.4	39.2	43 (4 year survival)	Age, bulbar, duration of symptoms at diagnosis COX: age, definite ALS (EEC)	Large proportion of suspected ALS (mostly PMA)	6%

Note: Only studies using Kaplan-Meier survival curves are included.

Abbrevations: ALS: amyotrophic lateral sclerosis; COX: Cox multivariate model; EEC: El Escorial diagnostic criteria; FALS: familial amyotrophic lateral sclerosis; FTLD: fronto-temporal lobe dementia; LMN: lower motor neuron; M: men; N: no; NA: not available; NIPPV: non-invasive positive pressure ventilation; NS: not stated; P: prospective; PBP: progressive bulbar palsy; PEG: percutaneous endoscopic gastrostomy; PMA: progressive muscular atrophy; R: retrospective; SALS: sporadic ALS; UMN: upper motor neuron; W: women; Y: yes.

§from diagnosis.

*incomplete ascertainment of cases.