Prognosis and epidemiology of amyotrophic lateral sclerosis

Analysis of a clinic population, 1997–2011

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Summary

Amyotrophic lateral sclerosis is a disease with highly variable clinical features and prognosis. We analyzed the prognostic indicators of age, sex, bulbar or spinal onset, body mass index (BMI), and forced vital capacity (FVC) for 728 deceased patients from the Emory ALS Clinic. The median overall survival was 29.8 months from symptom onset, 15.8 months from diagnosis, and 14.3 months from the initial clinic visit. While univariate analyses revealed that each of the identified clinical features was strongly associated with patient survival, in multivariable analyses only age, BMI, and FVC measured at the first clinic visit were independent prognostic indicators; bulbar onset and sex were not significantly associated with survival prognosis after adjustment for the other clinical features.

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder of upper and lower motor neurons. There is wide variability of ALS clinical phenotypes that include age at onset, degree of upper and lower motor neuron dysfunction, and limb, bulbar, or respiratory onset of

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disease. Prognosis for any individual patient is hard to predict, and survival after onset ranges from several months to more than a decade. It is unclear which, if any, of the clinical variables are important for predicting survival. Previous studies of ALS populations identified several negative prognostic factors,^{1–13} including older age at onset, female sex, and bulbar onset. As there is so much inconsistency in the published literature regarding the relative importance of prognostic factors, clinicians are challenged to provide a well-reasoned prognosis to newly diagnosed patients.

We addressed the issue of prognosis by querying our clinical database of deceased patients to associate time to death with multiple demographic variables, including sex, age at onset, delay from onset to the initial clinic visit, bulbar or spinal symptoms at onset, and sporadic vs familial forms of disease. Analysis also included baseline markers of disease severity, respiratory function as measured by forced vital capacity (FVC), and nutritional status as assessed by body mass index (BMI).

METHODS

The Emory ALS Clinic database consists of demographic and clinical data from patient visits since 1997. The Emory institutional review board approved analysis of these de-identified cases. We queried the database for all deceased patients as of July 31, 2011, for date of onset, date of diagnosis, and site of onset. Each clinic visit was searched for FVC and BMI. Patients maintained on mechanical ventilation were excluded. For our baseline statistics, we used the clinical data generated at the first visit to our ALS clinic, since this was when measures of FVC and BMI were first available. Date of death was confirmed through the social security death index.

The Emory Clinic is located in Atlanta, the largest city in Georgia, and the ALS patient population served by Emory is overwhelmingly from Georgia (83%), with bordering states contributing 15% of patients and the remainder from outside the region. Referrals are from community neurologists, or are self-referrals. Eighty percent of our patients are Caucasian (non-Hispanic) and 17% African American.

ALS was defined as adult-onset symptoms and signs of both upper and lower motor neuron degeneration in one or more regions, which could not be attributed to other causes. Categorization of patients by the El Escorial criteria was inconsistent, since these criteria were developed specifically for research purposes. However, it is unlikely that any patients included in this cohort had a disorder other than ALS. Age at diagnosis was defined by the date the patient was first told he or she had ALS. For 522 patients (72%), this was the same day as their initial visit to our clinic. For the remainder of the patients, 99 (13.5%) received their diagnosis between 1 and 12 months prior to the first visit, 40 (5.5%) between 12 and 24 months, 13 (1.8%) between 24 and 36 months, 12 between 36 and 48 months (1.6%), and 17 (2.3%) >48 months.

Preparation of descriptive statistics was carried out in Microsoft Excel and Access. Significance testing to compare means and proportions across groups, Kaplan-Meier survival analysis, and Cox regression modeling for adjusted hazard ratio estimation were all performed using the SAS and SAS JMP software. Any record with missing covariate information was removed in the regression analysis. All confidence intervals are reported assuming the nominal 0.05 level, with p values < 0.05 considered statistically significant.

RESULTS

We encountered 1,131 patients with ALS between 1997 and July 2011; 733 were deceased at the time of analysis. Four were excluded due to lack of clinical data, and one was excluded because of mechanical ventilation prior to death.

The male-female ratio for the cohort was 1.2:1. However, when stratified for age at onset, the M:F ratio varied from 2.5:1 for those <50 to 1:1 for those ≥ 50 ($p < 0.001$, χ^2). Women were more likely to exhibit bulbar as opposed to spinal disease onset (38% women vs 27% men; $p = 0.002$, χ^2).

Age at diagnosis ranged from 20 to 90 years; mean age was 61.5, with 66% of patients diagnosed between the ages of 50 and 74. Women were older than men at diagnosis: 63.4 vs 60 years ($p < 0.001$).

At time of diagnosis, 32% were found to have signs of bulbar disease, with average age of 64.8 years, vs 60 years for those with spinal symptoms at onset ($p < 0.001$). There were no differences between familial patients (4.5% of cohort) and sporadic patients for distributions of sex and site of onset.

The median time from symptom onset to diagnosis was 11.1 months (interquartile range [IQR] 6.8 to 19.0 months), and the median time from onset to initial visit was 12.1 months (IQR 7.7 to 21.5 months). Bulbar onset patients were diagnosed earlier, with a median lag of 8.8 months from start of symptoms to diagnosis, as compared to a median lag of 12.0 months for patients without bulbar symptoms ($p < 0.001$). This delay in diagnosis was also slightly longer for women (median lag of 11.7 vs 10.5 months; $p = 0.052$).

Baseline data for FVC were available in 596 patients, and for BMI in 502 patients. The majority of patients had already experienced respiratory decline at the time of the initial clinic visit, with 54% showing FVC below 75% of expected value. Baseline BMI was in the normal or above normal range for 92%.

Simple summaries of the lifetime distribution by prognostic factors

The median survival time from reported onset was 29.8 months (IQR 18.7–46.8). For comparison, median survival from diagnosis was 15.8 months (IQR 7.7–28.2), and median survival from the first clinic visit was 14.3 months (IQR 6.6–26.4). Taking the initial clinic visit as the baseline for measuring survival, we evaluated several patient characteristics independently as possible prognostic factors (table 1) and then in multivariable analyses (table 2). Survival differed based on the patient's age at the time of the initial visit. We separated patients into groups by decade of age, beginning with those younger than 50 and continuing until age 80 or older. The median survival time was 27.2 months in the youngest age group and, with the exception of the oldest group, steadily decreased to 17.0, 13.1, 8.1, and 9.9 months ($p < 0.001$; table 1). The difference in median survival between the 70–79 and the >80 -year-old groups was not significant. The presence of bulbar symptoms at the time of the initial visit was negatively associated with median survival: 13.1 months vs 15.3 months for spinal onset ($p = 0.002$). Men had marginally longer median survival than women, 14.8 months vs 13.6 months ($p = 0.06$). The first respiratory function measured by FVC was directly correlated with disease duration: median survival declined with each 25% decrease in percent of predicted FVC ($p < 0.001$; table 1).

Weight loss is always a focus of concern for patients with ALS, and BMI of patients at the time of their first clinic visit was predictive of survival. Patients with below-normal BMI showed lower median survival compared to those with normal BMI (6.3 vs 13.7 months), but those with above-normal BMI were similar to normal (15.3 months; table 1).

The length of time between first ALS symptoms and the initial clinic visit correlated with patient survival, likely because it is an indicator of rate of progression. A lag between presentation of symptoms and initial clinic visit of less than 12 months was associated with a median survival of 11.9 months, as opposed to 16.7 months for those with a lag of greater than 12 months ($p < 0.001$; table 1).

Table 1 Survival based on patient characteristics

Factor	N	%	Median survival from initial clinic visit, mo	95% Confidence interval	Log-rank test p value
Total sample	728	100	14.3	13.1-15.3	
Sex					
Male	402	55	14.8	13.1-16.4	0.06
Female	326	45	13.6	11.6-15.1	
Age at diagnosis					
<50 years	126	17	27.2	23.1-33.5	<0.001
50-59 years	185	25	17.0	14.3-19.5	
60-69 years	225	31	13.1	10.5-14.8	
70-79 years	148	20	8.1	6.5-9.3	
≥80 years	43	6	9.9	7.7-13.5	
Site of onset					
Spinal	495	68	15.3	13.6-17.3	0.002
Bulbar	233	32	13.1	9.9-14.2	
Lag from onset to initial visit					
≤12 months	354	49	11.9	10.4-13.8	<0.001
>12 months	364	51	16.7	14.8-18.7	
BMI					
<18.5	41	6	6.3	2.2-7.3	<0.001 ^a
18.5-24.9	217	30	13.7	12.0-16.6	
≥25	244	34	15.3	14.0-17.6	
Missing	226	31	15.9	11.1-20.0	
FVC (% predicted)					
≥100%	71	10	20.9	18.5-27.9	<0.001 ^a
75-99%	204	28	18.1	15.9-19.8	
50-74%	187	26	12.5	9.5-14.9	
25-49%	106	15	6.4	4.4-8.3	
<25%	28	4	2.6	1.7-5.6	
Missing	132	18	15.6	11.5-22.0	

Abbreviations: BMI = body mass index; FVC = forced vital capacity. ^aMissing category not included when calculating log-rank test statistic.

Survival estimation based on multivariable analysis

While age, site of onset, FVC, and BMI were all significant factors for predicting survival in univariate analyses, they are correlated predictors and require multivariable methods to control for their relative contributions to prognosis. As seen in table 2, age at initial visit emerged as the strongest independent risk factor using Cox regression analysis. Compared to patients <50 years, an initial increase in age of up to 1 decade carried an estimated adjusted hazard ratio of 1.73. For each subsequent subgroup based on decades of age, the estimated hazard ratios increased to 2.13, 2.23, and 2.57, respectively ($p < 0.001$; table 2). However, site of onset (bulbar vs spinal) was no longer statistically significant after adjusting for age, BMI, sex, FVC, and the lag between symptom onset and the initial clinic visit ($p = 0.97$; table 2).

Table 2 Multivariable comparison of survival by patient characteristics

	HR ^a	95% Confidence interval	p Value
Age (<50 reference)			<0.001
≥80 years	2.57	1.58-4.20	
70-79 years	2.23	1.59-3.11	
60-69 years	2.13	1.56-2.92	
50-59 years	1.73	1.27-2.82	
BMI (18.5-25 reference)			0.017
<18.5	1.86	1.22-2.82	
≥25	0.97	0.80-1.19	
FVC (>100% reference)			<0.001
<25%	6.40	3.24-12.63	
25%-49%	2.13	1.48-3.07	
50%-74%	1.66	1.20-2.29	
75%-99%	1.26	0.92-1.71	
Male	1.04	0.85-1.27	0.73
Site of onset (bulbar vs spinal)	1.00	0.80-1.26	0.97
Abbreviations: BMI = body mass index; FVC = forced vital capacity. ^a A total of 443 patients contributed to Cox regression model; estimated hazard ratios (HRs) are relative to stated reference groups; p values indicate overall significance of designated factor; model is adjusted for lag (in months) between first clinical visit and symptom onset.			

Although associated with other patient characteristics, clinical markers of ALS progression were still linked to duration of disease. The adjusted relationship between BMI at diagnosis and survival (table 2) showed that patients presenting with low (<18.5) BMI exhibited markedly shorter survival after diagnosis compared to those with normal and high BMI. As with age, there was a highly significant survival difference across subgroups of patients defined based on baseline FVC levels ($p < 0.001$), with a monotone trend in estimated hazard ratios as FVC decreased. The regression model summarized in table 2 also adjusts for the time lag (dichotomized as <12 vs >12 months) between symptom onset and the initial clinic visit. Those with shorter lags tended to exhibit shorter survival, as might be expected assuming that more severe symptoms led to earlier diagnosis and specialized care.

We note that there were patients with missing data for BMI ($n = 226$) and FVC ($n = 132$) at the initial clinic visit. Univariate survival analysis of those with missing BMI or FVC suggested that their overall prognosis was good to very good compared to the rest of the cohort (table 1). If the reasons for the missing data are assumed to be related only to the other variables included as predictors of survival in table 2, then we expect no serious threat to the validity of the multivariable analysis. When the regression model in table 2 was refit allowing for separate “missing” categories for BMI and FVC, the estimated hazard ratios and trends across the other subgroups remained qualitatively similar (results not shown).

There was a concern for a possible bias in our analysis because our deceased cohort excluded those patients who would be long-term survivors, which may comprise up to 10% of an ALS population.¹⁴ Using survival of >7 years from the date of onset as our definition of long-term survivor, 51 patients met this definition. We re-analyzed the cohort after exclusion of these 51 patients and found that the hazard ratio estimates showed minor changes (table 3), but that the conclusions based on analysis of the entire cohort did not change. Thus, we are comfortable reporting that the hazard ratio estimates are representative of the registry, and reasonably robust to the effect of long-term survivors.

Table 3 Multivariable comparison of survival by patient characteristics for patients who survived <7 years from the date of onset

	HR ^a	95% Confidence interval	p Value
Age (<50 reference)			<0.001
≥80 years	2.12	1.27-3.51	
70-79 years	2.15	1.51-3.06	
60-69 years	2.01	1.44-2.81	
50-59 years	1.78	1.28-2.49	
BMI (18.5-25 reference)			<0.001
<18.5	3.01	1.96-4.63	
≥25	1.00	0.81-1.23	
FVC (>100% reference)			<0.001
<25%	15.51	7.45-32.27	
25%-49%	2.08	1.43-3.03	
50%-74%	1.86	1.34-2.60	
75%-99%	1.33	0.97-1.82	
Male	1.03	0.84-1.27	0.75
Site of onset (bulbar vs spinal)	0.93	0.75-1.17	0.97

Abbreviations: BMI = body mass index; FVC = forced vital capacity. ^aA total of 425 patients contributed to Cox regression model; estimated hazard ratios (HRs) are relative to stated reference groups; p values indicate overall significance of designated factor; model is adjusted for lag (in months) between first clinical visit and symptom onset.

DISCUSSION

Contrary to suggestions in the literature, we found no evidence that there were biases in prognostic indicators using a registry derived from our Emory tertiary care center.^{9,13} It has been suggested that patients referred from tertiary care centers include younger patients participating in clinical trials and an overrepresentation of familial disease due to interest in research in this type of ALS, and thus prognosis would be biased.⁹ Patients with familial disease comprised fewer than 5% of our cohort, which is the expected proportion in an ALS population. The average age at diagnosis fell within the norms of population-based studies of 57 to 68.^{1,4,5,7,9,15,16} Although several authors report increased survival in referral cohorts compared to population-based cohorts,^{1,13} the median survival of 15.8 months in our registry is similar to that reported for other series.⁹ The concern for bias generated by the exclusion of long-term survivors was partially addressed by re-analysis of the cohort after exclusion of those patients surviving >7 years after onset. While there were differences in statistical comparisons, there were no alterations in the scientific conclusions of our study when long-term survivors were excluded. This does not preclude the existence of such bias but does suggest that relative hazards will likely be similar to those reported in table 2 even if “very long” survivors were included in the analysis.

Patient and disease characteristics, such as sex, age, FVC, or site of onset, are inextricably linked to one another, necessitating the need for multivariable analyses for predicting survival outcomes. While several epidemiologic evaluations of ALS report that female sex, bulbar onset of symptoms, and older age predict shorter disease duration, multivariable analyses with a large sample size provide a more powerful assessment of independent risk factors for poor prognosis. We determined that the unadjusted difference in survival by sex can be explained by significant differences in the age at diagnosis of men and women, or by the higher prevalence of bulbar symptoms among women. However, it is unclear why ALS tends to develop at an older age for women compared to men. Theories have included a possible protective effect from hormones prior to menopause,

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but there are scarce data on reproductive factors and sexual hormones.^{17,18} Female patients in our clinic were more likely to present with bulbar features at diagnosis. A recent epidemiologic study by Chio et al.² revealed a rapid increase in the incidence of bulbar disease for female patients as they age. It is unclear, however, whether the increased incidence of bulbar disease in women can be explained entirely by the finding that women are older than men at the time of diagnosis.

While many studies report that bulbar symptoms predict shorter survival,^{1–7,13,14,18} in this study the univariate finding of shorter survival in patients with bulbar symptoms disappeared when multivariable analyses were applied (table 2).^{1–7,12,13,16} While we observed a 2.2-month decrease in median survival for those with bulbar disease compared to spinal onset patients, the average age of those diagnosed with a bulbar form of ALS was also notably higher in our patient population, easily accounting for the shorter survival in this group.

As confirmed by others, in our study age stands out as the most important predictor of survival.^{1,4,13,19} Indeed, younger patients in our cohort were less likely to demonstrate bulbar symptoms at onset, and were more likely to have excellent respiratory reserve. In general, younger people also tend to have fewer comorbidities than those diagnosed at an older age. Particularly noteworthy, however, is the finding that BMI and lung function as measured by FVC were independent risk factors for survival in this patient cohort. The monotonic trends in estimated adjusted hazard ratios across categories of age and FVC are particularly striking (table 2).

Describing the clinical pattern and prognostic factors of ALS is of great importance to patients, their families, and their physicians in order to develop a useful, personalized medical treatment plan. Possibly more importantly, the better we can predict outcome, the more clearly we can make decisions about patient management and plan treatment trials for future research.

REFERENCES

1. Chancellor AM, Slattery JM, Fraser H, Swingler RJ, Holloway SM, Warlow CP. The prognosis of adult-onset motor neuron disease: a prospective study based on the Scottish Motor Neuron Disease Register. *J Neurol* 1993;240:339–346.
2. Chio A, Calvo A, Moglia C, Mazzini L, Mora G. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry* 2011;82:740–746.
3. Chio A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: a critical review. *Amyotroph Lateral Scler* 2009;10:310–323.
4. Chio A, Mutani R, Mora G. Prognosis in amyotrophic lateral sclerosis: a population-based study. *Neurology* 2003;61:1826–1827; author reply 1827.
5. Czaplinski A, Yen AA, Appel SH. Amyotrophic lateral sclerosis: early predictors of prolonged survival. *J Neurol* 2006;253:1428–1436.
6. Czaplinski A, Yen AA, Simpson EP, Appel SH. Predictability of disease progression in amyotrophic lateral sclerosis. *Muscle Nerve* 2006;34:702–708.
7. del Aguila MA, Longstreth WT Jr, McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population-based study. *Neurology* 2003;60:813–819.
8. Jablecki CK, Berry C, Leach J. Survival prediction in amyotrophic lateral sclerosis. *Muscle Nerve* 1989;12:833–841.
9. Logroscino G, Traynor BJ, Hardiman O, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J Neurol Neurosurg Psychiatry* 2008;79:6–11.

10. Okamoto K, Kobashi G, Washio M, et al. Descriptive epidemiology of amyotrophic lateral sclerosis in Japan, 1995-2001. *J Epidemiol* 2005;15:20-23.
11. Sabatelli M, Madia F, Conte A, et al. Natural history of young-adult amyotrophic lateral sclerosis. *Neurology* 2008;71:876-881.
12. Tysnes OB, Vollset SE, Larsen JP, Aarli JA. Prognostic factors and survival in amyotrophic lateral sclerosis. *Neuroepidemiology* 1994;13:226-235.
13. Lee JR, Annegers JF, Appel SH. Prognosis of amyotrophic lateral sclerosis and the effect of referral selection. *J Neurol Sci* 1995;132:207-215.
14. Zoccolella S, Beghi E, Palagano G, et al. Predictors of long survival in amyotrophic lateral sclerosis: a population-based study. *J Neurol Sci* 2008;268:28-32.
15. Forsgren L, Almay BG, Holmgren G, Wall S. Epidemiology of motor neuron disease in northern Sweden. *Acta Neurol Scand* 1983;68:20-29.
16. Murros K, Fogelholm R. Amyotrophic lateral sclerosis in Middle-Finland: an epidemiological study. *Acta Neurol Scand* 1983;67:41-47.
17. Rudnicki SA. Estrogen replacement therapy in women with amyotrophic lateral sclerosis. *J Neurol Sci* 1999;169:126-127.
18. Popat RA, Van Den Eeden SK, Tanner CM, et al. Effect of reproductive factors and postmenopausal hormone use on the risk of amyotrophic lateral sclerosis. *Neuroepidemiology* 2006;27:117-121.
19. Norris FH, Denys EH, Sang K, Mukai E. The natural history of ALS in a specified population, with comments on risk factors, prognosis and symptomatic treatments. *Rinsho Shinkeigaku* 1989;29:1485-1492.

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