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Effects of Demographic Factors on Survival Time after a Diagnosis of Amyotrophic Lateral Sclerosis

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Abstract

Background—The Agency for Toxic Substances and Disease Registry established surveillance projects to determine the incidence, prevalence, and demographic characteristics of persons with Amyotrophic Lateral Sclerosis (ALS) in defined geographic areas. There is a need to characterize and account for the survival and prognostic factors among a population- based cohort of ALS cases in the United States.

Methods—A cohort of incident cases diagnosed from 2009–2011 in New Jersey was followed until death or December 31, 2013, whichever happened first. Survival was assessed using Kaplan-Meier curves and Cox proportional hazards regression was used to identify prognostic factors.

Results—Sixty-four percent of incident cases died between 2009 and 2013, 93.7% specifically from ALS. Among the 456 cases studied in the survival analysis, the median survival from diagnosis was 21 months; 46% of cases survived longer than two years from diagnosis. Older age predicted shorter survival. While there is some indication of differences because of sex, race, and ethnicity, these differences were not statistically significant when accounting for age.

Conclusions—New Jersey mortality data were queried to determine the vital status of a cohort of incident ALS cases and used to investigate relationships between demographic factors and survival. Results are consistent with other population-based studies. Older age was a strong predictor of shorter survival time. Additional follow-up time is needed to characterize longer-term survival.

Keywords

Amyotrophic lateral sclerosis; Death certificates; Mortality; Survival curves; Hazard ratio

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Authors' Contributions

Concept and design: Jordan, Fagliano, Kaye; acquisition of data: Jordan, Rechtman, Kaye, Lefkowitz, Fagliano; analysis and interpretation of data: Jordan, Fagliano, Rechtman, Lefkowitz; drafting of manuscript: Jordan, Fagliano, Rechtman, Lefkowitz, Kaye; statistical analysis: Jordan, Fagliano; supervision: Fagliano, Kaye, Lefkowitz.

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare disease that is characterized by progressive degeneration of both the upper and lower motor neurons. The median crude incidence rate among studies conducted around the world was 2.1 per 100,000 person-years (range: 0.3–3.6), and the crude prevalence was 5.4 per 100,000 persons (range: 1.0–11.3) [1] . In New Jersey (N.J., USA), the age-adjusted incidence was 1.67 per 100,000 person-years (2009–2011), and the point prevalence as of December 31, 2011, was 4.40 per 100,000 persons [2] . A higher incidence is associated with being older, male, white, and non-Hispanic [1–5] .

Estimates of the median survival time from diagnosis range between 18 and 29 months [2, 6–9] and most ALS patients die within two to five years of diagnosis [10] . Older age is associated with shorter survival [7–9, 11–13] , and there are conflicting reports of sex being a prognostic indicator [6, 8, 9, 11] . Few studies have examined race as a prognostic factor [7, 8] . There are limited survival data for persons with ALS in the United States. This report describes the survival time from the time of diagnosis among cases of ALS reported by neurologists in a defined geographic area (N.J., USA). The El Escorial criteria [14] were used to determine case eligibility.

Materials and Methods

A detailed description of the case ascertainment methodology is presented elsewhere [2] . Cases were reported by neurologists for all ALS patients who were N.J., USA residents, under the physician’s care at some point between January 1, 2009 and December 31, 2011, and who met the El Escorial criteria [14] . There were 764 prevalent cases in this period, of which 493 cases were incident with the disease. Eighty-four percent of cases were 50 years of age or older at diagnosis, 55.1% were male, 83.2% were white, and 89.9% were non-Hispanic [2] .

Determination of Survival of Incident Cases

Vital status, as of December 31, 2013, of the 493 incident cases was determined through a query of N.J. death records. Death certificates are retained within the N.J., USA Department of Health, where a certified nosologist reviews all electronic or hand-written information on the death certificate to ensure conformity with the International Classification of Disease revision 10 (ICD-10) [15, 16] . Cases were matched to death records on a combination of variables: last name, first name, date of birth, last five digits of the social security number, sex, and address.

Cause of Death

Decedents were classified based on the causes assigned for death in their death certificates–that is, whether ALS was a cause for death–by a review of all contributing and underlying causes of death. A search of keywords was conducted and deaths were classified as due to ALS if any of the following keywords or variants appeared in any of the five causes of death: ‘amyotrophic lateral sclerosis’, ‘ALS’, ‘amyotrophic’, or ‘Gehrig’.

Analysis of Survival Time

Survival time of a patient was calculated from the month and year of diagnosis to the month and year of death, regardless of the cause of death. Race was identified on the case reporting form as 'White', 'Black', 'Asian', 'Other', or 'Unknown'. Cases were excluded from analyses if race was 'Other' or 'Unknown', or if Hispanic ethnicity was 'Unknown'. Age at diagnosis was categorized into four groups approximating quartiles of the distribution: less than 55 years; 55 to <65 years; 65 to <75 years; and 75 years or more.

Kaplan-Meier product-limit survival curves and median survival time were developed using the LIFETEST procedure in SAS ® version 9.2 [17, 18] . Confidence limits on median survival times were based on the log-log transformation of the survivor function. Homogeneity in median survival time across strata of demographic groups was assessed using the log-rank test. Differences across strata are considered statistically significant for p values less than 0.05. The percent of ALS cases surviving beyond 6, 12, 18, and 24 months past diagnosis was also determined for all cases and based on demographic strata. Confidence limits on survival percentages were derived using the normal approximation method or Wilson score method [17] . The multivariate Cox proportional hazard model was used to examine the effects of demographic factors on survival time, using the PHREG procedure in SAS ® [17] .

The project protocol was approved by the Centers for Disease Control and Prevention Institutional Review Board (IRB) and determined to be public health practice not requiring review by the N.J. Department of Health IRB.

Results

As of December 31, 2013, 64.1% of incident cases (316/493) were known to be deceased. This proportion was higher among those diagnosed in 2009 (68.4%) compared with those diagnosed in 2010 (65.5%) and 2011 (58.5%). For 93.7% (296/316) of those known to be deceased, ALS was specified as the cause of death on the death certificate. Respiratory failure, aspiration, pneumonia, other neuromuscular disorders, sepsis, acute cardiac events, malnutrition, and chronic obstructive pulmonary disorder were among the causes of death listed for the 20 cases that did not list ALS as one of the causes of death.

In the remaining analyses, we excluded 37 cases on the basis of race being 'Other' or 'Unknown' or Hispanic ethnicity being 'Unknown'. Among the remaining 456 incident cases diagnosed during 2009–2011, the median survival time from the time of diagnosis to the time of death was 21 months (95% CI 19, 25 months) (table 1). The median survival time varied significantly by age group from a high of 38 months (95% CI 28, 45 months) for the age group <55 years, to a low of 11 months (95% CI 9, 14 months) for those 75 years of age or older (table 1). The median survival time was shorter among females compared with that of males, among whites compared with that of blacks and Asians, and among non-Hispanics compared with that of Hispanics (table 1). Kaplan-Meier survival curves for all incident cases and for cases by age group and by sex are presented in figure 1.

The percentages of ALS cases surviving beyond 6, 12, 18, and 24 months are shown in table 2 . For the 456 incident cases, 67% (95% CI 63, 71) survived past 12 months and 46% (95% CI 41, 51) survived past 24 months. As age increases, the percentage of cases surviving beyond a certain time decreases; as many as 66% of those diagnosed with ALS before age 55 years survived 24 months, while only 23% of those diagnosed at age 75 years or older survived that long. This pattern of decreasing survival with age did not vary significantly by sex. In addition, there were no significant differences based on sex, race, or ethnicity group alone (table 2).

The multivariate Cox proportional hazards regression model demonstrated a strong age-group effect on survival time (table 3). In comparison to the age group 65 to <75 years, the probability of dying was almost half in the youngest group (hazard ratio (HR) = 0.54, 95% CI 0.38, 0.76), while the probability of dying in the oldest group (>75 years) was almost 70% higher (HR = 1.68, 95% CI 1.24, 2.27). Controlling for age group, the probability of dying did not differ significantly by sex, race, and ethnicity (table 3). Further, there was no statistically significant interaction between sex and age group; that is, HRs by age group were similar between males and females.

Discussion

There are limited survival data for persons with ALS in the United States [7, 8, 11, 13] , particularly for cases reported by all neurologists in a defined geographic area who used the El Escorial criteria [14] to determine case eligibility. This report contains the first description of the survival of a state-wide cohort of ALS patients in the United States.

The median survival time of 21 months from diagnosis is similar to reports in the literature [8, 9, 12, 13] . Older age at diagnosis has been found consistently to be a strong predictor of shorter survival [7–9, 11–13] . In this cohort, the median survival time among those aged less than 55 years at diagnosis was more than three times longer than those aged 75 years or older.

In this study, females had shorter survival than males, though not statistically significant in the multivariate proportional hazards model. Some studies have delineated a difference in survival by sex, perhaps due to differences in site of onset, while others have not [6, 8, 9, 11] .

From the life-table analysis, there were apparent differences in the median survival time based on race and ethnicity. After multivariate adjustment in the proportional hazards analysis, differences by race and ethnicity remained but were not statistically significant; however, these comparisons were based on small case counts among blacks, Asians and Hispanics. Little is known about differences in survival time among different races in the United States. Kazamel et al. found similar median survival times between African Americans (22 months) and Caucasians (19 months) in a clinic-based cohort of ALS cases in Alabama [7] . Based on only ten non-white cases, del Aguila et al. found shorter median survival time among non-whites (14 months) compared with whites (19 months) [8] . We found no other studies that have reported on ALS survival time by Hispanic ethnicity.

Since diagnoses of incident cases were between January 1, 2009 and December 31, 2011, the follow-up time to date has been insufficient to define longer-term survival. Incident cases had a minimum of 24 months and a maximum of 60 months of follow-up time. Nonetheless, follow-up time was sufficient to characterize median survival times as well as percentages of cases surviving up to 24 months in all cases and by demographic groups. The percentage of ALS cases in the N.J., USA cohort who survived past 12 months was 67% (66% among whites). This percentage is lower than the percentage reported from a population-based cohort in Lombardy, Italy (76%) [9] , but similar to the percentage reported in western Washington state (66%) [8] .

It is possible that some cases originally reported by neurologists relocated to other states, became residents of those states, and died there. It is also possible that some N.J., USA resident cases could have died in another state and their death certificates have not yet been transferred to N.J., USA. We do not know whether survival time among these possible decedents differs from those for whom we retrieved death certificates.

Conclusion

This study is the first to examine demographic prognostic indicators, including age, sex, race, and Hispanic ethnicity in a state-wide, population-based cohort of ALS cases. Older age is a strong predictor of shorter survival, and there is some indication of differences based on sex, race, and ethnicity, but these differences were not statistically significantly different when accounting for age. More time is required to fully characterize the shape of the survival curve among longer-term survivors.

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Heather Jordan and Jerald Fagliano had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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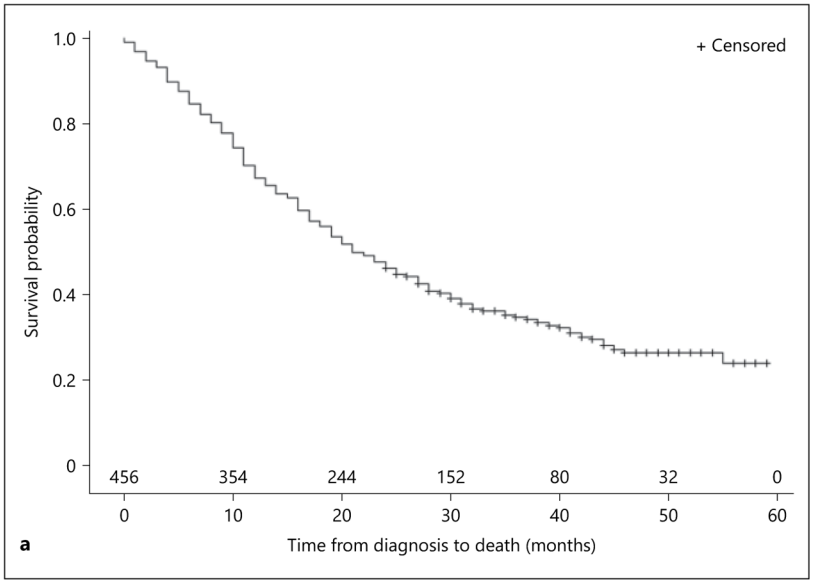

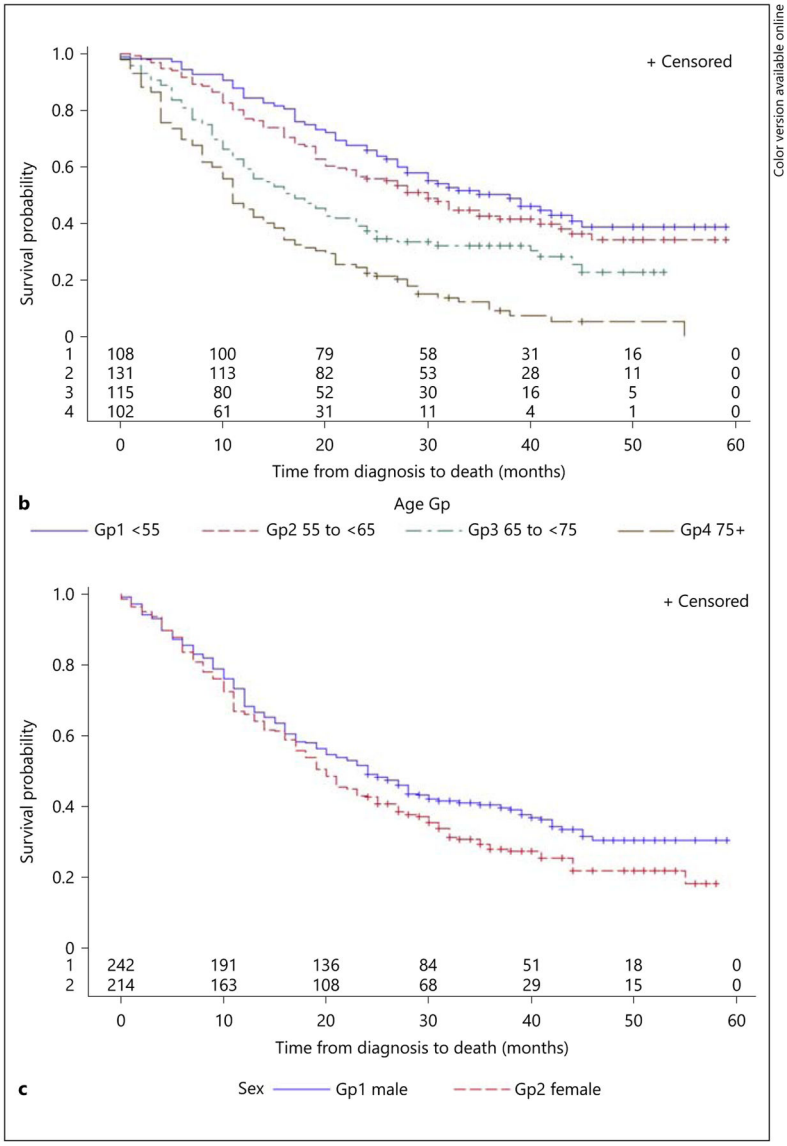

Fig. 1.

Kaplan-Meier survival curves for incident NJ ALS cases with vital status determined through December 31, 2013, n = 456, for all cases, by age group and by sex. (Of 493 incident cases, 37 cases were excluded whose race was ‘unknown’ or ‘other’, or whose Hispanic ethnicity was ‘unknown’.) **a** All cases. **b** By age group. **c** By sex.

Table 1

Median survival times by demographic characteristic, n = 456*

Parameter	Number of cases	Median survival time (95% CI) in months	log-rank test of equality over strata
All cases	456	21 (19, 25)	–
Age group			
<55	108	38 (28, 45)	
55 to <65	131	30 (22, 41)	p < 0.0001
65 to <75	115	17 (12, 23)	
75+	102	11 (9, 14)	
Sex			
Male	242	24 (19, 28)	p = 0.050
Female	214	20 (17, 23)	
Race			
White	405	20 (18, 24)	
Black	29	41 (22, –)	p = 0.031
Asian	22	30 (14, –)	
Ethnicity			
non-Hispanic	431	21 (19, 24)	p = 0.22
Hispanic	25	30 (16, –)	

* Of 493 incident cases, 37 were excluded whose race was ‘unknown’ or ‘other’, or whose Hispanic ethnicity was ‘unknown’.

– Upper confidence limit not estimated.

Table 2

Percent of ALS cases surviving beyond diagnosis month, by demographic characteristics, n = 456*

Parameter	Percent of cases (95% CI)			
	6 months	12 months	18 months	24 months
All cases	85 (81, 88)	67 (63, 71)	56 (51, 60)	46 (41, 51)
Age group				
<55	94 (90, 99)	84 (77, 91)	75 (67, 83)	66 (57, 75)
55 to <65	92 (87, 96)	77 (70, 84)	67 (59, 75)	56 (47, 64)
65 to <75	81 (74, 88)	59 (50, 68)	47 (38, 56)	37 (29, 46)
75+	70 (61, 79)	45 (35, 55)	31 (22, 40)	23 (14, 31)
Sex male	86 (81, 90)	68 (62, 74)	58 (52, 64)	49 (43, 55)
Male, age				
<55	95 (90, 100)	84 (75, 93)	77 (67, 88)	71 (60, 82)
55 to <65	92 (86, 98)	73 (63, 83)	64 (53, 75)	55 (44, 66)
65 to <75	79 (68, 89)	59 (46, 72)	50 (37, 63)	41 (28, 54)
75+	70 (56, 83)	50 (36, 64)	30 (17, 44)	20 (8, 31)
Sex female	84 (79, 89)	66 (60, 72)	54 (47, 60)	43 (36, 49)
Female, age				
<55	93 (86, 100)	85 (74, 95)	72 (59, 85)	59 (44, 73)
55 to <65	91 (83, 98)	83 (73, 93)	72 (60, 84)	57 (43, 70)
65 to <75	83 (73, 93)	59 (47, 72)	44 (31, 57)	34 (22, 46)
75+	70 (58, 82)	41 (28, 54)	32 (20, 44)	25 (14, 36)
Race				
White	84 (81, 88)	66 (61, 70)	54 (49, 59)	44 (39, 49)
Black	86 (69, 95)‡	79 (62, 90) ‡	76 (58, 88) ‡	69 (51, 83) ‡
Asian	86 (67, 95) ‡	77 (57, 90) ‡	64 (43, 80) ‡	50 (31, 69) ‡
Ethnicity				
Non-Hispanic	84 (81, 88)	67 (62, 71)	55 (51, 60)	45 (41, 50)
Hispanic	88 (70, 96) ‡	72 (52, 86) ‡	68 (48, 83) ‡	60 (41, 77) ‡

*Of 493 incident cases, 37 were excluded whose race was ‘unknown’ or ‘other’, or whose Hispanic ethnicity was ‘unknown’.

‡Confidence intervals based on Wilson score method, using OpenEpi Confidence Limits for a Simple Proportion (http://www.openepi.com/v37/Proportion/Proportion.htm). Otherwise confidence intervals based on normal approximation method (±1.96 (SE)).

Table 3

Adjusted hazard ratios from multivariate Cox proportional hazard model for incident ALS cases, as of December 31, 2013, n = 456*

Parameter	Hazard ratio (95% CI)
Age group	
<55	0.54 (0.38, 0.76)
55 to <65	0.64 (0.47, 0.88)
65 to <75	Referent
75+	1.68 (1.24, 2.27)
Sex	
Male	Referent
Female	1.13 (0.90, 1.41)
Race	
White	Referent
Black	0.69 (0.41, 1.17)
Asian	0.71 (0.40, 1.27)
Ethnicity	
Non-Hispanic	Referent
Hispanic	0.81 (0.47, 1.40)

* Of 493 incident cases, 37 were excluded whose race was ‘unknown’ or ‘other’, or whose Hispanic ethnicity was ‘unknown’.