Epidemiology and factors predicting survival of amyotrophic lateral sclerosis in a large Chinese cohort

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder associated with loss of motor neurons. Our objective was to explore the epidemiology, clinical features, and survival factors of 1809 patients with ALS.

Methods: We analyzed 1809 ALS patients, who were recruited from the Peking University Third Hospital from January 2005 to December 2015. Demographic data and disease-related parameters were collected. Kaplan-Meier curves were used to compare survival time. Cox proportional hazards function and the hazard ratio were used to identify adjusted prognostic predictors.

Results: The results showed that the average annual incidence in Beijing alone was 0.38 cases/100,000 person-years and the mean age of onset was 48.88 ± 11.35 (95% confidence interval [CI]: 48.17–49.85) years. The median survival time from onset to death/tracheostomy was 58.89 ± 33.03 (95% CI: 51.46–63.84) months. In the adjusted Cox proportional hazard model, age of onset, diagnosis delay, rate of disease progression (Amyotrophic Lateral Sclerosis Functional Rating Scale Revised decline [points/month]), and body mass index all had an independent effect on survival in ALS.

Conclusions: Our study provides information on epidemiology, clinical features, and survival factors of patients with ALS in China. These results can be helpful in clinical practice, clinical trial design, and validation of new tools to predict disease progression.

Keywords: Amyotrophic lateral sclerosis; Epidemiology; Clinical features; Occupation; Survival factors

Introduction

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease in adults and is characterized by neurodegeneration of motor neurons in the brain and spinal cord. The prevalence of ALS is 2 to 9 per 100,000 persons overall[1-5] and the incidence rate is 1 to 3 per 100,000 person-years.[5,6] Although approximately 5% to 10% of ALS cases can be attributed to genetic factors, the underlying cause of ALS remains largely unknown[7] and there is no effective treatment for the disease. Genetic and environmental factors may contribute to its development. To find better treatment strategies and obtain better outcomes, survival factors have been increasingly investigated in several studies.[8] Therefore, it is worth exploring the characteristics of survival with ALS in China. The purpose of this study is to provide information on epidemiology, clinical features, and survival factors of patients with ALS in China.

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Methods

Ethical approval

This study was approved by the Institutional Ethics Committee of Peking University Third Hospital (No. IRB00006761-L2010055). All ALS subjects provided written informed consent.

Patients and information collected

This study was a clinic-based prospective cohort study that analyzed information from the ALS patient database of Peking University Third Hospital between January 2005 and December 2015, covering most parts of China. All ALS patients were diagnosed by senior experts according to the El Escorial revised criteria and conformed to the criteria for laboratory supported, probable, or definite cases of ALS.[9] Patients with juvenile ALS, progressive

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muscular atrophy, progressive bulbar paralysis, and primary lateral sclerosis diagnoses were excluded. Patients with additional diagnoses of other neurodegenerative diseases including essential tremor, Parkinson disease, Kennedy's disease, and multiple system atrophy were also excluded. Information on the demographic data and clinical data were recorded, including age of onset, gender, marital status, nationality, residency, education, medical conditions, site of onset (bulbar or limb), body mass index (BMI), diagnostic delay (duration from onset to diagnosis), El Escorial classification at diagnosis, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) score at diagnosis and follow-up months, living environment, occupation, and any known contact with pesticides.[8] Residency was defined as a place where a patient had lived for >10 years.[10] Survival time was defined as the interval between the date of onset and date of death, tracheotomy, and follow-up date. Severity of ALS was assessed by the ALSFRS-R scale. Rate of disease progression (the decline rate for ALSFRS-R score) was calculated as the mean monthly number of point loss from the time of diagnosis to telephone follow-up, calculated in months.

Statistical methods

Comparisons between means were calculated via *t*-test or one-way (or two-way) analysis of variance; comparison between categorical variables was made via χ^2 test. All tests were two-fold. Levene test was used to confirm the equality of variances. Non-normal distribution was assessed with the Kruskal-Wallis test. Survival was calculated from onset to death, tracheostomy, or follow-up date, using the Kaplan-Meier method, and compared with the log-rank test; when more than two ordinal strata were assessed, the linear trend for factor level test was used. No patients were lost to follow-up. Multivariable analysis was performed with the Cox proportional hazards model. $P < 0.050$ was considered significant. Statistical analyses were carried out using the SPSS V.21.0 statistical package (SPSS, Chicago, IL, USA).

Results

The patients who were evaluated at Peking University Third Hospital came from throughout China, including North China (73.36%, most of the patients came from Beijing, 22.78%) and South China (26.64%); the average annual crude incidence of ALS in Beijing is approximately 0.38 cases per 100,000 persons (population data obtained from the National Bureau of Statistics). The non-coastal area to coastal area ratio was 1.54:1 and the urban to rural ratio for the cohort was 2.10:1 (1.05:1 at the end of 2015 in China). Only 103 patients (5.69%) are hereditary and termed familial ALS, whereas the remaining 94.31% are sporadic ALS that constitutes the large majority of cases. Occupations were coded as two categories: farming (including forestry and animal husbandry) and fishery, and others. The ratio was 1:4.76 using these two general categories.

We also collected some occupation-related factors, such as electric shock, toxic chemicals, vibration, and working state (nervous and no). In addition to occupation-related factors, environmental factors are also important (home remodeling, building materials, floor coverings, exposure to pesticides, and pesticide poisoning). The epidemiological data of all ALS patients are shown in Table 1. In our study, farming, forestry, animal husbandry and fishery, female, a low level of education (below senior high school: elementary school), and self-paying medical had a lower BMI ($P < 0.001$, $P < 0.005$, $P < 0.001$, $P < 0.001$) and mean ALSFRS-R score at diagnosis ($P < 0.002$, $P < 0.005$, $P < 0.001$, $P < 0.001$). The patients below senior high school were more often exposed to pesticides, performed farming, forestry, animal husbandry, and/or fishery ($P < 0.007$, $P < 0.001$). Farming, forestry, animal husbandry, and fishery were related to exposure to pesticides and pesticide poisoning ($P < 0.001$, $P < 0.007$). In our study, most ALS patients had been exposed to home remodeling and building materials or floor coverings.

Table 1: The epidemiological data of ALS patients ($n = 1809$).

Factor	Case, *n* (%)
Residency*	
South China	482 (26.64)
North China	1327 (73.36)
Coastal area	712 (39.36)
Non-coastal area	1097 (60.64)
Region	
Urban	1226 (67.77)
Rural	583 (32.23)
FALS	103 (5.69)
Electric shock	144 (7.96)
Toxic chemicals	406 (22.44)
Exposure to pesticides	216 (11.94)
Pesticide poisoning	26 (1.44)
Vibration†	139 (7.68)
Home remodeling‡	1639 (90.60)
Building materials or floor coverings	1526 (84.36)
Working state	
Nervous	488 (26.98)
No	1321 (73.02)
Occupation	
Farming, forestry, animal, husbandry, and fishery	314 (17.36)
Others	495 (82.64)

*Residency: a place where a patient had lived for >10 years. †Vibration: working with vibration. ‡Home remodeling: home remodeling 2 years before the onset of ALS. ALS: Amyotrophic lateral sclerosis; FALS: Familial amyotrophic lateral sclerosis.

Clinical features and demographic data of the samples are summarized in Table 2. The mean age of onset was 48.88 ± 11.35 (95% confidence interval [CI]: 48.17–49.85) years (range 18–99 years). The male to female ratio was 1.87:1. There were 264 (14.59%) patients who had the bulbar-onset form. The mean ALSFRS-R total score of patients at the baseline was 32.07 ± 6.60 and the mean diagnostic delay was 25.17 ± 30.46 (95% CI; 23.95–26.12) months. Median survival time was 58.89 ± 33.03 (95% CI; 51.46–63.84) months. This analysis showed that the probabilities of survival from symptom onset were 34.34% at 3 years and 14.97% at 5 years.

Table 2: Demographic and clinical characteristics of ALS patients ($n = 1809$).

Factor	Case
Gender (female), *n* (%)	631 (34.88)
Marriage (married), *n* (%)	1777 (98.23)
Nationality (the Han nationality), *n* (%)	1729 (95.58)
Education	
≥Senior high school, *n* (%)	735 (40.63)
<Senior high school*, *n* (%)	1074 (59.37)
Medical conditions (self-paying), *n* (%)	1397 (77.22)
Mean age at onset (years), mean (SD)	48.88 (11.35)
Mean diagnostic delay (months), mean (SD)	25.17 (30.46)
Site of onset (bulbar), *n* (%)	264 (14.59)
El Escorial classification at diagnosis, *n* (%)	
Definite	1131 (62.52)
Probable	347 (19.18)
Probable laboratory supported	106 (5.86)
Possible	225 (12.44)
Mean ALSFRS-R score at diagnosis, mean (SD)	32.07 (6.60)
Mean monthly decline of ALSFRS-R, mean (SD)	0.89 (0.81)
Mean BMI at diagnosis, mean (SD)	23.05 (2.67)
Median Survival time (months), mean (SD)	58.89 (33.03)

* Elementary school. ALS: Amyotrophic lateral sclerosis; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; BMI: Body mass index; SD: Standard deviation.

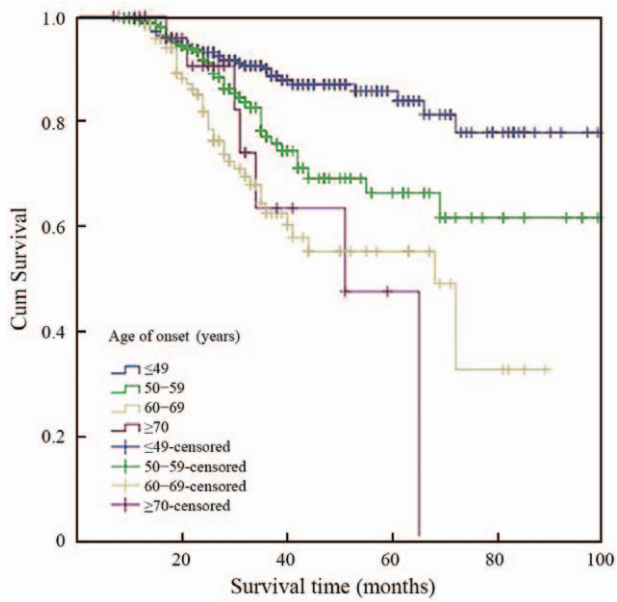

Figure 1: Kaplan-Meier analysis stratified by survival from onset to death/tracheostomy base on age at onset.

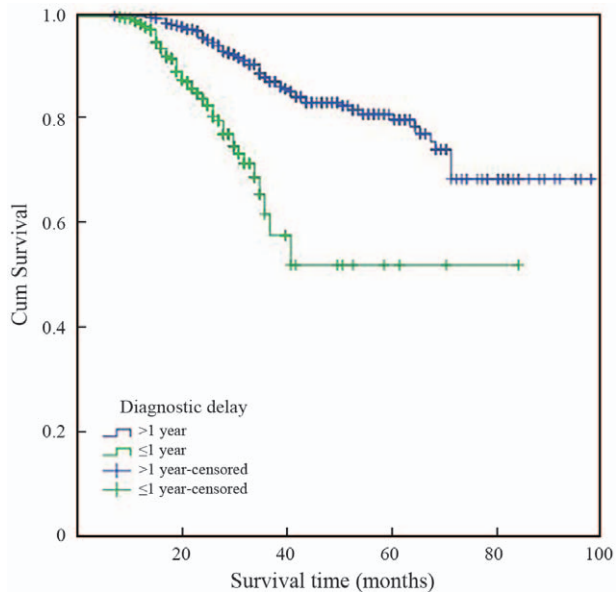

Figure 2: Kaplan-Meier analysis stratified by diagnostic delay, the diagnostic delay >1 year had a longer survival time than ≤1 year.

Kaplan-Meier analysis revealed that factors related to survival from onset to death/tracheostomy were: age at onset [Figure 1], diagnostic delay [Figure 2], site of onset [Figure 3], BMI at diagnosis [Figure 4], mean monthly decline of ALSFRS-R [Figure 5], occupation [Figure 6], and education [Figure 7]. In univariate analyses, age at onset, diagnostic delay, site of onset, BMI, etc are all important factors in predicting survival; they are relevant predictors and require multivariable approach to control their relative effect on prognosis. We separated patients with the age at onset into four groups: "≤49 years," "50 to 59 years," "60 to 69 years," and "≥70 years" for further analysis of disease duration. Likewise, diagnostic delay was divided into two groups: ">1 year" and "≤1 year." Moreover, the site of onset was divided further into two groups: "bulbar" and "spinal." The BMI at diagnosis was also separated into three groups: "<18.5," "18.5 to 25.0," and ">25.0" The mean monthly decline of ALSFRS-R was split into two groups: "≥0.75" and "<0.75." Study participants' occupation was divided into two groups: "farming, forestry, animal husbandry, and fishery" and "others." The demographic of education also was separated into two groups: "<senior high school" and "≥senior high school." Therefore, we performed a multivariate analysis in which the occupation and education were not independent risk factors; the main data of the adjustment using the Cox proportional hazard model are shown in Table 3. In the adjusted Cox proportional hazard model, age of onset, diagnosis delay, rate of disease progression (ALSFRS-R decline [points/month]), and BMI had an independent effect on survival in ALS. Multivariate Cox regression analysis [Table 3] showed that a poorer prognosis was observed with older age at disease onset ($P = 0.012$), shorter diagnostic delay ($P < 0.001$), and a quicker degenerative process ($P = 0.003$). The risk of death among patients aged 60 to 69 years and ≥70 years was approximately 3-fold higher (hazard ratio [HR]: 3.08, $P < 0.001$; HR: 3.41, $P = 0.012$) than that of patients aged ≤49 years. In contrast, the risk of death among patients in the age groups 50 to 59 years did not differ significantly compared with the age group ≤49 years. The diagnostic delay ≤1 year was approximately three-fold higher (HR: 3.43, $P < 0.001$) than >1 year. The risk of death among patients with a BMI <18.5 kg/m^2 was lower than BMI >25 kg/m^2 (HR: 0.36, $P = 0.038$). The ALSFRS-R decline (points/month) <0.75

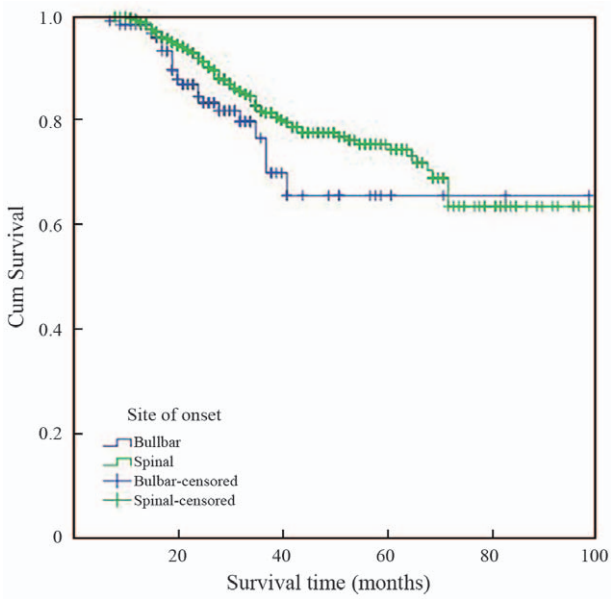

Figure 3: Kaplan-Meier analysis stratified by site of onset of amyotrophic lateral sclerosis patients.

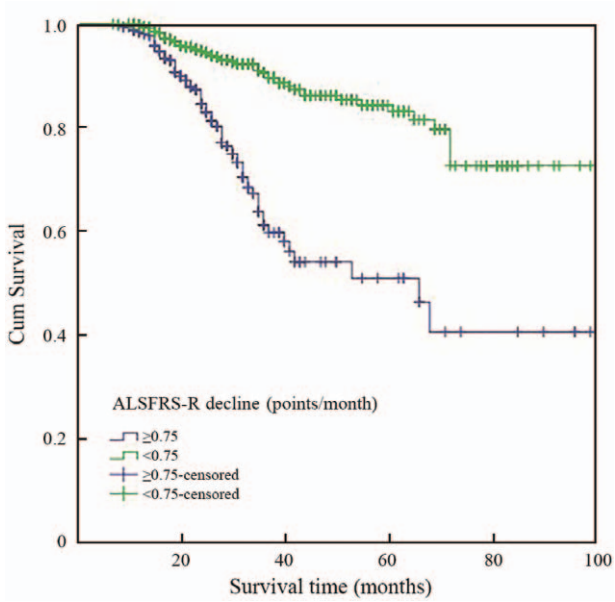

Figure 5: Kaplan-Meier analysis stratified by mean monthly decline of ALSFRS-R. ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale Revised.

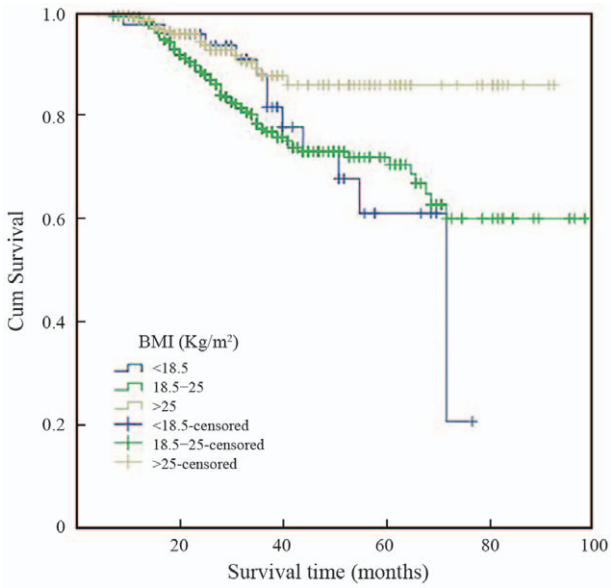

Figure 4: Kaplan-Meier analysis stratified by BMI at diagnosis. BMI: Body mass index.

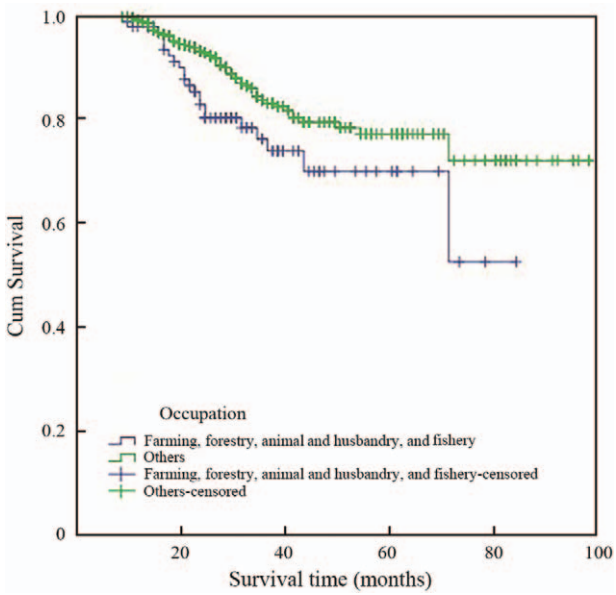

Figure 6: Kaplan-Meier analysis stratified by occupation.

was approximately half than which decline (points/month) ≥0.75 (HR: 0.47, $P = 0.003$).

Discussion

There are few studies on ALS epidemiology and factors predicting survival in the Chinese population. Some ALS researches instead are based on epidemiological and genetic studies of ALS patients from Caucasian populations of European origin. The Chinese are significantly different from Caucasians in terms of ethnic, social, cultural background, and quality of healthcare. Therefore, the epidemiological characteristics of ALS in Chinese people are different from those in other countries. In China, the average annual crude incidence of ALS in Beijing is approximately 0.38 cases per 100,000 persons (population data obtained from the National Bureau of Statistics), lower than that in Japan, Europe, and North America (1.5–2.5 per 100,000 of the population).[1-5] The current study may have missed some undiagnosed cases, which might be one of the reasons for the low incidence of ALS in Beijing. Geographic clusters of individuals with an apparently increased risk of a disease according to residence and region were sought, but no significant variations were observed.

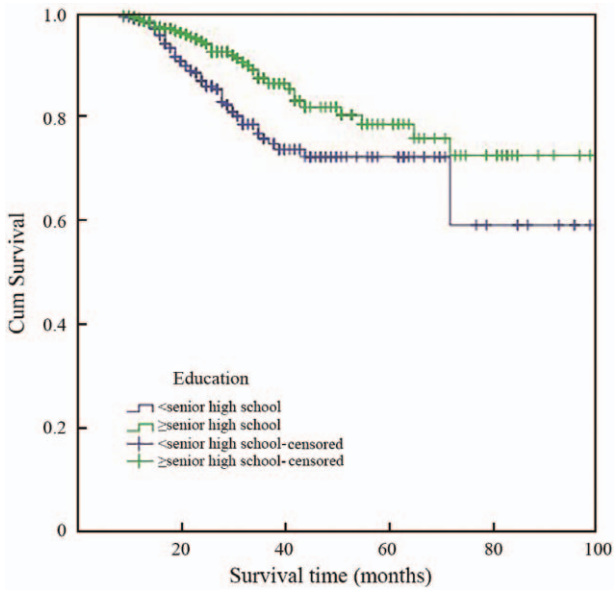

Figure 7: Kaplan-Meier analysis stratified by education.

Table 3: Multivariable model including all cases.

Factor	HR (95% CI)	*P* value
Age at onset, years		
≤49	1	–
50–59	1.70 (0.93–3.09)	0.083
60–69	3.08 (1.64–5.78)	<0.001
70+	3.41 (1.31–8.87)	0.012
Site of onset		
Bulbar	1	–
Spinal	0.74 (0.40–1.38)	0.350
Diagnostic delay		
>1 year	1	–
≤1 year	3.43 (2.01–5.85)	<0.001
ALSFRS-R decline, points/month		
≥0.75	1	–
<0.75	0.47 (0.28–0.77)	0.003
BMI, kg/m^2		
<18.5	1	–
18.5–25	0.51 (0.24–1.08)	0.079
>25	0.36 (0.14–0.94)	0.038
Occupation		
Farming, forestry, animal and husbandry, and fishery	1	–
Others	0.66 (0.36–1.20)	0.172
Education		
<Senior high school	1	–
≥Senior high school	0.62 (0.36–1.06)	0.080

ALS: Amyotrophic lateral sclerosis; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; BMI: Body mass index; CI: Confidence interval; HR: Hazard ratio.

With respect to demographic characteristics, a predominance of male victims was observed; this finding is consistent with previous reports.[11] The mean age of onset in Chinese ALS patients is 48.88 (11.35) years, which is younger than patients from Japan and Europe, which tend to be around 62.1[12] and 62.1 to 66.3 years old,[13] respectively. It has been suggested that age of onset is younger in less developed regions which are more likely to have a higher level of environmental pollution. There were more than five-sixths of ALS patients (85.41%) to have limb onset in the study, which was similar to the previous literature in China,[14] which is also higher than that of Europe and Italy.[15,16] The diagnostic delay 25.17 (standard deviation 30.46) months of ALS in our study is longer than Europe and the United States (12 months),[11] possibly due to differences in health care systems or for the seemingly more aggressive disease phenotype in Europe and the United States. The percentage of familial ALS identified was 5.69%, which is consistent with the 5% to 10% of familial ALS frequently reported in the literature.

These environmental and geographical factors may have effects on ALS development; however, the mechanism of and interaction between these environmental and geographical factors needs further investigation. As regards prognosis, our study confirms the expected role of some well-known factors on ALS survival: age at onset (younger patients surviving longer), diagnostic delay, and mean monthly decline of ALSFRS-R (with shorter diagnostic delay and a quicker degenerative process having a shorter survival).

In our study, the prognostic role of the site of the disease's onset was not confirmed. There is a general consensus that age and diagnostic delay were strong prognostic factors for ALS. Our study found that decreased survival time is associated with increased age, but the exact relationship is unclear and may be related to motor neuron damage during aging. At the same time, we found that the shorter the diagnostic delay, the shorter the survival period. In our cohort, BMI also had an impact on ALS survival[17-19]; a higher BMI may be associated with a longer survival, because it is associated with higher baseline energy reserves, and with a lower degree of hypermetabolism among ALS subjects.

In our current study, the Kaplan-Meier analysis revealed that there was a significant association among education, occupation, and survival. However, the multivariate analysis showed that they were not independent risk factors. There has been less research performed on occupation and education and this needs further investigation.[20] Our study found no relationship between El Escorial classification at diagnosis and survival, which is inconsistent with previous studies.[14,21]

Nevertheless, there are several limitations of the present study which should be noted. First, we excluded other spectra of possible ALS populations. Second, other factors, such as cognitive status and tracheostomy, may also be implicated as prognostic predictors, but we did not investigate these factors as part of the present study.

This study provides information on epidemiology and survival factors for Chinese ALS patients. Although the age of onset is earlier than that of Caucasian patients, survival factors, including age of onset, diagnostic delay, and

ALSFRS-R decline (points/month), are similar to those in Caucasian ALS populations.

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Conflicts of interest

None.

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