Prognostic factors of key outcomes for motor neuron disease in a multiracial Asian population

Xiao Deng (✉ deng.xiao@sgh.com.sg)

National Neuroscience Institute <https://orcid.org/0000-0003-4489-9663>

Ying Hao

singapore general hospital

Bin Xiao

National Neuroscience Institute

Eng-King Tan

National Neuroscience Institute

Yew-Long Lo

National Neuroscience Institute

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Abstract

Objective To determine potential prognostic factors for survival, need for feeding and ventilation support in motor neuron diseases (MND) patients in a multi-racial Asian population. **Methods** One hundred and four MND patients from the Singapore General Hospital (SGH) between January 2004 and December 2017 were reviewed. All relevant clinical data, demographic information were collected. Kaplan-Meier and cox regression model were performed to identify potential prognostic factors for crucial outcomes (survival, need for feeding support and ventilation support). **Results** Mean age of onset was 59.54 ± 10.91 years, Mean age of onset in Malays was significantly younger than that of other ethnic groups (Malay: 54.18 ± 12.95 years; Non-Malay: 60.39 ± 10.38 years, $p=0.035$). Fifty six of the male and 33 of the female were diagnosed with ALS (90.3% vs 78.6% $p=0.048$). Mean overall survival duration from symptom onset was significantly longer in female than male patients (female: 39.2 ± 29.04 months; male: 29.4 ± 24.06 months, $P=0.03$). Bulbar onset was a significant risk predictor for both the need of feeding support ($HR=3.87$, $p<0.001$) and respiratory aid ($HR=3.43$, $p=0.01$). A longer interval from symptom onset to diagnosis was correlated with a longer time to the need for feeding support ($HR=0.94$, $p=0.002$) and respiratory aid ($HR=0.9$, $p=0.009$). In the univariable cox regression analysis, need for respiratory support ($HR=2.1$, $p=0.03$) indicated poor survival outcome significantly, while MND subtypes other than ALS ($HR=0.25$, $p=0.008$) and slower disease progression, including longer duration from symptom onset to second symptom ($HR=0.97$, $p=0.005$), to feeding support ($HR=0.95$, $p<0.001$), to ventilation support ($HR=0.96$, $p=0.004$), significantly suggested lower risk of death. In the multivariable cox regression model, bulbar onset ($aHR=5.28$, $p=0.035$) correlated with poor survival outcome while longer duration from onset to second symptom ($aHR=0.96$, $P=0.037$) indicated better survival. **Conclusions** Bulbar onset was a significant risk predictor for survival, need of feeding support and ventilation aid. Slower disease progression correlated with better outcomes. Age of onset may differ among ethnic groups. Male patients are more likely to develop ALS and have shorter survival duration.

Introduction

Motor neuron diseases (MND) are a group of neurodegenerative disorders which include amyotrophic lateral sclerosis (ALS), progressive bulbar palsy (PBP), primary lateral sclerosis (PLS) and progressive muscular atrophy (PMA). ALS, the most common motor neuron disease, is clinically characterized by progressive weakness and amyotrophy due to selective loss of both lower (LMN) and upper motor neurons (UMN), leading to significant disability and death. The median survival of ALS ranged from 20 to 48 months [1]. Annual worldwide prevalence of ALS is estimated to be 4.48 per 100 000 individuals [2], and the standardized worldwide ALS incidence rate is 1.68 per 100 000 person-years [3], varying with geography, sex, and age. MND is caused by genetic and environmental factors. Relatively lower incidence and mortality rates of ALS were previously observed in Asians compared to Caucasian population [4]. It is therefore of interest to explore ethnic differences of disease presentation and factors influencing progression among MND patients in Singapore, with a mixed Asian population of varied ethnic, social and cultural backgrounds.

In the most advanced stages, ALS patients will develop symptoms of dyspnea and dysphagia[5].

Dysphagia leads to malnutrition, a major cause of morbidity and mortality in ALS. Weight loss and malnutrition are common presentations and predict a poor outcome in ALS [6].Respiratory failure is the most common cause of death in ALS[7], and the presence of respiratory muscle weakness serves as a major poor predictor for survival [1].We have reported for the first time that the need of feeding support was significantly associated with assisted ventilation[8]. There is lack of information about prognostic factors related to dysphagia and respiratory failure of MND subjects in the Asian setting. This prompted us to investigate the potential predictive factors associated with these two crucial outcomes in MND.

Poor prognostic factors for survival also include bulbar onset, older age of onset, shorter interval from symptom onset to diagnosis and rapid disease progression [1, 9].However, and knowledge of prognostic factors related to ALS survival remains scarce in Southeast Asia. The current study, in addition, sought to identify the possible predictors associated to MND survival in this region.

Methods

Study population

We recruited patients with the diagnosis of MND from the Singapore General Hospital (SGH), a tertiary referral center from January 2004 and December 2017.The study has been approved by Sing Health Centralized Institutional Review Board (CIRB Ref: 2014/685/A) and all methods were performed in accordance with the approved guidelines and regulations.

We diagnosed MND according to clinical findings of a progressive pure motor disorder with muscle weakness, atrophy and fasciculation, without sensory defects and sphincter disturbances. We utilized nerve conduction study and electromyography to support the diagnosis. The classification of clinically definite, probable or possible ALS was made based on the El Escorial criteria[10]. In particular, we excluded pseudo bulbar palsy of vascular origin, multifocal motor neuropathy, spinal muscular atrophy, and paraneoplastic disease from our patient sample.

Data collection

We reviewed all the medical records of patients with the diagnosis of MND in SGH from January 2004 and December 2017. All the relevant clinical data including demographic information, disease milestones, and treatments were collected retrospectively. In terms of mortality, family member were contacted if information was not really available from case records.

We estimated the speed of disease progression based on the interval from symptom onset to the next milestone, such as second symptom, need for feeding support, need for respiratory support or death. Shorter durations of the above intervals indicate rapid disease progression and longer durations reflect slower disease progression.

Statistical analysis

The R version 3.4.2 (www.r-project.org) was employed to perform all statistical analyses. Frequency together with proportion was reported for categorical data, while mean with standard deviation (SD) was reported for continuous variables. Fisher's exact test was carried out to compare the categorical variables between different groups, while Student's T-test or Mann-Whitney U test was performed to compare continuous variables, where applicable.

Kaplan-Meier analysis and univariable cox regression were performed to identify potential factors and covariates correlating with the crucial outcomes (survival, need for feeding support and ventilation support). All identified candidate factors or covariates were used to build the final multivariable model for survival.

Results

Subject characteristics and ethnic distribution

Overall, we have recruited 104 patients in this retrospective study, of which 52 subjects (50%) were deceased. Our study included 62 (59.6%) males and 42(40.4 %) females. Male to female ratio was 1.48:1. The ethnic distribution of all patients in our study was as follow: 77 Chinese (74.0%), 14 Malay (13.5%), 7 Indian (6.7%) and 6 of other races (5.8%).

Clinical features

Diagnosis Subtype

We further classified MND patients into 4 subgroups: ALS, PBP, PLS and PMA based on the involvement of upper or/and lower motor neurons. Of the 104cases reviewed, 89 (85.6%) patients were diagnosed with ALS. Five were classified as PBP, 5 as PMA and the remaining 5 as PLS. Among 89 diagnosed ALS, 56 (90.3%) were males while 33(78.6%) were females, this difference was significant ($p=0.048$). (Table 1)

Onset location

Onset location can be classified into spinal onset (presenting mainly weakness over limbs) and bulbar onset (mainly weakness of bulbar muscles). Twenty four patients (23.1 %) had bulbar onset, while 80 patients (76.9%) had spinal onset. Bulbar onset patients have shorter intervals from symptoms onset to diagnosis comparing to spinal onset patients. However, the difference was not significant (bulbar onset: 7 ± 5 months; spinal onset: 11 ± 9 months, $p=0.071$). There were no significant differences between bulbar and spinal onset group in terms of gender, ethnicity, and age of onset.

Onset age

The mean age of onset in our study was 59.5 ± 10.9 years. There was no significant difference between the genders (male: 57.7 ± 11.4 years; female: 60.8 ± 10.4 years, $p=0.134$). Mean age of onset in Malays was

significantly younger than that in the other ethnic groups (Malay: 54.2 ± 13 years; Non-Malay: 60.4 ± 10.4 years, $p=0.035$).

Diagnosis age

The mean age of diagnosis was 59.9 ± 11.5 years. Mean duration from symptoms onset to diagnosis in our study was 10 ± 8.4 months. This duration did not differ significantly among different ethnic groups (Chinese: 10.4 ± 8.9 months; Malay: 8.1 ± 7.3 months; Indian: 11.5 ± 7.7 months, $p=0.614$). Neither was there significant gender difference (male: 9.0 ± 7 months; female: 11 ± 10 months, $p=0.824$).

Management

With regard to the management, 12.5% of the patients used Riluzole, 52.9% needed feeding support, and 34.6% required respiratory aid. The mean overall survival duration was 33.4 ± 26.5 months from symptom onset and 23.4 ± 25.0 months from diagnosis. The mean interval from symptom onset to feeding support was 22.0 ± 18.1 months; the mean interval from symptom onset to ventilation aid was 20.2 ± 15.7 months. Male patients had significantly shorter survival duration than female (male: 29.4 ± 24.1 months; female: 39.2 ± 29.0 months, $p=0.03$). (Table 1)

For dysphagia and dyspnea

Bulbar onset was a significant risk predictor for both the need of feeding support ($HR=3.87$, $p<0.001$) and respiratory aid ($HR=3.43$, $p=0.01$). We found that a longer interval from symptom onset to diagnosis was correlated with a longer time to the need for feeding support ($HR=0.94$, $p=0.002$) and respiratory aid ($HR=0.9$, $p=0.009$). (Table 2b and 2c)

For survival

In the univariable cox regression analysis, the need of respiratory support ($HR=2.1$, $p=0.03$) indicated poor survival outcome significantly. In contrast, MND subtypes other than ALS ($HR=0.25$, $p=0.008$) (Figure 2) and slower disease progression, which includes longer duration from symptom onset to second symptom ($HR=0.97$, $p=0.005$), to feeding support ($HR=0.95$, $p<0.001$), to ventilation support ($HR=0.96$, $p=0.004$), suggesting better survival outcome. (Table 2a) By using multivariable cox regression model, we found that bulbar onset ($aHR=5.28$, $p=0.035$) (Figure 1) correlated with poor survival outcome while longer duration from onset symptom to second symptom ($aHR=0.96$, $P=0.037$) indicated better survival for our MND patients. (Table 3)

Discussion

To our knowledge, this is the first study to investigate the prognostic factors of survival and key outcomes (need for feeding support and ventilation support) in MND in South-east Asia. We found that bulbar onset and rapid disease progression were significant risk predictors for survival, which were consistent with the previous studies in other countries [1, 9]. Notably, our study indicated that the ALS

diagnosis subtype predicted worse survival outcome comparing to other MND phenotypes. It was reported that PBP phenotype of pure bulbar onset had rapid disease progression and shorter survival time than the other MND subsets [11, 12]. However, Fan[13] and colleagues distinguished Isolated Bulbar Palsy (IBP) as another MND variant, which is often confused with PBP. IBP is characterized by the predominance of female patients, pure LMN bulbar signs, older age of onset, a relatively benign prognosis and longer survival compared to PBP. The PBP patients in our study may be similar to the IBP category as they are mainly female (80%) and they had better survival outcome. Currently, IBP is not a well understood clinical entity. It is important to distinguish IBP from PBP since it can provide useful strategies in terms of prognosis, patient care, and even future treatment options.

For the first time, we reported that bulbar onset and shorter interval from symptom onset to diagnosis were the significant prognostic factors for the need of feeding and ventilation support. The finding could help identify high risk patients who may require more frequent follow-up and closer monitoring.

It is of value to investigate the clinical pattern of MND among different racial population as the incidence rate, clinical features and disease prognosis of MND vary greatly. Singapore is a multi-ethnic Asian country where the main ethnic groups include Chinese, Malay and Indian. The mean age of onset of our cohort was 59.5 ± 10.9 years, which was comparable with the other Asian studies such as in Japan and South Korea [14, 15], but older than that reported in Indian and China [16, 17], which ranged from 46.2 to 54.3 years old. This suggests that the socioeconomic and environmental factors may play roles in the etiology of MND. There were inconclusive results about the survival of Indian patients. Goh [18] reported that Indian patient had shorter survival duration, which was in contrast to another Indian study showing a slower disease course [16]. In our study, the mean survival from symptoms onset of Indian patients was mildly but not significantly shorter than that of Chinese patients (30.2 months vs. 35.8months). We found that the mean onset age of Malay patients was 54.2 ± 13.0 , significantly younger than the other races, which was consistent with a similar study performed in Malaysia [18]. Currently more than 20 genes have been associated with ALS[19].Our finding may reflect differential genetic backgrounds of ALS patients of varied races.

The male to female ratio was 1.48 in our study, which is comparable to that of Caucasian patients, showing a higher male to female ratio between 1.5-1.7[20]. Most studies were not conclusive for gender effect on ALS outcome. Recently, Chen reported that female gender or Flail arm syndrome phenotype of ALS may have a better prognosis in Chinese populations[21].However, Studies from America and Scotland reported that females had a significantly shorter survival in Caucasians[22, 23]. Our study revealed that the survival duration from symptom onset was significantly shorter in male patients, which is consistent with the Chinese study [21]. Again, this finding may suggest a unique pattern of Asian ALS. It is also notable that lower limb onset ALS has a higher percentage in females comparing to males (58.1% vs. 40.8%) in our study. It has been reported that lower limb-onset ALS, likely have a slower disease progression. It would be of importance to confirm the better survival pattern of females and its potential correlation with lower limb-onset ALS in Asian population with a larger sample size than that in our current study.

In summary, for the first time we reported that bulbar onset and shorter disease interval from symptom onset to diagnosis were the risk predictors for the need of feeding and ventilation support. In addition, we found that bulbar onset, faster disease progression, the need for ventilation support and ALS subtype indicated worse survival outcome. Furthermore, we reported a novel finding that male patients were more likely to develop ALS and their survival duration from symptom onset to death were significantly shorter than females in an Asian cohort.

Declaration

1. Ethics approval and consent to participate

Our study was approved by Sing Health Centralized Institutional Review Board (CIRB Ref: 2014/685/A) and was carried out in accordance with the approved guidelines.

2. Consent for publication

Not applicable

3. Availability of data and materials

The datasets during the current study available from the corresponding author on reasonable request.

4. Competing interests

The authors declare no competing interests.

5. Funding

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6. Authors' contributions

Y.L. , X.D. designed the study. Y.L. , X.D. and B.X. wrote the main manuscript text. X.D. prepared all the tables. X.D., Y.H. conducted the statistical analysis. E.T and Y.L. and B.X. gave revision of the manuscript. X.D. , B.X. , Y.L. , E.T. , conducted the research project. All authors read and approved the final manuscript

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References

1. Chio A, Logroscino G, Hardiman O, Swingler R, Mitchell D, Beghi E, Traynor BG: Prognostic factors in ALS: A critical review. *Amyotroph Lateral Scler* 2009, 10(5-6):310-323.

2. Chio A, Logroscino G, Traynor BJ, Collins J, Simeone JC, Goldstein LA, White LA: Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. *Neuroepidemiology* 2013, 41(2):118-130.
3. Marin B, Boumediene F, Logroscino G, Couratier P, Babron MC, Leutenegger AL, Copetti M, Preux PM, Beghi E: Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. *Int J Epidemiol* 2017, 46(1):57-74.
4. Cronin S, Hardiman O, Traynor BJ: Ethnic variation in the incidence of ALS: a systematic review. *Neurology* 2007, 68(13):1002-1007.
5. Leigh PN, Abrahams S, Al-Chalabi A, Ampong MA, Goldstein LH, Johnson J, Lyall R, Moxham J, Mustfa N, Rio A *et al*: The management of motor neurone disease. *J Neurol Neurosurg Psychiatry* 2003, 74 Suppl 4:iv32-iv47.
6. Limousin N, Blasco H, Corcia P, Gordon PH, De Toffol B, Andres C, Praline J: Malnutrition at the time of diagnosis is associated with a shorter disease duration in ALS. *J Neurol Sci* 2010, 297(1-2):36-39.
7. Corcia P, Meininger V: Management of amyotrophic lateral sclerosis. *Drugs* 2008, 68(8):1037-1048.
8. Deng X, Hao Y, Xiao B, Tan EK, Lo YL: Risk factors for respiratory failure of motor neuron disease in a multiracial Asian population. *J Clin Neurosci* 2017, 39:137-141.
9. Couratier P, Corcia P, Lautrette G, Nicol M, Preux PM, Marin B: Epidemiology of amyotrophic lateral sclerosis: A review of literature. *Rev Neurol (Paris)* 2016, 172(1):37-45.
10. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron D: El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotrophic lateral sclerosis and other motor neuron disorders : official publication of the World Federation of Neurology, Research Group on Motor Neuron Diseases* 2000, 1(5):293-299.
11. 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(7):740-746.
12. Argyriou AA, Polychronopoulos P, Papapetropoulos S, Ellul J, Andriopoulos I, Katsoulas G, Salakou S, Chroni E: Clinical and epidemiological features of motor neuron disease in south-western Greece. *Acta Neurol Scand* 2005, 111(2):108-113.
13. Zhang HG, Chen L, Tang L, Zhang N, Fan DS: Clinical Features of Isolated Bulbar Palsy of Amyotrophic Lateral Sclerosis in Chinese Population. *Chin Med J (Engl)* 2017, 130(15):1768-1772.
14. Bae JS, Hong YH, Baek W, Sohn EH, Cho JY, Kim BJ, Kim SH: Current status of the diagnosis and management of amyotrophic lateral sclerosis in Korea: a multi-center cross-sectional study. *J Clin Neurol* 2012, 8(4):293-300.

15. Watanabe H, Atsuta N, Nakamura R, Hirakawa A, Ito M, Senda J, Katsuno M, Izumi Y, Morita M, Tomiyama H *et al*: Factors affecting longitudinal functional decline and survival in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degener* 2015, 16(3-4):230-236.
16. Nalini A, Thennarasu K, Gourie-Devi M, Shenoy S, Kulshreshtha D: Clinical characteristics and survival pattern of 1,153 patients with amyotrophic lateral sclerosis: experience over 30 years from India. *Journal of the neurological sciences* 2008, 272(1-2):60-70.
17. Fang DF, Zhang SS, Guo XY, Zeng Y, Yang Y, Zhou D, Shang HF: Clinical and genetic features of patients with sporadic amyotrophic lateral sclerosis in south-west China. *Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases* 2009, 10(5-6):350-354.
18. Goh KJ, Tian S, Shahrizaila N, Ng CW, Tan CT: Survival and prognostic factors of motor neuron disease in a multi-ethnic Asian population. *Amyotroph Lateral Scler* 2011, 12(2):124-129.
19. Al-Chalabi A, Hardiman O: The epidemiology of ALS: a conspiracy of genes, environment and time. *Nat Rev Neurol* 2013, 9(11):617-628.
20. Marin B, Logroscino G, Boumediene F, Labrunie A, Couratier P, Babron MC, Leutenegger AL, Preux PM, Beghi E: Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin. *Eur J Epidemiol* 2016, 31(3):229-245.
21. Chen L, Zhang B, Chen R, Tang L, Liu R, Yang Y, Liu X, Ye S, Zhan S, Fan D: Natural history and clinical features of sporadic amyotrophic lateral sclerosis in China. *J Neurol Neurosurg Psychiatry* 2015, 86(10):1075-1081.
22. 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(6):339-346.
23. 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(5):813-819.

Tables

Table 1: Demographics of patients and comparison by gender

Variable	Total(N=104)	Male(N=62)	Female(N=42)	p-value
Onset Age(years)	59.54 ±10.91	57.71±11.44	60.81±10.43	0.134
Duration from onset to diagnosis(months)	10±8	9 ±7	11±10	0.824
Duration from first to second symptom (months)	22.3±22.0	19.0±17.1	25.0±27.1	0.347
Duration from onset to feeding support(months)	22.0±18.1	23.1 ± 17.0	21.0±20.3	0.832
Duration from onset to ventilation support(months)	20.2 ±15.7	23.3 ±18.2	19.1±14.0	0.435
survival duration from onset(months)	33.4±26.0	29.38 ±24.1	39.22 ±29.0	0.030
survival duration from diagnosis(months)	23.4±25.0	28.31±28.1	20.15±22.4	0.068
Diagnosis subtypes (%)				0.048
Amyotrophic Lateral Sclerosis(ALS)	89 (85.6)	33 (78.6)	56 (90.3)	
Progressive bulbar palsy(PBP)	5 (4.8)	1 (1.6)	4(9.5)	
Primary lateral sclerosis(PLS)	5 (4.8)	1 (1.6)	4(9.5)	
Progressive muscular atrophy(PMA)	5 (4.8)	4 (6.5)	1(2.4)	
Riluzole use (%)	13 (12.5)	7 (11.3)	6 (14.3)	1
Feeding support (%)	55 (52.9)	32 (51.6)	23 (54.8)	0.758
Respiratory support (%)	36 (34.6)	21 (33.9)	15 (35.7)	0.964
Onset location (%)				0.702
Bulbar onset	24 (23.1)	11 (26.2)	13 (21)	
Spinal onset	80 (76.9)	31 (73.8)	49 (79)	
Ethnicity (%)				
Chinese	77 (74)			0.067
Malay	14 (13.5)			
Indian	7 (6.7)			
Others	6 (5.8)			

Abbreviations: Duration from first to second symptom: interval from onset to next different symptom involved, e.g. from limb weakness (in a different muscle group in the same limb or spread to a different limb) to dysarthria, dysphagia, spasticity, excessive yawning or fasciculation.

Table2a: Univariate cox regression analysis for survival

Variables significantly affecting survival	Total(N=104)	HR	95% CI	p-value
Need for Respiratory support (%)	36 (34.6)	2.10	(1.07, 4.09)	0.03
Non-ALS phenotypes (%)	15 (14.4)	0.25	(0.09, 0.69)	0.008
Duration from first to second symptom (months)	21.7±22	0.97	(0.94, 0.99)	0.005
Duration from onset to diagnosis(months)	10±8.4	0.96	(0.93, 1)	0.046
Duration from onset to feeding support(months)	22 ±18.1	0.95	(0.93, 0.98)	< 0.001
Duration from onset to ventilation support(months)	21.1±16.1	0.96	(0.93, 0.99)	0.004

Abbreviations: HR: hazard ratio; 95% CI: 95% Confidence Interval;

Table2b: Univariate cox regression analysis for feeding support

Variables significantly affecting need for feeding support	Total(N=96)	HR	95% CI	p-value
Spinal onset (%)	73 (76)	Reference	Reference	Reference
Bulbar onset (%)	23 (24)	3.87	(1.96, 7.62)	< 0.001
Duration from first to second symptom (months)	21.7±22.3	0.89	(0.83, 0.94)	< 0.001
Duration from onset to diagnosis(months)	9.9±8.5	0.94	(0.91, 0.98)	0.002

Abbreviations: HR: hazard ratio; 95% CI: 95% Confidence Interval;

Table2c: Univariate cox regression analysis for ventilation support

variables significantly affecting need for ventilation support	Total(N=85)	HR	95% CI	p-value
Spinal onset(%)	66 (77.6)	Reference	Reference	Reference
Bulbar onset(%)	19 (22.4)	3.43	(1.34, 8.77)	0.01
Duration from first to second symptom (months)	21±22.4	0.85	(0.77, 0.95)	0.004
Duration from onset to diagnosis(months)	9.7±8.3	0.9	(0.82, 0.97)	0.009

Abbreviations: HR: hazard ratio; 95% CI: 95% Confidence Interval;

Table3: Multivariable cox regression model for survival

Variable	aHR	95%CI	p value
Bulbar onset	5.28	(1.13, 24.92)	0.035
Need for feeding support	4.25	(0.72, 25.09)	0.11
Need for respiratory support	1.04	(0.18, 6.05)	0.968
Duration from first to second symptom	0.96	(0.93, 1)	0.037

Abbreviations: aHR: adjusted hazard ratio; 95% CI: 95% Confidence Interval;

Figures

Figure 1

Figure 2

Kaplan-Meier survival plots by onset place and diagnosis subtype