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# Clinical characteristic and prognosis of amyotrophic lateral sclerosis in a cohort of Thai patients

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### *Abstract*

*Background & Objective:* Clinical course and prognosis in amyotrophic lateral sclerosis (ALS) patients were highly variable. The information in the Thai population is still lacking. This study aimed to determine the clinical association with disease progression and prognostic factors in ALS in Thailand. *Methods:* This prospective cohort study evaluated 62 patients who has a diagnosis of ALS and followed up at Neurological Institute of Thailand between January 2014 and December 2018. These patients were classified into an alive group and a deceased group. The demographics, clinical characteristics, disease-related severity, and prognosis were analyzed. *Results:* Of the included patients, there were 40 male and 22 female, the median age at onset was 53.2 years. The median diagnosis time was 13.1 months and median follow-up duration was 18.5 months; 72.6% of patients presented with spinal onset ALS, and 27.4% with bulbar-onset. There were 20 deaths during follow-up, and the median survival time in the deceased cases was 14 months. Worse prognosis factors were bulbar symptoms at onset and low amyotrophic lateral sclerosis functional rating scale (ALSFRS) at diagnosis.
*Conclusion:* The factors associated with lower survival in ALS patients were bulbar symptoms at onset and low ALSFRS at diagnosis.

*Keywords:* Motor neuron disease (MND), amyotrophic lateral sclerosis (ALS), predicting prognosis, assessment of disease progression

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive muscle paralysis reflecting degeneration of motor neurons in the primary motor cortex, brainstem, and spinal cord leading to severe disability and death.[1] The rate of disease progression among patients was highly variable. Disease duration from onset to death varied from a few months to more than 10 years.[2]

The prevalence and incidence of ALS among Asian countries are also varies. The incidence was 0.5 per 100,000 person-years in Taiwan and 2.2 per 100,000 people person-years in Japan.[3,4] The prevalence was 1.97 per 100,000 in Taiwan and 9.9 per 100,000 in Japan.[3,4] The male: female ratio was 1.27 to 2.9 :1.[5-10] The mean age of disease onset was 49.8 to 61.2 years.[5,7-11] The most common phenotype was limb onset.[8,10,11] Previous study in Thailand showed that, among Thai ALS patients, male gender was predominant with a mean age of onset of 53.2 to 60.1 years old.[12,13] The average time from onset to diagnosis was 19.8 months; 56% of Thai ALS was distal upper limb onset, 24% was lower limb onset and 20% was bulbar onset. At the time of diagnosis, mean modified Ranking Scale (mRS) was 2.3, and mean amyotrophic lateral sclerosis functional rating scale (ALSFRS) was 26.4 points. However, the data on long-term outcome of Thai ALS patients was not available.

Previous population-based ALS registries identified factors predicting early death as advanced age, short interval between symptom onset and first diagnosis, the rapid decline of body weight before diagnosis, advanced functional impairment, and bulbar onset patients.[2,14-17] In previous studies, ALS outcome and prognosis were significantly related to the decline of ALSFRS[18] and ALSFRS score at presentation.[19] Similarly, the progression rate of ALSFRS was strongly related to survival.[20]

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The primary goal of the present study was to determine the clinical characteristics of Thai ALS patients. The secondary goal was to determine the prognostic factors of these patients.

## METHODS

A prospective study was conducted in the setting of a referral hospital in Thailand. Enrolled participants were from the outpatient and inpatient departments of the Neurological Institute of Thailand between January 1st, 2014, and December 31st, 2018. The inclusion criteria included patients diagnosed with ALS according to Revised El Escorial criteria[21], who had been followed up at our institute. All patients were older than 18 years old. Patients with other types of motor neuron disease were excluded. The medical records and data from the ALS registry were reviewed to assess demographic, and clinical data including gender, age at onset, body mass index (BMI) at diagnosis, disease duration before diagnosis, first symptom at onset, diagnosis classification according to the Revised El Escorial criteria[21], amyotrophic lateral sclerosis functional rating scale (ALSFRS) at diagnosis[22], respirator usage, follow up duration, disease duration before respiratory failure, disease duration before death, nerve conduction studies and electrodiagnostic features including a summation of compound muscle action potential (summation CMAP).[23] Current patient status including alive, deceased or ALSFR scale were collected by telephone interviewing.

The present study was approved by the Neurological Institute of Thailand ethic committee.

The patients were divided into an alive group and a deceased group. The results were presented as frequencies and percentages for categorical variables and median/mean for continuous variables. Those two groups were compared using $\chi^2$ and Fisher's exact test. All statistical analyses were done by using SPSS 16.0 for Windows and p values <0.05 were considered statistically significant.

## RESULTS

A total of 62 ALS patients were followed- up in the ALS clinic between January 1st, 2014, and December 31st, 2018 at the Neurological Institute of Thailand. The demographic and clinical characteristics are shown in Table 1. The male: female ratio was 1.8:1. Median age at onset was 53.2 years (interquartile (IQ) range 45.8-59.3 years). The time to diagnosis was 13.1 months (IQ range 6.1-25.2 months). Forty-two patients (68%) were alive and 20 patients (32%) were deceased at the last evaluation. According to ALS classification based on Revised El Escorial

**Table 1: The demographics and clinical characteristics of Thai amyotrophic lateral sclerosis patients**

| Parameter | Total (n = 62) | Alive group (n = 42) | Deceased group (n = 20) | p-value |
|---|---|---|---|---|
| Sex (M: F) | 1.8:1 | 2.2:1 | 1.2: 1 | 0.283 |
| BMI (kg/m$^2$; median, IQ25,75) | 22.4 (19.4, 25.0) | 22.3 (19.4, 25.0) | 22.6 (19.4, 25.1) | 0.583 |
| Age at symptom onset (years-old; median, IQ25,75) | 53.2 (45.8, 59.3) | 53.3 (45.0, 59.3) | 54.5 (48.5, 59.8) | 0.598 |
| Diagnosis time (month; median, IQ25,75) | 13.1 (6.1, 25.2) | 13.1 (7.3, 29.5) | 11.2 (5.0, 20.6) | 0.470 |
| Follow up duration (month; median, IQ25,75) | 18.5 (12.0, 24.0) | 24 (12.0, 27.0) | 14 (12.0, 24.0) | 0.514 |
| ALS phenotype (%) | | | | |
| -Bulbar weakness | 27.4 | 16.7 | 50 | **0.023** |
| -Upper limb weakness | 45.2 | 52.3 | 30 | |
| -Lower limb weakness | 27.4 | 31 | 20 | |
| Sensory symptom (%) | 3 (3%) | 2 (4.8%) | 1 (5%) | 1.000 |
| Diagnosis classification (El Escorial criteria; %) | | | | |
| -Definite ALS | 53.2 | 45.2 | 70 | 0.307 |
| -Probable ALS | 19.4 | 23.8 | 10 | |
| -Probable ALS with laboratory support | 24.2 | 26.2 | 20 | |
| -Possible ALS | 3.2 | 4.8 | 0 | |

criteria, 33 patients (53.2%) were definite ALS, 12 patients (19.4%) were probable ALS, 15 patients (24.2%) were probable ALS with laboratory support, and 2 patients (3.2%) were possible ALS. The median disease duration before respiratory failure was 13 months (IQ range 6 -18 months). In the deceased group, median survival time was 15 months (IQ range 9.5-29.5 months) and median follow-up duration was 24 months (IQ range 12-27 months) in the alive group. There were no significant differences in baseline demographic data including age, gender, age at onset, BMI, ALS classification, diagnostic time, and disease duration before developing respiratory failure between the two groups. Most of our patients did not receive riluzole, therefore the information regarding this was not available in the present study.

The causes of death encompassed respiratory failure due to weakness of breathing muscle (72%), pneumonia (18%), committed suicide (5%; only 1case) and the cause of death of the other patient could not be determined (5%).

Patients in the deceased group had more bulbar onset (50% vs 16.7%, p = 0.023), lower total score of ALSFRS at diagnosis (18.5 vs 32.5 points, p = 0.001), lower bulbar function score (5.4 vs 8.6 points, p = 0.001), lower fine motor function score (2.0 vs 5.5 points, p = 0.001), lower gross motor function score (1.0 vs 6.5 points, p = 0.001), and lower respiratory function score (5.3 vs 6.2 points, p = 0.030), compared to the alive group. The summation of CMAP at diagnosis in the deceased group was lower than the alive group, but did not reach statistical significance (16.0 vs 17.3 mV, p = 0.072). Disease duration before respiratory failure was slightly longer in the deceased group, but did not reach statistical significance (12 vs 14 months, p = 0.660). The number of patients with invasive respiratory usage were not different between both groups.

In multivariate Cox regression analysis, factors associated with worse prognosis were bulbar weakness as the first symptom (p = 0.022, 95% CI; 0.013-0.708) and low ALSFRS at onset (p = 0.038, 95% CI; 0.631- 0.987) (Table 2).

## DISCUSSION

In our cohort, we focused on the demographics, clinical characteristics including disease duration, functional scale including ALSFRS, and long-term outcome in 62 Thai ALS patients at a single referral center. The M: F ratio was 1.8:1, median age at onset was 53.2 years and the most common phenotype was upper limb onset (45.2%). These results were not different from the previous studies in Thailand[12,13], and other Asian and Western countries.[3-11,24,25] The diagnostic time in our cohort was 13.1 months, which was similar to previous studies in Western and in Oriental populations.[24,26]

In our cohort, gender, age at onset, and diagnosis time were not different between the alive and decreased groups. However, patients in the deceased group had more bulbar onset, and lower ALSFRS at diagnosis. In addition, not only total score and bulbar function of ALSFRS were lower in the decreased group, but also the gross motor, fine motor, and respiratory functions. ALSFRS in the decreased group decreased by 9 points in 14 months (0.64 point/month by estimation), while it decreased by 12 points in 24 months (0.5 point/month by estimation) in the alive group. This implies that the decreased group had more rapid progression, and bulbar symptom at onset was associated with worse outcomes similar to the previous studies.[15,17,19,20,27-29]

In a previous study, the presence of Frontotemporal dementia and genetic mutation such as C90RF72 mutation were related to a worse outcome.[16] However, cognitive test and genetic study were not the focus in our present study. Our cohort provided information on survival time in Thai ALS patients. In the decreased group, the survival time was 15 months (IQ range 9.5-29.5 months) which was shorter than in previous studies (20-36 months).[16] The most common causes of death in our cohort encompassed respiratory failure due to respiratory muscle weakness, followed by pneumonia. The causes of death were not different from a previous retrospective post-mortem pathological study.[30]

Multidisciplinary care in ALS was shown to improve survival and quality of life. At our institute, the multidisciplinary approach was conducted, which included care by neurologist, respiratory physician, rehabilitationist, and psychiatrist. In advanced stage, respiratory failure and upper airway obstruction are common problems. The utility of tracheostomy positive pressure ventilation (TPPV) in the present study was 22.6% and was not different in the alive and the deceased group. The rest of patients chose palliative care. These were similar to Japan (25% to 46%) and Taiwan (21%) but contrasted to those Western countries (less than 10%) (6,31). This may be due to cultural differences. Even though the utility of TPPV in our cohort was similar to those in Japan and Taiwan, but survival time in our cohort was shorter. Subgroup analysis in

**Table 2. The disease severity of ALS patients at diagnosis and last evaluation.**

| Parameter | Total (n = 62) | Alive group (n = 42) | Deceased group (n = 20) | p-value |
|---|---|---|---|---|
| ALSFRS$^{\phi}$ at diagnosis (points; median, IQ25,75) | 28 (18.8, 38.0) | 32.5 (25.0, 41.0) | 18.5 (12.0, 27.5) | **<0.001** |
| - ALSFRS - Bulbar function (points; mean, SD) | 7.6 (3.4) | 8.6 (3.1) | 5.4 (3.0) | **0.001** |
| - ALSFRS – Fine motor function (points; median, IQ25,75) | 4 (1.0, 9.0) | 5.5 (1.7, 10.0) | 2 (0.3, 6.3) | **0.043** |
| - ALSFRS - Gross motor function (points; median, IQ25,75) | 5 (2.0, 10.3) | 6.5 (4.0, 11.3) | 1 (0, 5.3) | **<0.001** |
| - ALSFRS – Respiratory function (points; mean, SD) | 5.9 (1.9) | 6.2 (1.9) | 5.3 (1.8) | **0.030** |
| ALSFRS at last follow-up (points; median, IQ25,75) | 13.5 (9.0, 26.0) | 20.5 (11.8, 32.0) | 9.5 (6.3, 11.8) | **<0.001** |
| - ALSFRS - Bulbar function (points; median, IQ25,75) | 4 (2.0, 8.0) | 7.5 (3.0, 10.0) | 2.5 (2.0, 3.8) | **<0.001** |
| - ALSFRS - Fine motor function (points; median, IQ25,75) | 1.5 (0, 5.5) | 1 (0, 8.0) | 0.5 (0, 1.0) | **<0.001** |
| - ALSFRS – Gross motor function (points; median, IQ25,75) | 1 (0, 3.0) | 3 (0.8, 5.0) | 1 (0, 1.5) | **<0.001** |
| - ALSFRS – Respiratory function (points; median, IQ25,75) | 7 (4.0, 11.0) | 9 (5.8, 11.3) | 5.5 (3.0, 8.0) | **<0.005** |
| Summation CMAP at diagnosis (MV, mean; SD) | 14.8 (7.34) | 16 (7.1) | 11.3 (7.3) | 0.072 |
| Respiratory failure (%) | 35.4 | 33.3 | 40 | 0.671 |
| - respirator used | 30.6 | 31 | 30 | |
| - non-invasive respirator | 8.1 | 9.5 | 5 | |
| - invasive respirator | 22.6 | 21.4 | 25 | |
| - no respirator used | 4.8 | 2.4 | 10 | |
| Disease duration prior to respiratory failure (month; median, IQ25,75) | 13 (6.0, 18.0) | 12 (5.5, 17.0) | 14 (5.0, 20.8) | 0.660 |
| - non-invasive respirator | 12 (7.5, 14.5) | 10 (7.3, 15.0) | 13 (13.0, 13.0) | 0.480 |
| - invasive respirator | 13 (3.5, 19.3) | 13 (3.0, 20.5) | 15 (4.0, 23.5) | 0.738 |
| Duration of invasive respiratory usage (month; median, IQ25,75) | 6 (2.8, 8.5) | 6 (4.0, 7.0) | 6 (2.5, 15.0) | 0.780 |
| Survival time (month; median, IQ25,75) | 15 (9.5, 29.5) | - | 15 (9.5, 29.5) | - |

mRS$^{O}$- modify Rankin scale, ALSFRS$^{\phi}$ - amyotrophic lateral sclerosis functional rating scale

the patients who required invasive respirators showed that, the median duration of invasive respirator usage in the decreased group was 6 months. This might reflect the quality of home respiratory care. More proactive attitude to treat respiratory infections and improve the quality of home respiratory care could improve survival.

Limitations in this study included, 1) The study was done in a single center, so it may not provide representative data of Thailand. 2) The follow-up periods were short in some patients. 3) The follow-up information including ALSFRS

**Table 3. Multivariate Cox regression model of survival in patients with ALS**

| Parameter/category | p-value | Odd ratio | 95% CI |
|---|---|---|---|
| Bulbar phenotype ALS | 0.022 | 0.095 | 0.013-0.708 |
| ALSFRS at diagnosis | 0.038 | 0.789 | 0.631-0.987 |
| Summation CMAP | 0.892 | 0.892 | 0.744-1.070 |

and patient status were collected by telephone interviewing. 4) The incidence of ALS is low and the diagnosis is difficult so the present study had a small sample size. Further studies with more detail and subjects are needed.

In conclusion, this study demonstrated that some clinical characteristics such as bulbar symptoms at onset, and low ALSFRS at onset are associated with a poorer prognosis. This information may help the neurologists in the care planning of the patients.

## REFERENCES


1. Wijeseka LC, Leigh PN. Amyotrophic lateral sclerosis. *Orphanet J Rare Dis* 2009;4:3. doi: 10.1186/1750-1172-4-3.
2. Czaplinski A, Yen AA, Apple SH. Amyotrophic lateral sclerosis: early predictors of prolonged survival. *J Neurol* 2006;253(11):1428-36. doi: 10.1007/s00415-006-0226-8.
3. Tsai CP, Wang KC, Hwang CS, *et al*. Incidence, prevalence, and medical expenditures of classical amyotrophic lateral sclerosis in Taiwan, 1999–2008. *J Formos Med Assoc* 2015;114:612–19. doi: 10.1016/j.jfma.2013.01.008.
4. Doi Y, Atsuta N, Sobue G, *et al*. Prevalence and incidence of amyotrophic lateral sclerosis in Japan. *J Epidemiol* 2014;24:494–9. doi: 10.2188/jea.JE20140059.
5. Fong GC, Cheng TS, Lam K, *et al*. An epidemiological study of motor neuron disease in Hong Kong. *Amyotroph Lateral Scler* 2005;6:164–8. doi: 10.1080/14660820510028412a.
6. Lee CT, Chiu YW, Wang KC, *et al*. Riluzole and prognostic factors in amyotrophic lateral sclerosis long-term and short-term survival: a population-based study of 1149 cases in *Taiwan*. *J Epidemiol* 2013;23:35–40. doi: 10.2188/jea.je20120119.
7. Yoshida S, Uebayashi Y, Kihira T, *et al*. Epidemiology of motor neuron disease in the Kii Peninsula of Japan, 1989–1993: active or disappearing focus? *J Neurol Sci* 1998;155:146–55. doi: 10.1016/s0022-510x(97)00300-6.
8. Chen L, Zhang B, Chen R, *et al*. Natural history and clinical features of sporadic amyotrophic lateral sclerosis in China. *J Neurol Neurosurg Psychiatry* 2015;86:1075–81. doi: 10.1136/jnnp-2015-310471.
9. Bae JS, Hong YH, Baek W, *et al*. Current status of the diagnosis and management of amyotrophic lateral sclerosis in Korea: a multi-center cross-sectional study. *J Clin Neurol* 2012;8:293–300. doi: 10.3988/jcn.2012.8.4.293.
10. Abdul Aziz NA, Toh TH, Goh KJ, *et al*. Natural history and clinical features of ALS in Malaysia. *Amyotroph Lateral Scler Frontotemporal Degener*. 2021;22(1-2):108-16. doi: 10.1080/21678421.2020.1832121.
11. Watanabe H, Atsuta N, Nakamura R, *et al*. Factors affecting longitudinal functional decline and survival in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:230–6. doi: 10.3109/21678421.2014.990036.
12. Kulkantrakorn K, Suksasunee D. Clinical, electrodiagnostic, and outcome correlation in ALS patients in Thailand. *J Clin Neurosci* 2017;165-9. doi: 10.1016/j.jocn.2017.05.034.
13. Chotimongkol V. Amyotrophic lateral sclerosis in Srinagarind hospital. *Srinagarind Med J* 1990;5:191–6.
14. Joachim W, Anton S. Factor predicting one-year mortality in amyotrophic lateral sclerosis patients-data from population-based registry. *BMC Neurology* 2014;14:197. doi: 10.1186/s12883-014-0197-9.
15. Louwerse ES, Visser CE, Bossuyt PM, *et al*. Amyotrophic lateral sclerosis: mortality risk during the course of the disease and prognosis factors, The Netherlands ALS Consortium. *J Neurol Sci* 1997;152 Suppl 1:S10-7. doi: 10.1016/s0022-510x(97)00238-4.
16. Chiò A, Logroscino G, Hardiman O, *et al*. Prognostic factors in ALS: A critical review. *Amyotroph Lateral Scler*. 2009;10(5-6):310-23. doi: 10.3109/17482960802566824.
17. Stambler N, Charatan M, Cedarbaum JM, Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. *Neurology* 1998;50:66–72. doi: 10.1212/wnl.50.1.66.
18. Chiò A, Mora G, Leone M, *et al*. Early symptom progression rate is related to ALS outcome: a prospective population-based study. *Neurology* 2002;59(1):99-103. doi: 10.1212/wnl.59.1.99.
19. Kimura F, Fujimura C, Ishida S, *et al*. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. *Neurology* 2006;66: 265–7. doi: 10.1212/01.wnl.0000194316.91908.8a.
20. Kollewe K, Mauss U, Krampfl K, *et al*. ALSFRS-R score and its ratio: a useful predictor for ALS progression. *J Neurol Sci* 2008;275(1-2):69-73. doi: 10.1016/j.jns.2008.07.016.
21. Brooks BR, Miller RG, Swash M, *et al*. World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2000;1(5):293-9. doi: 10.1080/146608200300079536.
22. Cedarbaum JM, Stambler N, Malta E, *et al*. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J Neurol Sci*. 1999;169(1-2):13-21. doi: 10.1016/s0022-510x(99)00210-5.
23. Dyck PJ. Dynamic assessment in CIDP. *Muscle Nerve* 2009;39(4):421-2. doi: 10.1002/mus.21181.
24. Chiò A, Logroscino G, Traynor BJ, *et al*. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. *Neuroepidemiology* 2013;41(2):118-30. doi: 10.1159/000351153.
25. Couratier P, Corcia P, Lautrette G, *et al*. Epidemiology of amyotrophic lateral sclerosis: A review of literature. *Rev Neurol* (Paris). 2016;172(1):37-45. doi: 10.1016/j.neurol.2015.11.002.
26. Richards D, Morren JA, Pioro EP. Time to diagnosis and factors affecting diagnostic delay in amyotrophic lateral sclerosis. *J Neurol Sci* 2020; 417: 117054. doi: 10.1016/j.jns.2020.117054.

27. Magnus T, Beck M, Giess R. Disease progression in amyotrophic lateral sclerosis: predictors of survival. *Muscle Nerve* 2002;25:709-14. doi: 10.1002/mus.10090.
28. Kaufmann P, Levy G, Thompson JL, *et al*. The ALSFRS-R predicts survival time in an ALS clinic population. *Neurology* 2005;64:38-43. doi: 10.1212/01.WNL.0000148648.38313.64.
29. Del Aguila MA, Longstreth WT Jr, McGuire V, *et al*. Prognosis in amyotrophic lateral sclerosis: a population-based study. *Neurology* 2003;60:813-9. doi: 10.1212/01.wnl.0000049472.47709.3b.
30. Corcia P, Pradat PF, Salachas F, *et al*. Causes of death in a post-mortem series of ALS patients. *Amyotroph Lateral Scler* 2008;9(1):59-62. doi: 10.1080/17482960701656940.
31. Rabkin J, Ogino M, Goetz R, *et al*. Tracheostomy with invasive ventilation for ALS patients: neurologists' roles in the US and Japan. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14:116–23. doi: 10.3109/17482968.2012.726226.