Original Article

Survival Analysis of Amyotrophic Lateral Sclerosis: An Ambispective Cohort Study in a Thai Tertiary Care Center

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ABSTRACT

Objectives: To determine the median survival time and identify independent prognostic factors for mortality in amyotrophic lateral sclerosis (ALS) patients at a tertiary-care hospital in Thailand.

Study design: Ambispective cohort study

Setting: Outpatient rehabilitation department of a tertiary care hospital in Thailand

Participant: Forty-four patients diagnosed with ALS according to the Awaji criteria

Methods: We analyzed clinical data from patients treated between January 2012 and July 2022. Survival time curves were generated using the Kaplan-Meier method. To identify predictors of mortality, a full multivariable Cox proportional hazards model was first constructed, followed by a parsimonious model retaining variables with $p < 0.20$.

Results: The cohort had a male-to-female ratio of 1.3:1 and a mean age at onset of the study of 56.6 years. The median overall survival time from symptom onset to death was 37.0 months (95%CI: 31.0, 44.0). In the final multivariable Cox model (C-index = 0.80), a longer interval from symptom onset to diagnosis was the only statistically significant independent predictor of improved survival time (HR = 0.11, 95%CI: 0.01, 0.90, $p = 0.04$). While the presence of major complications (HR = 3.05, $p = 0.06$), hypertension (HR = 2.98, $p = 0.08$), and male sex (HR = 2.24, $p = 0.17$) showed strong clinical trends toward increased mortality, none reached statistical significance in the refined model. Riluzole use was not associated with a survival benefit in this cohort (HR = 0.77, $p = 0.74$).

Conclusions: The median survival time of Thai ALS patients was 37 months. The time from symptom onset to diagnosis is a key indicator of survival time, likely reflecting the underlying biological speed of the disease. While complications and comorbidities such as hypertension influence the clinical course, larger multicenter studies are needed to validate these prognostic markers in the Southeast Asian population.

Keywords: amyotrophic lateral sclerosis, motor neuron disease, survival analysis, prognosis, tertiary-care hospital

ASEAN J Rehabil Med. 2026; 36(2): 65-70.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with a global incidence of 1.7 per 100,000, primarily affecting males between ages 55-75.[1,2] Diagnosis relies on clinical and electrodiagnostic evidence of multi-regional denervation. While most cases present with asymmetric limb weakness, approximately 20.0% involve bulbar onset, which significantly increases mortality risk through early dysphagia and respiratory complications.[1,2]

Clinical phenotype and subsequent survival rates exhibited significant geographic and ethnic variability. A comprehensive meta-analysis by Marin et al. highlighted this heterogeneity, reporting median survival times from symptom onset ranging from 24 months in Northern Europe to 48 months in Central Asia.[3] These discrepancies suggest that a complex interplay of local demographic, genetic, and environmental factors influences disease progression. Supporting this, individual country studies have reported vastly different outcomes. For instance, an extensive Indian cohort (n = 1,153) demonstrated an overall median survival time of 114.8 months, with limb-onset patients surviving significantly longer (177.9 months) than those with bulbar onset (55.9 months).[4] Conversely, a Mexican series reported a much shorter mean survival time of 64.7 months.[5] Such regional variations underscore the necessity of robust local data, particularly in understudied populations.

Identifying reliable prognostic factors is essential for accurate clinical counseling and for optimizing multidisciplinary care. While bulbar-onset, advanced age, and rapid functional decline are established predictors of shorter survival time,[4,5] the relative impact of these factors appears to vary by population. Notably, while some Asian cohorts report exceptionally prolonged survival exceeding 100 months, data from Southeast Asia remains notably scarce.[4,6]

In Thailand, existing research is currently limited to small, retrospective samples that constrain the precision of survival time estimates.[6] Furthermore, Thai patients often face signifi-

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Received: November 11, 2025 Revised: December 20, 2025 Accepted: February 1, 2026

cant diagnostic delays, which may obscure the relationship between disease velocity and outcomes. Consequently, this study aimed to evaluate median survival time and identify independent predictors of mortality in a cohort of Thai ALS patients treated at a university hospital over a period of 10 years. By analyzing variables such as onset site, sex, and the timing of major complications, we sought to provide locally relevant data to enhance clinical management in the region.

Methods

Study design

This ambispective cohort study included ALS patients who received care at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University between January 2012 and July 2022. This study was conducted and reported in accordance with the STROBE guidelines. It was approved by the Khon Kaen University Human Research Ethics Committee (HE661049).

Inclusion criteria: 1) diagnosis of ALS confirmed by a neurologist according to the Awaji criteria[7] during the study period; 2) having undergone electrodiagnostic testing to ensure diagnostic certainty and exclude ALS mimics; 3) The absence of other chronic comorbidities likely to cause long-term complications affecting outcomes (e.g., stroke, spinal cord pathology, chronic obstructive pulmonary disease).

Exclusion criteria: Incomplete medical records that precluded the determination of the survival time or key baseline characteristics.

Data collection

Medical records including electronic medical records (EMR) were searched using ICD-10 code G12.2 for the study period. Data collected included sex, comorbidities, age at symptom onset, age at diagnosis, clinical onset region (spinal vs bulbar), clinical manifestations before diagnosis (spinal, bulbar, or both), interval from symptom onset to diagnosis, major complications (aspiration pneumonia, tracheostomy, bedridden status, enteral feeding via NG or PEG), death and time from onset to death, cause of death, and riluzole use. To ensure robust analysis, hospital records were cross-referenced to fill in missing information on complications, yielding a dataset with no missing values for the primary predictive variables.

If records were incomplete or patients were lost to follow-up, researchers mailed information and consent forms to the patients or their relatives. A telephone follow-up was conducted when consent was provided. If no response was received, the analysis used all available data up to the patient's most recent visit at University Hospital, resulting in censoring at that date.

Sample size calculation

The sample size for this descriptive study was determined based on the precision required for estimating the median survival time. Based on preliminary data suggesting a mean survival of approximately 65 months and a 5-year survival rate of 44.4%, we anticipated that a significant number of events would occur during follow-up.[5]

A sample size of 44 patients was chosen to achieve an acceptable level of precision for the median survival time estimate. With this sample size, it was projected that the 95% confidence interval (CI) for the median survival time would have a total width of approximately 35-40 months. Calculations were based on the method described by Machin et al.[8] for precision-based sample size estimation.

Statistical analysis

Analyses were performed using Python version 3.12.12 (CPython) on the Google Collaboratory platform. Descriptive statistics are reported as mean and standard deviation (SD) or median (interquartile range, IQR). Continuous variables, including the onset-to-diagnosis interval and age at onset, were included in the Cox proportional hazards model in their original units (months and years). The lifelines library (version 0.30.0) was used to fit Cox proportional hazards models.

Overall survival time was defined as the number of months from symptom onset to death; patients alive at last contact were censored at the date of last follow up. Survival time curves were estimated using the Kaplan-Meier method and compared using the Log-Rank test. The proportional hazards assumption was verified for all covariates using the Schoenfeld residuals test and visual inspection of log-minus-log plots before multivariable modeling. Given the limited sample size and number of observed events, this study was designed as an exploratory analysis. Consequently, the variable selection process and multivariable modeling were conducted with an exploratory strategy aimed at identifying potential prognostic factors and generating hypotheses rather than confirming definitive causal relationships.

To determine the independent predictors of survival time, we initially constructed a full multivariable Cox proportional hazards model incorporating clinically relevant covariates. Covariates were coded as follows: age at onset (continuous, per 1 year increase), sex (male vs female), onset region (spinal vs bulbar), time from symptom onset to diagnosis (continuous, per month), underlying diseases (hypertension, diabetes mellitus, dyslipidemia), riluzole use (yes vs no), and major complications (baseline binary: present vs absent). Variables were selected a priori on clinical grounds.

Subsequently, to derive a stable and parsimonious final model, variables were retained only if they exhibited a $p < 0.20$ in the full model adjustment. This selection criterion was adopted to balance the need to control for potential confounders while minimizing model complexity, given the limited number of events.[9] To ensure model stability, we formally assessed multicollinearity among predictors using Variance Inflation Factors (VIF). Furthermore, to address the potential for overfitting due to the low events-per-variable ratio, we performed a sensitivity analysis using Ridge-penalized Cox regression (L2 regularization), which shrinks coefficients to

provide more stable estimates in small-sample settings.[10] Hazard ratios (HR) and 95% CI were calculated for the final model, with statistical significance for the final independent predictors defined at $p < 0.05$.

Results

A total of 44 ALS patients diagnosed according to the Awaji criteria[7] were included in the study. The cohort consisted of 25 males (56.8%) and 19 females (43.2%), yielding a male-to-female ratio of 1.3:1. The mean age at symptom onset was 56.6 years (SD = 7.6), and the mean age at diagnosis was 57.8 years (SD = 7.6). The mean interval from symptom onset to diagnosis was 13.2 months (SD = 9.8).

Regarding clinical presentation, spinal onset occurred in 34 patients (77.3%) and bulbar onset in 10 patients (22.7%). At the time of diagnosis, the majority of patients presented with widespread involvement of the upper and lower extremities and the bulbar region (n = 23, 52.3%). The most common comorbidities were hypertension (25.0%) and diabetes mellitus (18.2%), although the majority of participants (63.6%) had no underlying disease.

Complications were observed in 22 of the cohort (50.0%). The most frequent complications included bedridden status (31.8%), aspiration pneumonia (18.2%), and the requirement for nutritional support via NG tube or PEG (18.2%). Only 13 patients (29.5%) received Riluzole therapy.

By the end of the study period, 18 patients (40.9%) had died, while 26 (59.1%) were censored (alive or lost to follow-up). The median follow-up time was 22.8 months (IQR: 6.4, 30.0). Causes of death among the 18 decedents included sudden cardiac arrest (n = 10, 55.6%), pneumonia (n = 7, 38.9%), and myocardial infarction (n = 1, 5.6%). Patients who died had a notably higher rate of complications compared to the censored group, particularly regarding bedridden status (72.2% vs. 3.8%) and aspiration pneumonia (44.4% vs. 0%). (Table 1)

The median overall survival time for the entire cohort of ALS patients was 37.0 months (95%CI: 31.0, 44.0). Estimated survival probabilities were 97.4% at 12 months, 85.9% at 24 months, 54.8% at 36 months, 27.7% at 48 months, and 13.8% at 60 months (Figure 1).

To identify independent predictors of survival time, we

Table 1. Demographic and clinical characteristics of ALS patients

Clinical characteristics	Total participants (n = 44)	Death (event) (n = 18)	Censored (Alive or lost to follow-up) (n = 26)
Male, n (%)	25 (56.8)	12 (66.7)	13 (50.0)
Region, n (%)			
Bulbar	10 (22.7)	5 (27.8)	5 (19.2)
Spinal	34 (77.3)	13 (72.2)	21 (80.8)
Comorbidities, n (%)			
No underlying disease	28 (65.1)	8 (44.4)	20 (76.9)
Diabetes Mellitus	8 (18.2)	6 (33.3)	2 (7.7)
Hypertension	11 (25.0)	6 (33.3)	5 (19.2)
Dyslipidemia	6 (13.9)	3 (16.7)	3 (11.5)
Age at onset (years); mean (SD)	56.6 (7.6)	57.3 (6.6)	56.0 (8.3)
Age at diagnosis (years); mean (SD)	57.8 (7.6)	58.6 (7.6)	57.2 (8.3)
Clinical involvement before diagnosis, n (%)			
Upper extremity only	2 (4.5)	2 (7.7)	0 (0.0)
Lower extremity only	1 (2.3)	1 (5.6)	0 (0.0)
Bulbar only	4 (9.1)	2 (11.1)	(7.7)
Upper and lower extremity	6 (13.6)	1 (5.6)	5 (19.2)
Upper extremity and bulbar	7 (15.9)	2 (11.1)	5 (19.2)
Lower extremity and bulbar	1 (2.3)	1 (5.6)	0 (0.0)
Upper extremity, lower extremity and bulbar	23 (52.3)	11 (61.1)	12 (46.2)
Onset to diagnosis interval (months); mean (SD)	13.2 (9.8)	13.4 (9.4)	13.1 (10.2)
Complications n (%)			
Yes	22 (50.0)	14 (77.8)	8 (30.8)
Aspiration pneumonia	8 (18.2)	8 (44.4)	0 (0.0)
Require NG or PEG feeding	8 (18.2)	7 (38.9)	1 (3.8)
Require tracheostomy	3 (6.8)	3 (16.7)	0 (0.0)
Bedridden status	14 (31.8)	13 (72.2)	(3.8)
No complications	22 (50.0)	4 (22.2)	18 (69.2)
Riluzole Use, n (%)	13 (29.5)	3 (16.7)	10 (38.5)

ALS, amyotrophic lateral sclerosis; NG, Nasogastric tube; PEG, percutaneous endoscopic gastrostomy

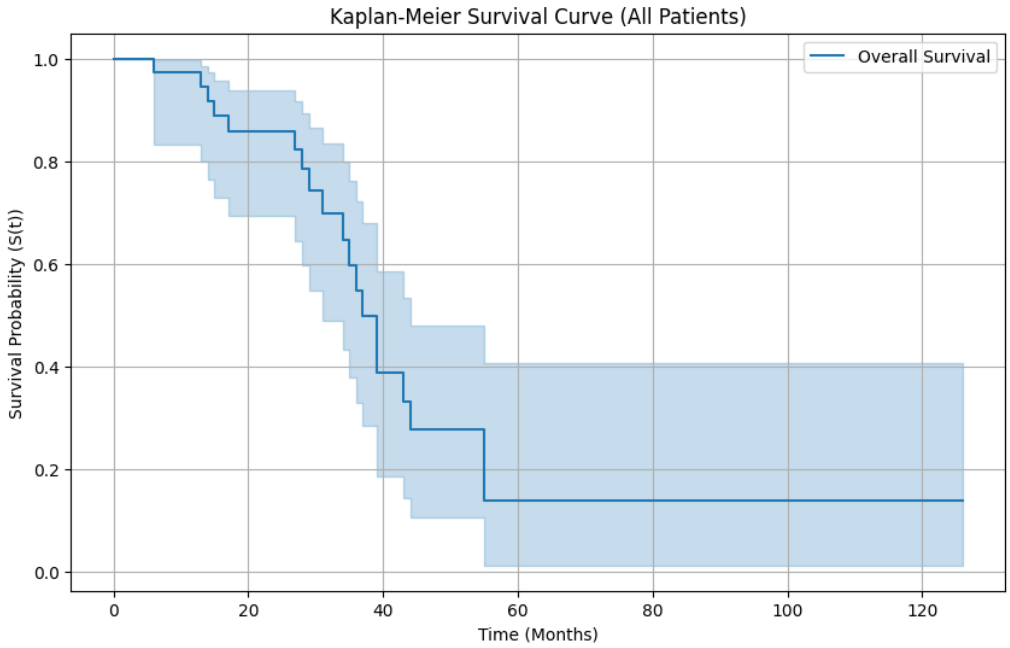


Figure 1. Kaplan–Meier overall survival time for the cohort (n = 44). Median survival time is 37.0 months (95% CI: 31–44); deaths = 18; censored = 26

Table 2. Full multivariable Cox proportional hazards model for predictors of mortality in ALS patients (n = 44).

Variable	Hazard ratio	95% CI	*p*, value
Spinal onset	0.75	0.17, 3.23	0.70
Male	2.71	0.68, 10.82	0.16*
Comorbidities			
Diabetes	0.89	0.19, 4.28	0.89
Hypertension	5.19	0.91, 29.61	0.06*
Dyslipidemia	0.30	0.05, 1.97	0.21
Age at onset	0.84	0.04, 17.51	0.91
Onset to diagnosis interval	0.20	0.02, 1.78	0.15*
Complications Present	4.56	1.09, 19.05	0.04*
Riluzole Use	0.77	0.15, 3.83	0.74

CI, confidence interval

*Indicates variables meeting the $p < 0.20$ criterion for inclusion in the final parsimonious model (male, comorbidity: hypertension, onset to diagnosis interval, and complication present)

initially constructed a full multivariable Cox proportional hazards model that incorporated all 9 clinical covariates (Table 2). This comprehensive model was used as a screening step to identify variables with a potential prognostic signal. Based on an a priori selection criterion of $p < 0.20$ within the full model, four variables—sex, hypertension, onset to diagnosis interval, and the presence of complications—were identified for inclusion in the final parsimonious model.

The final parsimonious model (Table 3) demonstrates high discriminative ability with a Concordance Index (C-index) of 0.80. In this refined analysis, a longer interval from onset to diagnosis was the only statistically significant independent predictor of improved survival time (HR = 0.11, 95% CI: 0.01, 0.90, $p = 0.04$). Although the presence of complications, male sex, and hypertension did not meet the traditional threshold

Table 3. Final parsimonious multivariable Cox model for predictors of survival time

Variable	Hazard ratio	95% CI	z-score	*p*-value
Complication present	3.05	0.96, 9.65	1.90	0.06
Hypertension	2.98	0.88, 10.09	1.76	0.08
Male	2.24	0.70, 7.17	1.36	0.17
Onset to diagnosis interval	0.11	0.01, 0.90	-2.06	0.04*

Concordance index = 0.80.

*Indicates statistical significance at $p < 0.05$.

for statistical significance, they demonstrated strong clinical trends toward increased mortality risk. They were retained to optimize the model's predictive power.

Discussion

In this ambispective cohort of 44 ALS patients in Northeast Thailand, the median overall survival time from symptom onset was 37.0 months. This result is consistent with the global range of 2-5 years,[3,5,11,12] but differs from the exceptionally long survival times reported in other Asian regions, such as India.[4] Our findings suggest that while the clinical phenotype of Thai ALS patients aligns with international patterns, the primary drivers of mortality risk in this population are clinical complications and the velocity of disease progression.

The most significant finding in our multivariable analysis was the independent association between the onset-to-diagnosis interval and survival time (HR = 0.11, $p = 0.04$). This inverse relationship—where a longer diagnostic delay correlates with a lower hazard of death—is a recognized phenomenon in ALS research often attributed to "reverse causation".[5]

Patients with aggressive, rapidly progressing phenotypes typically reach diagnostic criteria quickly but have poor outcomes.[13] Conversely, those with slower-progressing disease may experience longer delays due to the subtle nature of their symptoms but ultimately have a more favorable prognosis. In our cohort, this interval serves as a proxy for the disease's inherent biological velocity.

Regarding other clinical predictors, the refined model identified major complications (HR = 3.05, p = 0.06) and hypertension (HR = 2.98, p = 0.08) as factors with strong clinical trends toward reduced survival time, although they fell just outside the traditional threshold for statistical significance. The presence of complications—such as aspiration pneumonia or bedridden status—represents a critical turning point in the disease course. Similarly, the role of hypertension may reflect underlying vascular fragility that potentially accelerates neurodegenerative processes. Although the updated model provides more conservative hazard ratios than our initial analysis, the estimates remain clinically substantial. These results underscore the necessity of proactive, multidisciplinary interventions aimed at preventing respiratory and nutritional failure, which remain the primary drivers of mortality in ALS.[2,5]

Interestingly, male sex was retained in our final model (HR = 2.24, p = 0.17) but showed a much less pronounced effect than initially observed. While some literature suggests sex differences in ALS survival,[14] our data suggest that in the Thai population the impact of sex may be secondary to other factors like complication rates and diagnostic timing. Similarly, bulbar onset did not emerge as a significant independent predictor in the final multivariable model, despite being a well-established risk factor globally.[1,2] This may be due to the relatively small number of bulbar-onset cases in our Northeast Thai cohort, or it may suggest that once complications and progression velocity are accounted for, the site of onset carries less weight in this specific population.

The lack of a significant survival time benefit for riluzole (HR = 0.77, p = 0.74) remains consistent with our prior analysis. This is likely due to the study being underpowered to detect the modest survival time extension (typically 3-6 months) associated with the drug, combined with low utilization rates (29.5%) in our cohort, which may reflect barriers to access or cost in the Thai healthcare context.

Several limitations of this study warrant consideration. Primarily, the small sample size (n = 44) and the limited number of observed events (n = 18 deaths) restricted the statistical power for multivariable regression. With four predictors retained in the final model, the events-per-variable (EPV) ratio is approximately 4.5 which is below the traditional recommendation of at least 10 events per variable,[15] increasing the risk of overfitting where the model may capture statistical noise rather than true underlying patterns.

Furthermore, the lack of statistical significance for certain predictors should be interpreted with caution. Variables such as hypertension and sex demonstrated clinically large effect sizes (hazard ratios > 2) but failed to reach statistical significance. This discrepancy is likely attributable to limited statistical power due to an inadequate sample size, rather than a definitive absence of association. Therefore, these variables warrant further investigation in larger cohorts to confirm their prognostic value.

We did, however, take several steps to ensure the reliability of these results. Our final model demonstrated strong discrimination (C-index 0.80) and low multicollinearity, with Variance Inflation Factor (VIF) values below 2.0 for all variables.[10] Furthermore, a sensitivity analysis using Ridge-penalized Cox regression (L2 regularization) yielded hazard ratios that were consistent in direction and magnitude with those from our standard model. This consistency suggests that the estimates are stable and not severely inflated by the low EPV ratio. Nevertheless, the small event count resulted in wide 95% CI for some predictors—most notably for complications. Therefore, while the direction of these associations is clear, the absolute magnitude of the hazard ratios should be interpreted with caution.

It is important to state explicitly that this study is exploratory. Consequently, the associations identified should be viewed as hypothesis-generating signals rather than definitive causal relationships. The single-center design may have introduced referral bias toward more complex cases, and the median follow-up of 22.8 months suggests that survival time estimates beyond the 3-year point remain preliminary.

Despite these constraints, this study provides critical, locally relevant data from Northeast Thailand, where published ALS survival time evidence is sparse. By consolidating clinical outcomes over 10 years, these findings provide a baseline for prognostic counseling and a necessary foundation for the design of future, larger, multi-center regional studies.

Conclusions

In this single-center cohort from Northeast Thailand, the median survival time from symptom onset was 37 months. A longer interval from symptom onset to diagnosis was the only statistically significant independent predictor of improved survival time, likely reflecting the naturally slower progression of certain ALS phenotypes. While the presence of major complications, hypertension, and male sex showed strong clinical trends toward increased mortality risk, they did not reach independent statistical significance in our refined model.

These findings provide important baseline data for prognostic counseling in the Thai population and highlight the critical role of disease velocity in determining outcomes. Given the exploratory nature of this study and the limited sample size, further large-scale, multicenter research is necessary. Establishing a national ALS registry would provide the statistical power required to validate these prognostic markers and optimize standardized multidisciplinary care protocols for Thai patients.

Conflict of interest declaration

The authors declare that they have no conflicts of interest.

Generative AI declaration

The authors confirm that no large language models (LLMs) or artificial intelligence (AI) tools were used to create the content of this manuscript. Grammarly was used solely to check and refine grammar throughout the manuscript prior to submission. All content was critically reviewed and finalized by the research team.

Acknowledgements

The authors gratefully acknowledge the assistance of the Medical Records Department, Srinagarind Hospital, Khon Kaen University.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

Chinakit Idsaraphorn: conceptualization, data collection, formal analysis, writing - original draft,

Preeda Arayawichanon: supervision, methodology, validation, review & editing,

Jukrapope Jitpimolmard: methodology, investigation, data curation, visualization, review & editing,

Pitchaya Wiratchotisatian:data curation, visualization, data analysis, software, manuscript revision,

Nantaporn Jitpimolmard: conceptualization, methodology, supervision, investigation, validation, writing - review & editing.

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