Staging model for amyotrophic lateral sclerosis in Singapore

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ABSTRACT

Introduction: A clinical-based staging model would guide physicians in the prompt management of the evolving symptoms and functional needs of patients with amyotrophic lateral sclerosis (ALS).

Methods: We aimed to delineate the clinical trajectory of ALS in Singapore and test the degree of congruity of King’s College staging for ALS (King’s staging) among Singapore patients. In this retrospective cohort study, clinical milestones used for staging were identical to King’s staging: stage 1 corresponded to symptom onset; stage 2A corresponded to diagnosis; stage 2B corresponded to two central nervous system (CNS) regions; stage 3B corresponded to three CNS regions; stage 4A corresponded to requirement of supportive enteric feeding; and stage 4B corresponded to requirement of non-invasive ventilation, of which bulbar, diaphragmatic, upper and lower limb pyramidal involvements each constituted one CNS region. Standardised timings from disease onset (0) to death (1) among Singapore patients with ALS were measured.

Results: 46 patients with ALS were reviewed. Results were largely congruous with King’s staging. Results for patients with limb-onset ALS were: diagnosis (0.35); two CNS region involvement (0.42); three CNS region involvement (0.63); diaphragmatic involvement (0.81); and bulbar involvement (0.73). Results for patients with bulbar-onset ALS were: diagnosis (0.14); two CNS region involvement (0.28); three CNS region involvement (0.42); diaphragmatic involvement (0.62); and bulbar involvement (0.67).

Conclusion: King’s staging can be used to model ALS trajectory in Singapore due to the large degree of congruity seen. Easily remembered and accessible knowledge of ALS staging will allow prompt management of the evolving needs of patients with ALS.

Keywords: amyotrophic lateral sclerosis, motor neuron disease, neurodegenerative disease, prognosis, staging model
INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by progressive deterioration of upper and lower motor neurons. It is a terminal disease, with the progression from symptom onset to death bearing a median duration of 2–4 years. Most patients pass on in their sleep from hypercapnia arising from underlying neuromuscular respiratory failure.

The trajectory of ALS follows a curvilinear course. Disease management tailored to addressing functional deficits and symptoms has been shown to improve quality of life and prolong survival. For example, patients with impending respiratory muscle weakness and neuromuscular respiratory failure have been shown to benefit from non-invasive ventilation. Similarly, insertion of percutaneous endoscopic gastrostomy has been shown to enhance survival in patients by providing nutritional support to halt weight loss. Moreover, prompt multidisciplinary intervention for needs that arise throughout each disease phase has been shown to enhance both quality of life and survival.

Thus, a model delineating the trajectory of ALS is essential for the opportune implementation of these management strategies. Disease progression in ALS has been associated with greater functional decline and poorer median survival. As such, an effective staging model must fulfil two purposes: (a) staging milestones must accurately capture the progression of disease; and (b) staging milestones must accurately predict the onset of symptoms. In the United Kingdom, King’s College, London, proposed a staging model (King’s staging) based on easily identifiable clinical milestones along the course of disease to delineate the clinical trajectory of ALS. This allows physicians to objectively assess disease progression and augment patient-centred care towards the evolving needs of patients at different stages of the disease. Currently, there are no known staging models recognised and used actively for patients with ALS in Singapore. Locally, Amyotrophic Lateral Sclerosis Functional Rating
Scale (ALSFRS) has been used to assess the degree of disability in patients with ALS. However, this rating scale has been shown to correlate more with gross functional deterioration rather than the natural progression of the disease itself.\(^{(7)}\)

Thus, this retrospective cohort study aims to delineate the clinical trajectory of ALS in Singapore and study the degree of congruity of King’s staging for ALS among our patients.

**METHODS**

The study adapted a recognised staging model\(^{(3)}\) for the progression of ALS to the local populace through a two-step process. The first step involved delineating the clinical trajectory of ALS within the Singaporean patient population. The second step assessed the degree of congruity of King’s staging for modelling the trajectory of ALS in Singapore patients.

This was a retrospective cohort study, which was approved by the institutional review board of the National Neuroscience Institute (NNI), Singapore.

Patients with ALS being treated at the NNI at Tan Tock Seng Hospital, Singapore, who had died between 1 January 2011 and 31 December 2016 were enrolled into the study. These patients had satisfied the diagnosis of probable motor neuron disease as defined by the revised El Escorial and Arlie House diagnostic criteria for ALS.\(^{(8)}\) Date and cause of death was ascertained using digitalised patient clinical records, death certificates and correspondences with family members of patients. Patients included had cause of death attributed as a direct complication of ALS, and included neuromuscular respiratory failure, asphyxiation and aspiration pneumonia, sepsis secondary to pneumonia, urinary tract infection and falls. Patients whose death was not deemed to be a direct cause of the complications of ALS were excluded. Such examples included deaths due to motor vehicle accidents, malignancy, suicides and ischaemic heart disease.
Patients were then stratified into those with limb-onset ALS and bulbar-onset ALS. Disease trajectory of the two groups were delineated and compared to their corresponding trajectory when modelled by King’s staging.\(^{(3)}\) Statistical analysis was conducted to determine whether Singaporean patients with ALS could be modelled after the King’s staging system.

We used the definitions for clinical milestones provided by King’s College,\(^{(3)}\) where bulbar, diaphragmatic, and upper and lower limb pyramidal involvements would each constitute one central nervous system (CNS) region. King’s staging is presented in Table I. Of note, King’s staging employed these milestones solely for patients with definite ALS, as opposed to our study, where patients with probable ALS were also included.

<table>
<thead>
<tr>
<th>Staging</th>
<th>Clinical milestone</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>Involvement of one region</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>Diagnosis of probable ALS</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>Involvement of two regions</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Involvement of three regions</td>
</tr>
<tr>
<td>Stage 4A</td>
<td>Supportive enteric feeding (e.g. gastrostomy)</td>
</tr>
<tr>
<td>Stage 4B</td>
<td>Respiratory support with non-invasive ventilation</td>
</tr>
</tbody>
</table>

*A single central nervous system region was defined as involvement of motor neurons originating from either the brainstem, or the cervical, thoracic or lumbosacral spinal cord. ALS: amyotrophic lateral sclerosis*

Patients were stratified based on the region of CNS affected at the onset of symptoms. Limb-onset ALS was defined as the onset of symptoms attributed to lesion of motor neurons of the cervical, thoracic or lumbosacral regions (e.g. patients who presented with symptoms suggestive of lumbosacral involvement, such as lower limb weakness). Bulbar-onset ALS was defined as the onset of symptoms attributed to lesion of motor neurons within the brainstem (e.g. patients who presented with symptoms suggestive of bulbar involvement, such as dysphagia and dysarthria).

The date of onset of symptoms for the particular CNS region was regarded as the date of attainment of the clinical milestone. These symptoms included muscle weakness, muscle
wasting, spasticity, dysarthria and dysphagia. The date of diagnostic confirmation of probable ALS was taken as the date on which diagnosis was documented by the neurologist. Need for supportive enteral feeding was the date on which the patient was documented as having been offered gastrostomy or nasogastric tube. Need for non-invasive ventilation was taken as the date on which non-invasive ventilation was documented as having been offered to the patient. Advanced clinical staging milestones took precedence over early clinical staging milestones. For example, a patient who presented to the neurologist with involvement of three CNS regions at diagnosis was labelled as stage 3 instead of stage 2A.

Milestone timings were proportions of time elapsed through the course of disease. It was standardised as a ratio where the numerator was the time elapsed from the onset of symptom to the milestone assessed and the denominator was the time elapsed from the onset of symptom to death. As such, the time to each milestone was given a value between 0 and 1, with 0 being the date of onset of symptom and 1 the date of death. For patients who died before completion of all clinical milestones, the most advanced milestone recorded was used for analysis.(3)

Details of the clinical milestones were assessed from patients’ clinical records. This included hardcopy documentation and computerised medical records. Hardcopy documentation were clinical notes written by physicians, nurses and allied health professionals. Computerised medical records were clinical entries stored within the institution’s intranet created by healthcare professionals detailing the care of patients. This encompassed both inpatient and outpatient records, such as home visit documentation and telephone correspondences by physicians, allied health professional and nurses. Raw data was collected by an advanced nurse practitioner, while data analysis was completed by a medical student.

Milestone timing was expressed as mean, with a 95% confidence interval (CI). Since it has been demonstrated that limb-onset ALS and bulbar-onset ALS have distinctly different
survival outcomes and clinical trajectory, the two groups of patients were analysed separately.\(^9\)

Standardised milestone timings of our local study were compared to the hypothesised milestone timings in King’s staging using the Wilcoxon signed-rank test. For both groups, the null hypothesis was that there would be no difference in the onset timing of clinical milestones between the local population and that studied by King’s College. The alternative hypothesis was otherwise.

Since studies have observed that riluzole therapy might have a positive influence on the survival of patients with ALS,\(^9\) our patients were further sub-stratified based on history of riluzole therapy consumption. Further subgroup analysis of standardised milestone timings was conducted using Mann-Whitney \(U\) test. The null hypothesis was that there would be no significant difference between the milestone timings in both subgroups. The alternative hypothesis was otherwise.

**RESULTS**

Overall, 47 patients with ALS treated at the NNI, who died between 2011 and 2016, were enrolled. Of these, 46 patients satisfied the inclusion criteria. One patient was excluded on account of death not being attributed to a direct complication of ALS (the cause of death in that instance being suicide.).

Among these 46 patients, there were 22 (47.8\%) women and 24 (52.2\%) men. 13 (28.3\%) of 46 patients had bulbar-onset ALS. Mean age of onset among patients with bulbar-onset ALS was 63.77 (95\% CI 57.93–69.61) years and median survival was 27.4 (95\% CI 18.2–36.6) months. The remaining 33 (71.7\%) of 46 patients had limb-onset ALS. Mean age of onset among patients with limb-onset ALS was 60.42 (95\% CI 56.46–64.38) years and median survival was 32.06 (95\% CI 24.07–40.05) months.
With regard to disease trajectory among our patients with limb-onset ALS, diagnosis was reached at 35% of disease course, involvement of two neurological regions at 42%, involvement of three regions at 63%, offer of gastrostomy at 81% and offer of non-invasive ventilation at 80% into the disease course (Table II).

**Table II. Findings for limb-onset ALS.**

<table>
<thead>
<tr>
<th>Staging</th>
<th>Mean milestone timing (95% CI)</th>
<th>p-value</th>
<th>Median survival (95% CI) (mth)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>King’s College (μo)</td>
<td>Present study (μ)</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>0</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>0.37</td>
<td>0.35 (0.23–0.47)</td>
<td>0.376</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>0.40</td>
<td>0.42 (0.29–0.54)</td>
<td>0.793</td>
</tr>
<tr>
<td>Stage 3</td>
<td>0.63</td>
<td>0.63 (0.50–0.73)</td>
<td>0.299</td>
</tr>
<tr>
<td>Stage 4A</td>
<td>0.81</td>
<td>0.81 (0.71–0.90)</td>
<td>0.75</td>
</tr>
<tr>
<td>Stage 4B</td>
<td>0.73</td>
<td>0.80 (0.70–0.90)</td>
<td>0.035*</td>
</tr>
</tbody>
</table>

*p < 0.05 was statistically significant for difference between findings of our study and King’s College. ALS: amyotrophic lateral sclerosis; CI: confidence interval*

When compared to the corresponding milestone timings, as proposed by King’s College, there was no statistical difference (α = 0.05) for stages 2A, 2B, 3 and 4A. However, stage 4B, which was the need for non-invasive ventilation (p = 0.035), arose much later in the course of disease among our patients.

Pertaining to the disease trajectory of bulbar-onset ALS, diagnosis was clinched at 14% of the disease course, involvement of two neurological regions occurred at 28%, involvement of three regions at 42%, offer of supportive enteral feeding at 62% and offer of non-invasive ventilation at 67% into the disease course for our patients (Table III).
Table III. Findings for bulbar-onset ALS.

<table>
<thead>
<tr>
<th>Staging</th>
<th>Mean milestone timing (95% CI)</th>
<th>p-value</th>
<th>Median survival (95% CI) (mth)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>King’s College&lt;sup&gt;(3)&lt;/sup&gt; (μ&lt;sub&gt;o&lt;/sub&gt;)</td>
<td>Present study (μ)</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>0</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>0.38</td>
<td>0.14 (0.01–0.26)</td>
<td>0.019&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>0.39</td>
<td>0.28 (0.01–0.47)</td>
<td>0.152</td>
</tr>
<tr>
<td>Stage 3</td>
<td>0.45</td>
<td>0.42 (0.21–0.63)</td>
<td>0.701</td>
</tr>
<tr>
<td>Stage 4A</td>
<td>0.71</td>
<td>0.62 (0.45–0.78)</td>
<td>0.65</td>
</tr>
<tr>
<td>Stage 4B</td>
<td>0.81</td>
<td>0.67 (0.49–0.86)</td>
<td>0.213</td>
</tr>
</tbody>
</table>

<sup>*</sup>p < 0.05 was statistically significant for difference between findings of our study and King’s College. ALS: amyotrophic lateral sclerosis; CI: confidence interval

Compared to their corresponding milestone timings, as proposed by King’s College<sup>(3)</sup>, there was no statistical difference (α = 0.05) between Singapore milestone timings for stages 2B, 3, 4A and 4B. However, ALS was diagnosed earlier (p = 0.019) in the course of disease for our patients.

Stratified analysis of the groups of patients with limb-onset ALS who had received riluzole and those who had not received riluzole during the course of disease revealed no significant difference between the milestone timings of these two subgroups across all stages (Table IV). Subgroup analysis for bulbar-onset ALS was not conducted, as the sample size was too small to yield meaningful analysis. (n = 2).

Table IV. Subgroup analysis of patients with limb-onset ALS for riluzole therapy.

<table>
<thead>
<tr>
<th>Staging</th>
<th>Mean milestone timing (95% CI)</th>
<th>p-value&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not on riluzole therapy (n = 35)</td>
<td>On riluzole therapy (n = 11)</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>0.35 (0.22–0.48)</td>
<td>0.33 (0.10–0.55)</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>0.42 (0.30–0.55)</td>
<td>0.46 (0.25–0.66)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>0.63 (0.48–0.78)</td>
<td>0.76 (0.67–0.84)</td>
</tr>
<tr>
<td>Stage 4A</td>
<td>0.77 (0.68–0.87)</td>
<td>0.79 (0.55–1.00)</td>
</tr>
<tr>
<td>Stage 4B</td>
<td>0.84 (0.73–0.95)</td>
<td>0.81 (0.69–0.92)</td>
</tr>
</tbody>
</table>

<sup>*</sup>p < 0.05 was statistically significant for Wilcoxon rank-sum test. ALS: amyotrophic lateral sclerosis; CI: confidence interval
DISCUSSION

From the retrospective review of the clinical records of 46 patients with ALS in our study, we were able to delineate the clinical trajectory of ALS among Singapore patients, and establish similarity between the progression of our milestones and that of King’s staging.\(^3\) The only exceptions were that in our study, patients with bulbar-onset ALS were diagnosed earlier in the disease trajectory, while those with limb-onset ALS needed non-invasive ventilation later in the disease trajectory. Riluzole therapy was not found to significantly alter disease trajectory in patients with limb-onset ALS. For patients with limb-onset ALS, diagnosis was observed at 0.35, two CNS region involvement at 0.42, three CNS region involvement at 0.63, diaphragmatic involvement at 0.81 and bulbar involvement at 0.73. For patients with bulbar-onset ALS, diagnosis was observed at 0.14, two CNS region involvement at 0.28, three CNS region involvement at 0.42, diaphragmatic involvement at 0.62 and bulbar involvement at 0.67.

The similarities found between the milestones assessed by our study and that by King’s College have several clinical implications. First, the various stages of ALS could be easily remembered, broadly with approximately 20% of the disease course being attributed to each stage, so that the patient would have gone through 40% of the disease course at stage 2A (or diagnosis), 60% at stage 3 and 80% at stage 4. Clinicians would therefore remain cognisant of the prognosis of disease, and this would facilitate easier discussion of management strategies and advance care planning with patients and their families.

Second, the staging system empowers clinicians with accessible knowledge that can be leveraged to promptly plan interventions in relation to the evolving symptoms and needs of patients with ALS. Timely gastrostomy implementation has been shown to provide patients a safer route of supplemental feeding, and to improve nutrition and weight gain.\(^10\) Likewise, non-invasive ventilation, offered in advanced disease with respiratory involvement, has been shown to prolong survival and ameliorate dyspnoea in patients.\(^11\)
Third, referencing the staging system will allow the healthcare team to anticipate the evolving needs of patients by delineating the disease course. In the absence of this, patients are subjected to overt compulsivity in their decision-making process due to the pressure of disease progression on themselves and their family members.\(^{(12)}\)

In essence, the staging system confer applicable knowledge that can be used to advise patients and their families on the prognosis of disease. Physicians can also more swiftly initiate discussion of advance care planning and facilitate timely patient-centred care, helping to ultimately improve the quality of life of patients, particularly for those in advanced stages of disease.\(^{(13)}\)

With regard to dissimilarities between our milestones and those in King’s staging, surprisingly, Singaporean patients with bulbar-onset ALS were diagnosed earlier in the disease trajectory and Singaporean patients with limb-onset ALS needed non-invasive ventilation later in the course of disease. The former could be attributed to a difference in the methodologies adopted by the two studies. Specifically, the definition of stage 2A in King’s staging was definitive ALS while, for our study, it was probable ALS. We postulated that the discrepancy with respect to patients with limb-onset ALS arose due to the fact that, in local practice, screening for respiratory symptoms mainly revolved around evaluation of breathlessness. The lack of routine evaluation of portentous symptoms of respiratory insufficiency (e.g. declining sleep quality) or objective measurements (e.g. forced vital capacity and peak expiratory flow rate) may have delayed the offering of non-invasive ventilation to our patients. In view of these findings, our centre now routinely assesses these parameters for patients with ALS. However, further prospective cohort studies are necessary to investigate and confirm the associations identified here.

Our study was not without limitations. Being a retrospective cohort study, our findings were constrained by information bias. Analyses were limited to data recorded in the
documentations available. It is possible that scenarios where clinical milestones were reached but not documented, particularly in the years prior to the advent of centralised computerised medical record-keeping for patient documentation at our centre, may have occurred but could not be mitigated. This has a bearing on the documentation of milestone timings. To overcome this, we propose a future prospective cohort study, with survival analysis.

In conclusion, King’s staging provides a convenient staging system for ALS that can be easily remembered and used to model the disease trajectory of limb-onset and bulbar-onset ALS in Singapore patients. Knowledge of disease prognosis empowers clinicians to discuss disease prognosis with patients based on their symptomology. Moreover, knowledge of disease trajectory inferred from the staging model can be utilised by physicians to construct a patient-centred treatment plan that promptly anticipates and addresses the evolving needs of ALS patients. There is room for future nationwide, multicentre prospective studies that place greater focus on the survival of patients with ALS.

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REFERENCES


