Predicting respiratory failure in amyotrophic lateral sclerosis: recruiting a few good pulmonologists

Noah Lechtzin

Affiliation: Dept of Medicine, Division of Pulmonary, Critical Care and Sleep, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Correspondence: Noah Lechtzin, Dept of Medicine, Division of Pulmonary, Critical Care and Sleep, Johns Hopkins University School of Medicine, 1830 E. Monument Street, 5th Floor, Baltimore, MD 21205, USA. E-mail: nlechtz@jhmi.edu

@ERSpublications
People with ALS die from pulmonary complications and pulmonologists have interventions that improve survival and quality of life. The study by Ackrivo and colleagues provides a clinically relevant model to prognosticate respiratory failure in ALS. http://ow.ly/CfMF30o0MWB

Cite this article as: Lechtzin N. Predicting respiratory failure in amyotrophic lateral sclerosis: recruiting a few good pulmonologists. *Eur Respir J* 2019; 53: 1900360 [https://doi.org/10.1183/13993003.00360-2019].

In the 1980s the United States Marine Corps had an advertising campaign built around the phrase, "The Marines are looking for a few good men" (figure 1). This non-gender-neutral slogan would probably not succeed today, but the sentiment could be applied toward the care of amyotrophic lateral sclerosis (ALS). We're looking for a few good pulmonologists. ALS is a progressive neuromuscular disease in which there is degeneration of both upper and lower motor neurons, leading to diffuse muscle weakness and spasticity. It is commonly known as Lou Gehrig's disease in the USA, and motor neurone disease in the UK. As ALS progresses, patients lose the use of their limbs, develop dysarthria and dysphagia, and most commonly die from respiratory failure [1]. Most cases of ALS are sporadic and idiopathic, but about 10% of cases are due to identified genetic mutations [2]. While a great deal has been learned about the pathophysiology of ALS and efforts have been made to improve multidisciplinary care, the average survival from the time of diagnosis remains only 3–5 years [3]. One challenge in the diagnosis and management of ALS is that there is a great deal of variability in what region of the body is affected first and how quickly the disease progresses. Limb onset ALS is the most common presentation, but it can affect corticobulbar pathways first, which results in difficulties with speech and swallowing. This is commonly referred to as bulbar ALS and can be particularly difficult to treat due to problems with dysphagia, malnutrition, dehydration, aspiration, and the inability to clear oral and upper airway secretions. Patients with bulbar ALS may also have difficulty performing pulmonary function tests due to spasticity and mouth weakness. They are also less likely to tolerate and benefit from noninvasive ventilation (NIV). This makes decisions around the respiratory management of individuals with bulbar ALS particularly challenging.

The incidence of ALS is approximately 1–2 individuals per 100 000 and the prevalence is about 5 per 100 000. Because survival is so short, more than 1 in 500 deaths in adults in the UK are due to ALS [2]. There are only two medications approved by the US Food and Drug Administration to treat ALS, riluzole [4] and edaravone [5], and the effects are rather small. The former was shown to improve survival by several months and the latter slowed the decline in functional ability in a subset of patients. However, pulmonary interventions have the potential to improve quality of life and survival in ALS more than any other current

Received: Feb 20 2019 | Accepted after revision: March 03 2019

FIGURE 1 An example of a 1974 recruiting poster for the United States Marine Corps with the slogan "The Marines are Looking for a Few Good Men ...".

therapy. Routine measurement of forced vital capacity is recommended by consensus guidelines as an important tool to estimate prognosis and to help time interventions, such as gastrostomy tube insertion [6]. Use of NIV is standard of care for ALS and has been shown in multiple observational studies [7–9] and in one randomised trial [10] to improve survival. ALS is considered a rare disease, but the prevalence is similar to pulmonary diseases such as cystic fibrosis and idiopathic pulmonary fibrosis. These pulmonary disorders are a common part of the curriculum in pulmonary training programmes and commonly fall under the purview of pulmonary specialists, but ALS and other neuromuscular diseases are often ignored by pulmonologists and care for these patients is left in the hands of neurologists and respiratory therapists.

Ackrivo *et al.* [11] deserve credit for their work to develop a prognostic model to predict the risk of developing respiratory insufficiency within 6 months. Their study aimed to provide pulmonary clinicians and clinical trialists an easily applicable tool to determine if patients are at high or low risk for impending respiratory insufficiency based on their initial presentation. This study used a large single-centre ALS cohort to develop their prognostic model and then validated their model using the PRO-ACT database, a large dataset from patients enrolled in 23 clinical trials [12]. The authors found that a model including increasing age, longer time to diagnosis, bulbar disease, lower forced vital capacity (FVC), more functional limitation, and the presence of respiratory symptoms was strongly predictive of respiratory insufficiency at 6 months. They used stepwise logistic regression to determine their model. The area under the receiver operating characteristic curve was 0.86 in the derivation cohort and 0.74 in the validation cohort. This study had several strengths. It used readily available clinical measures in the prognostic model, it was based on data from a single initial visit, and the single centre cohort from the University of Pennsylvania was quite large at 765 patients. The primary outcome, respiratory insufficiency, can be defined in several ways in ALS. Many previous studies have used a composite outcome including use of NIV, tracheostomy or death. The Ackrivo *et al.* [11] study also included FVC <50% predicted in their definition of respiratory insufficiency. This makes sense from a clinical standpoint but could be problematic from a methodological standpoint in this study. In the USA, initiation of NIV is often dictated by an FVC <50% predicted, and there will therefore be a lot of overlap between FVC <50% predicted and NIV use. This probably does not impact the study design in a meaningful way, but use of FVC as a predictor in the model may. Certainly, a patient with a lower FVC at their initial clinic visit is more likely to have an FVC <50% predicted at

6 months, when compared to someone with a higher FVC at baseline, and will therefore also be more likely to be prescribed NIV. The authors attempted to address this issue by performing several sensitivity analyses. These included removing NIV use from the outcome, removing FVC from the outcome, and using FVC as the only predictor. The performance of the model was maintained in the first two analyses and using FVC as the only predictor did not perform as well as the full model. However, they did not do a sensitivity analysis with both FVC and NIV excluded from the outcome. Doing so would certainly have resulted in far fewer individuals reaching the outcome by 6 months, which would have impacted the accuracy of their model.

While the Ackrivo *et al.* [11] study is the first to predict respiratory insufficiency at 6 months as the outcome, and the study has a stronger respiratory focus than earlier studies, it is reassuring that the findings are very consistent with others. Older age at diagnosis and bulbar onset of disease have long been recognised as poor prognostic factors [13, 14]. Additionally, shorter time from symptom onset to diagnosis suggests a more rapidly progressive form of ALS, and is associated with shorter ventilator free survival [15]. Similarly, lower scores on the ALSFRS-R, which is the most widely used measure of functional ability in ALS, at the time of diagnosis suggest faster progression and shorter survival [16, 17]. Low FVC at presentation is also consistent with a faster progressing disease phenotype and has repeatedly been shown to predict shorter survival [18].

There are other recent publications in the *European Respiratory Journal* relevant to the discussion above regarding the ALS prognostic model. A 2018 study evaluated healthcare utilisation for individuals with neuromuscular disease in Canada [19]. This study identified 185 586 adults with neuromuscular disease, of whom 864 had ALS. Neuromuscular disease patients, as a whole, had a relatively high number of healthcare encounters for respiratory complications. For example, 22% of these individuals went to an emergency room for a respiratory complication over an 11-year period, for a total of 85 066 visits, and 8% had respiratory hospitalisations. In ALS, 22% of patients had a respiratory emergency room visit and 17% had a respiratory hospitalisation. Interestingly, only a quarter of ALS patients had an outpatient pulmonary encounter and only 17% had pulmonary function testing. This study suggests that respiratory morbidity is high in ALS, but there is substantial room to improve upon ongoing, outpatient pulmonary care.

Another interesting study was published earlier this year using data collected during the RespistimALS trial of diaphragm stimulation for ALS [20]. The investigators obtained biopsies of the diaphragm at the time of laparoscopic surgery and quantified diaphragmatic atrophy. Of 50 consenting patients, 39 had adequate biopsy specimens for evaluation. The study group had ALS for an average of 53 months since symptom onset, but had generally well-preserved vital capacities (median 83% predicted). The investigators determined which measures of lung function correlated with diaphragmatic atrophy. Surprisingly FVC, maximal inspiratory pressure, sniff nasal inspiratory pressure and transdiaphragmatic pressure did not correlate with the degree of diaphragmatic atrophy. In univariate analyses, inspiratory capacity correlated with slow-twitch fibre atrophy and supine fall in FVC correlated with fast-twitch atrophy. In multivariate analyses, inspiratory capacity, sniff nasal inspiratory pressure and functional residual capacity were independently associated with slow twitch atrophy. This study highlights the challenges inherent in accurately identifying respiratory muscle weakness in ALS and reinforces the need for knowledgeable pulmonary physicians to be involved in the ongoing care of individuals with ALS, rather than relying on well-intentioned neurologists to manage respiratory complications.

ALS is a devastating fatal disease and extensive research is underway to more fully understand the pathophysiology and find a cure. There is excitement about the potential for novel therapies such as stem cells [21] or antisense oligonucleotides [22]. But until more definitive therapy is available, pulmonologists need to understand the evaluation and care of ALS patients, as appropriate pulmonary care can do more to improve quality of life and prolong survival than any other current therapy. The study by Ackrivo *et al.* [11] will help pulmonologists prognosticate respiratory insufficiency, which will help in determining how aggressively to pursue NIV and other forms of respiratory care. Hopefully this study will help to recruit a few good pulmonologists to the cause.

Conflict of interest: N. Lechtzin has nothing to disclose.

References

1 Lechtzin N, Wiener CM, Clawson L, *et al.* Hospitalization in amyotrophic lateral sclerosis: causes, costs, and outcomes. *Neurology* 2001; 56: 753–757.
2 Taylor JP, Brown RH Jr, Cleveland DW. Decoding ALS: from genes to mechanism. *Nature* 2016; 539: 197–206.
3 Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. *Lancet* 2007; 369: 2031–2041.
4 Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med* 1994; 330: 585–591.

5 Edaravone ALS 16 Study Group. A post-hoc subgroup analysis of outcomes in the first phase III clinical study of edaravone (MCI-186) in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2017; 18: Suppl. 1, 11–19.
6 Miller RG, Jackson CE, Kasarskis EJ, *et al.* Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009; 73: 1218–1226.
7 Aboussouan LS, Khan SU, Meeker DP, *et al.* Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. *Ann Intern Med* 1997; 127: 450–453.
8 Kleopa KA, Sherman M, Neal B, *et al.* Bipap improves survival and rate of pulmonary function decline in patients with ALS. *J Neurol Sci* 1999; 164: 82–88.
9 Pinto AC, Evangelista T, Carvalho M, *et al.* Respiratory assistance with a noninvasive ventilator (Bipap) in MND/ALS patients – survival rates in a controlled trial. *J Neurol Sci* 1995; 129: 19–26.
10 Bourke SC, Tomlinson M, Williams TL, *et al.* Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol* 2006; 5: 140–147.
11 Ackrivo J, Hansen-Flaschen J, Wileyto EP, *et al.* Development of a prognostic model of respiratory insufficiency or death in amyotrophic lateral sclerosis. *Eur Respir J* 2019; 53: 1802237.
12 Atassi N, Berry J, Shui A, *et al.* The PRO-ACT database: design, initial analyses, and predictive features. *Neurology* 2014; 83: 1719–1725.
13 Preux PM, Couratier P, Boutros-Toni F, *et al.* Survival prediction in sporadic amyotrophic lateral sclerosis. Age and clinical form at onset are independent risk factors. *Neuroepidemiology* 1996; 15: 153–160.
14 Stambler N, Charatan M, Cedarbaum JM. Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. *Neurology* 1998; 50: 66–72.
15 Knibb JA, Keren N, Kulka A, *et al.* A clinical tool for predicting survival in ALS. *J Neurol Neurosurg Psychiatry* 2016; 87: 1361–1367.
16 Wolf J, Safer A, Wohrle JC, *et al.* Factors predicting one-year mortality in amyotrophic lateral sclerosis patients--data from a population-based registry. *BMC Neurol* 2014; 14: 197.
17 Hothorn T, Jung HH. RandomForest4Life: a Random Forest for predicting ALS disease progression. *Amyotroph Lateral Scler Frontotemporal Degener* 2014; 15: 444–452.
18 Westeneng HJ, Debray TPA, Visser AE, *et al.* Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. *Lancet Neurol* 2018; 17: 423–433.
19 Rose L, McKim D, Leasa D, *et al.* Patterns of healthcare utilisation for respiratory complications of adults with neuromuscular disease: a population study. *Eur Respir J* 2018; 52: 1800754.
20 Guimaraes-Costa R, Similowski T, Rivals I, *et al.* Human diaphragm atrophy in amyotrophic lateral sclerosis is not predicted by routine respiratory measures. *Eur Respir J* 2019; 53: 1801749.
21 Boulis NM, Federici T, Glass JD, *et al.* Translational stem cell therapy for amyotrophic lateral sclerosis. *Nat Rev Neurol* 2011; 8: 172–176.
22 Miller TM, Pestronk A, David W, *et al.* An antisense oligonucleotide against SOD1 delivered intrathecally for patients with SOD1 familial amyotrophic lateral sclerosis: a phase 1, randomised, first-in-man study. *Lancet Neurol* 2013; 12: 435–442.