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Patterns of VC Decline in Amyotrophic Lateral Sclerosis
A More Robust Prognostication?

Amyotrophic lateral sclerosis (ALS) is a progressive disease of the upper and lower motor neurons that leads to skeletal (including respiratory) muscle weakness. The decrease in respiratory function is commonly assessed by the FVC or slow VC (1), depending on the magnitude of skeletal muscle denervation (2). Complications of functional decline include hypoventilation, pneumonia, and respiratory failure, necessitating initiation of assisted ventilation (3). There have been few descriptions of the different patterns of respiratory function decline in ALS. In this issue of the *Journal,* Ackrivo and colleagues (pp. 1513–1521) describe the creation of a group-based trajectory model (GBTM) that identified three distinct trajectory groups of FVC in ALS, termed "stable low," "rapid progressor," and "slow progressor" (4). Patients were followed until they developed respiratory insufficiency, were lost to follow-up, or completed the study. Five variables were found to have a significant association with the trajectory groups: diagnosis delay, body mass index, bulbar-onset disease, ALS Functional Rating Scale-Revised (ALSFRS-R) orthopnea score, and ALSFRS-R total score. The authors found that compared with the slow progressors group, rapid progressors tended to have longer diagnosis delays, a lower body mass index, more bulbar-onset disease, lower ALSFRS-R total scores, and an orthopnea score. The potential clinical value of this analysis of functional decline is that it can predict the initiation of noninvasive ventilation or tracheostomy, or death. The study is based on an earlier investigation in which Ackrivo and colleagues created and validated a model to be used at baseline "at the bedside" to discriminate patients at high risk of developing respiratory insufficiency at 6 months (5).

A few points regarding the computational model used by the authors should be noted. GBTM involves a procedure in which individuals are gathered into meaningful subgroups that show statistically similar trajectories (6). It is facilitated by use of the Bayesian information criterion, a criterion for model selection among a finite set of models that is based, in part, on the likelihood function. In this study, the authors selected the model in which all groups had stable or declining FVC values while following significantly different trajectories. This strategy left out groups with increasing FVC values (which would be highly unlikely in ALS) while it preserved the least number of groups, which would suggest separate phenotypes. The source population used to derive the group-based trajectory model was a University of Pennsylvania cohort of patients ($n = 873$). The source population for the validation cohort was a clinical trial database (PRO-ACT [Pooled Resource Open-Access ALS Clinical Trials]) from 23 phase II/III clinical trials ($n = 7{,}461$). The pattern of overall functional decline was approximately the same in the derivation and validation cohorts. The main finding was that there were distinct differences between the patterns of VC decline and the curves depicting the proportion of patients who were free of respiratory insufficiency.

Could the different trajectories of VC decline represent genetic variants among ALS patients? Technological advances in gene mapping and DNA analysis have led to the identification of multiple ALS genes. More than 120 genetic variants had been identified as of 2016 (7) and have been reported to be involved in protein homeostasis, RNA homeostasis, and cytoskeletal dynamics (2). Among these, SOD1 (superoxide dismutase 1) and C9ORF72 (chromosome 9 open reading frame 72) are the most common in familial and sporadic cases (2). Skeletal muscle integrity is facilitated by genes that encode proteins that are important for normal cytoskeletal dynamics, including DCTN1 (dynactin 1), PFN1 (profilin 1), TUBA4A (tubulin 4A), and possibly the modifier gene *EPHA4* (ephrin type-A receptor 4), all of which are involved in aspects of axonal structural maintenance and transport. Diminished expression of the latter is associated with longer survival in ALS. This finding may account for the longevity of the slow progressors in this study. Other genes have been implicated in protein degradation and neuroinflammation, depositions of intranuclear RNA, impaired nuclear membrane transport, and perturbations of gene transport, all of which contribute to motor neuron degeneration (2). Environmental factors such as a remote history of head trauma (8) and smoking (9) have also been implicated in an increased risk for ALS.

In any analysis of disease onset and rate of progression in different cohorts, a concern may be raised regarding the issue of lead time to diagnosis and first measurement of VC. The time when the patient is first assessed may not be related to the disease itself but rather to social and financial considerations such as distance from the referral center, referral patterns, and insurance coverage, with the result that different time points are designated for individual patients at different stages of their disease. The authors accounted for this potential source of analytical error by using the initial clinic presentation as time zero (as opposed to the date of diagnosis), by controlling for diagnosis delay, and by indicating the time from symptom onset to the first visit and survival since symptom onset. They concluded that the GBTM model's ability to separate trajectories regardless of when the functional decline was first observed attested to its reliability.

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In their conclusions, the authors state that early initiation of noninvasive ventilation (NIV) may have impacted patients' quality of life and survival, particularly in the rapid progressor group. This is debatable, as studies in other neuromuscular disorders (such as muscular dystrophy) have shown that "preventive" initiation of NIV was not successful in slowing or preventing progression of disease (10). In fact, patients with close to normal VC often resist the use of NIV until their VCs have decreased to low levels (<30% predicted or 1 L) or there is associated bulbar dysfunction.

The authors are to be commended for performing a thoughtful and sophisticated analysis of a feature of ALS that has been described in general terms for the last half century, namely, the variability in functional decline. Clearly, the next step would be to conduct genetic analyses in a large population of patients in an attempt to identify plasma biomarkers that predict the onset and timing of respiratory insufficiency long before patients are confronted with decisions regarding goals of care. Better yet, identification of such genetic biomarkers could lead to targeted, patient-centered therapies that would halt and perhaps even reverse the (currently) inexorable decline in respiratory function. ■

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Heart of the Matter? Early Ventricular Dysfunction in Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) represents one of the most challenging causes of respiratory failure managed in neonatal critical care. These challenges arise from the pathophysiological triad of pulmonary hypoplasia, pulmonary vascular disease, and left ventricular (LV) dysfunction associated with herniated abdominal contents, impaired fetal lung growth, and perturbations in umbilical venous return to the developing left ventricle (1). The management of CDH has evolved from a primarily surgical problem to one of integrated prenatal, surgical, respiratory, and cardiac care, principally focusing on lung-protective approaches to support the hypoplastic lungs and reducing the burden of pulmonary hypertension (2–4). Unfortunately, mortality remains persistently high (25–30%) (5), and, in contrast to what has been observed with other causes of severe neonatal respiratory failure, the rates of extracorporeal membrane oxygenation use have not decreased with incremental improvements in ventilatory care (Figure 1). LV hypoplasia has long been recognized as a fetal manifestation of CDH (6), and resultant cardiac dysfunction has been postulated as an important and underappreciated determinant of outcome (1, 7).

Early cardiac function in CDH is poorly understood, and investigations have been limited to small observational studies (8, 9). The study presented in this issue of the *Journal* by Patel and colleagues (pp. 1522–1530) is thus timely and provides valuable insight into CDH pathophysiology (10). They report echocardiographic categorizations of LV and right ventricular function performed in the first 48 hours after delivery in 1,173 infants enrolled in the CDH Study Group Registry (59 centers) from 2015 to 2018, a period encompassing current lung-protective

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