UNIVERSITY OF CALIFORNIA,
IRVINE

Understanding Disease Heterogeneity and Patient Characteristics in Patients with Amyotrophic Lateral Sclerosis (ALS)

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Veena Mathew

Thesis Committee:
Professor Tahseen Mozaffar, Chair
Professor Sherrie Kaplan
Professor Sheldon Greenfield

2019

DEDICATION

To all the fighters –

A disease may be rare, but hope should not be.

TABLE OF CONTENTS

LIST OF FIGURES

Page

LIST OF TABLES

Page

ACKNOWLEDGMENTS

I would like to express the deepest appreciation to my committee chair and mentor, Professor Tahseen Mozaffar, whose simple response to my discontent after another failed clinical trial set me on this path: “so do something about it.”

I would like to thank my committee members, Professor Sherrie Kaplan and Professor Sheldon Greenfield, for their expertise and encouragement along the way.

I would also like to express my most sincere gratitude to Marissa Saplala for being a beacon of light while I navigated my way through the program.

I would like to thank Drs. Tahseen Mozaffar, Annabel Wang, Namita Goyal, Ali A Habib, and Manisha Kak and UC Irvine Health for contributing clinic data for abstraction and analysis.

I would also like to thank the following organizations that contributed to the design and implementation of the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database and the data it houses: Neurological Clinical Research Institute (NCRI) at Massachusetts General Hospital; Northeast ALS Consortium (NEALS); Novartis; Prize4Life; Regeneron Pharmaceuticals, Inc; Sanofi; Teva Pharmaceuticals Industries, Ltd.

I thank the ALS Association Golden West Chapter for supporting the dissemination of the prospective data collection through their monthly newsletter. In addition to advancing the search for effective treatments through research, the Golden West Chapter supports people living with ALS and their loved ones in 31 counties throughout California and Hawaii.

ABSTRACT OF THE THESIS

Understanding Disease Heterogeneity and Patient Characteristics in Patients with Amyotrophic Lateral Sclerosis (ALS)

By

Veena Mathew

Master of Sciences in Biomedical and Translational Science

University of California, Irvine, 2019

Professor Tahseen Mozaffar, Chair

Background:

Amyotrophic lateral sclerosis (ALS) is a fatal neurologic disease that is projected to double in worldwide incidence in the next 20 years. The heterogenic nature of the disease and relatively limited research data, compared to non-rare diseases, have made it difficult for clinician researchers to alter the course of the disease within the short life expectancy after symptom onset.

Methods:

This was a mixed-method retrospective review and live sampling study using three distinct data sources. Retrospective data was abstracted from the electronic medical record systems for a select group of ALS patients seen at the University of California, Irvine Neuromuscular Center (UCI NMC). Additional retrospective datasets curated by the Pooled Resources Open-Access Clinical Trials (PRO-ACT) database were also analyzed. Observational data was collected using a 9-item survey developed on Google Forms and disseminated through the ALS Association Golden West Chapter. The items measured symptom onset, diagnostic journey, and patient demographics.

Results:

The analyses confirmed current reports of higher disease incidence in Caucasian populations, usually comprising at least 60% of each dataset. The gender prevalence towards males was only observed in the PRO-ACT dataset. There was also a difference in mean age between PRO-ACT (56 years), UCI (61 years), and Online Questionnaire respondents (66 years).

Discussion:

Ultimately retrospective data analyses were limited by substantial missing, not at random data. Large data repositories can bridge the gap between non-rare and rare disease research, but only with robust and methodologic data collection across all participating sites.

INTRODUCTION

As populations continue to age in developing nations, future projections estimate the number of people afflicted with ALS will nearly double to 800,000 worldwide by 2040. The variable phenotypic presentations and rates of functional decline prove challenging for clinician researchers to alter the disease course in the relatively short life expectancy following disease onset. Researchers and patients alike hope to see a breakthrough therapy emerge, but only 20% of the past 50 ALS trials have evolved to late-stage development; only one is currently continuing its late-stage development. The ongoing clinical practice is to treat ALS as a homogeneous disease, addressing symptoms as they arise; however, this approach fails to account for the broad spectrum of survival between patients. A group in the United Kingdom developed a model for predicting survival based on known factors linked to survival; however, the model is restricted to patients of European ancestry and does not include any patient demographics beyond ALS traits.

Considering the varying prognosis between patients, identifying predictors of survival is crucial to improving clinical trial outcomes, providing personalized care, and bettering overall quality of life. In this thesis, the following questions will be addressed:

Question 1: Will an in-depth analysis of the PRO-ACT database confirm the longstanding average demographics associated with ALS?

Hypothesis 1: The PRO-ACT database will trend towards younger patients, but still Caucasians and males will predominate the demographic characteristics of that sample with 50% of survival beyond five years from symptom onset.

Question 2: Are there associations between patient characteristics (i.e., race/ethnicity, gender) and the incidence of ALS, rate of decline, and mortality?

Hypothesis 2: The PRO-ACT database will have greater incidence of ALS in non-minorities and males, but equal rate of decline and mortality independent of these characteristics.

Question 3: Will the observational data from the patient survey identify trends associated with diagnostic delay or patient characteristics?

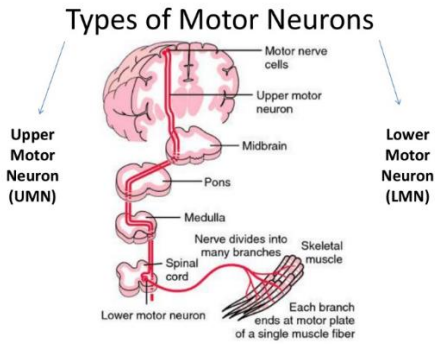
Hypothesis 3: The diagnostic delay in the observational population will be shorter than that seen in the PRO-ACT dataset and patient characteristics will align with those of the national averages.

In addressing these questions, the results from this study may update current demographics and help develop a prognostic survival model applicable to all patients with ALS. Additionally, it will identify problem areas in ALS clinical trials and improve the design of future trials.

BACKGROUND

Amyotrophic lateral sclerosis (ALS) is a progressive, neurodegenerative disease affecting upper and lower motor neurons in the brain stem, motor cortex, and spinal cord. Motor neurons extend from the brain to the spinal cord and to the muscles throughout the body. They initiate and serve as the communication relay between the brain and the voluntary muscles (Figure 1). This relay is disrupted in patients with ALS, which causes the muscles to gradually weaken. Over time the brain loses its ability to initiate and control all voluntary movements (1). The progressive loss of motor neurons clinically presents as myasthenia, atrophy, spasticity, dysphagia, dysarthria, and dyspnea. Patients afflicted with this terminal disease suffer total paralysis and usually die from complications secondary to respiratory failure. Current data suggests that the average life expectancy for a person with ALS is three to five years from the time of symptom onset.

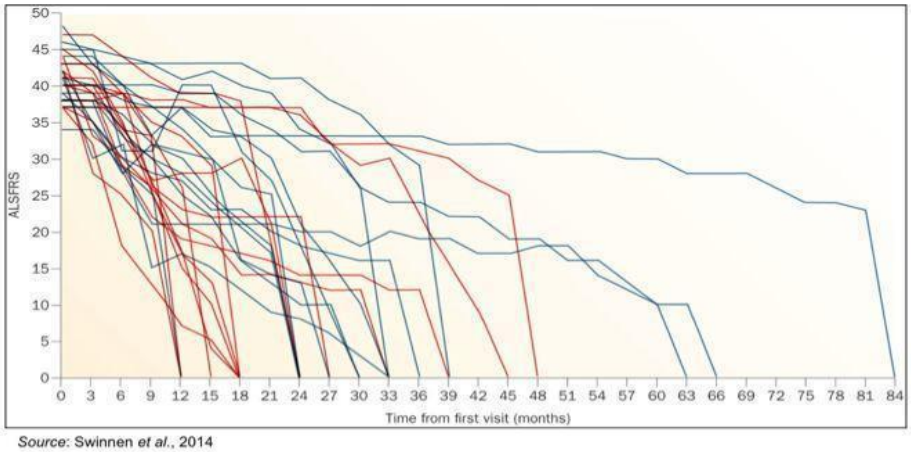
Figure 1. Types of Motor Neurons



Prior to receiving a diagnosis, most patients will see multiple physicians, possibly receiving one or two misdiagnoses along the way. A recent study by Paganoni reviewed such data for 304 subjects and found that the median total diagnostic time was 11.5 months (IQR: 7-20 months). A subset of patients (n=122) had data available for median time from presenting

symptom to first doctor visit (four months, IQR: 2-7 months) and first doctor visit to suspected ALS diagnosis (three months, IQR: 1-6, n=100). The study found that approximately 52% received at least one other diagnosis before ALS was confirmed. Additionally, each patient saw an average of three physicians before ALS was confirmed. In most cases, the diagnosis was first suspected by either a general neurologist (57%) or an ALS specialist (20%) but confirmed by an ALS specialist in 85% of cases and by a general neurologist in 12% of cases (2). One of the factors adding to the diagnostic delay is that early symptoms are difficult to differentiate from other neurological illnesses. Early symptoms of ALS include weakness to a muscle region, fasciculations and/or cramps, tripping, decreased dexterity, slurred speech, muscle spasticity, and difficulty chewing or swallowing. Current data suggests that the average life expectancy for a person with ALS is two to five years from the time of diagnosis. However, half of all affected live at least three years, 20% live five years or more, and up to 10% survive for more than 10 years. (3) The survival variability between patients was best demonstrated by a study of 30 randomly selected ALS patients at the Leuven University Hospital in Belgium. As seen in Figure 2, in plotting the ALSFRS-r scores from first visit to death, the Swinnen study supported the concept of ALS as highly heterogeneous. (4)

Figure 2. Heterogeneity of Disease Progression Between ALS Patients



Source: Swinnen *et al.*, 2014

1.1 Disease Incidence

The FDA define a rare disease as one that affects fewer than 200,000 people in the U.S. At this time, ALS still meets this criterion; however, as previously mentioned, future projections will shift it out of this designation. A unique project conducted by the Texas State Department of Health Services studied Texas-specific epidemiological data regarding ALS. Interestingly, each of the large metropolitan areas studied showed increasing incidence rates every year, with an average of 325 new cases per year. (5) This localized increase is similar to that projected for the national average established by the congressionally mandated National ALS Registry. Furthermore, as recently demonstrated by a review of worldwide ALS incidence, the disease exhibits a heterogeneous distribution with notably lower reported incidences in South Asia ([0.58-0.89]/100,000 person-years) and higher reported incidences in North Europe ([1.46-2.32]/100,000 person-years). (6) This review is set apart from other ALS epidemiology studies because it is one of the few meta-analyses conducted in this population. Even so, there were several limitations that impacted the overall incidence report rates, particularly with U.S. data acquisition. Cases from the U.S. spanned from 2009-2011, prior to and in the early phase of the National ALS Registry.

As exemplified by the several long-standing and robust European registries that have engendered the predictive survival model, the value of a disease registry is considerable. Unfortunately, the National ALS Registry has three substantial flaws that must be addressed for viable data use. First, researchers cannot access data in the registry as “it does not yet contain enough data to be useful to most researchers.” (7) Thus, after a decade of existence, the data remains accessible only to the Agency for Toxic Substances and Disease Registry (ATSDR) with periodic data released by the Centers for Disease Control and Prevention (CDC). Second, also of

concern for the registry is its heavy dependence upon household access to the internet to complete initial and interval questionnaires. Of the total 2015 Census household respondents, nearly 35.5% of non-Hispanic, Black households and 29.5% of Hispanic (any race) households responded as not having any internet subscription. (8) As such, the incidence rate is likely higher than currently reported. Lastly, despite being congressionally mandated, registry enrollment remains voluntary in all states except Massachusetts.

1.2 Race and Ethnicity

ALS has higher prevalence in non-Hispanic whites than any other group. Given the rarity of the disease, incidence is often calculated from mortality data. Previously epidemiologic studies suggest there are race/ethnicity discrepancies in patients diagnosed with ALS. The largest sample size reported to date was a recent study conducted at the Massachusetts General Hospital which obtained mortality information through the National Longitudinal Mortality Study (NLMS) and the National Death Index (NDI) to determine whether race/ethnicity and socioeconomic status (SES) are associated with ALS mortality in the United States. The study observed higher rates of ALS among whites compared to other race/ethnicity groups. (9) However, as the NLMS relies on data collected through the Census report, the dependence upon the Census response rate introduces a potential bias. The CDC lists ALS prevalence rates calculated for the four U.S. Census regions with the rates, per 100,000 population, as follows: Midwest (5.7), Northeast (5.5), South (4.7), West (4.3). (10) Historically, the response rate remained below 70% until the 2000 Census. Although the Census is meant to count every person, not legal citizen, unauthorized residents fear that participation will expose them to immigration raids or government harassment. (11) Consequently, prevalence rates of ALS in the

South and West may be underreported, which is significant when taking into consideration that 9 out of 10 of America's most diverse metros are in just these two regions. (12)

Although the specific racial/ethnic disparity was possibly confounded by Census methods, the Roberts study did conclude this rate is likely reflective of actual higher risk of ALS rather than the effect of SES on risk, thus placing heavier emphasis on the influence of racial/ethnic background. (9) These data further supported the role of race/ethnicity and its involvement in ALS.

1.3 Disease Management

Since its discovery in 1869 by Jean-Martin Charcot, the actual mechanism behind the development of ALS largely remains a mystery making the treatment of it an enigma. There are currently two FDA approved therapies for this disease, Riluzole (Rilutek®) and Edaravone (Radicava®); however, neither are considered therapeutically beneficial.

1.3.1 Riluzole (Rilutek®)

In 1995, this glutamate blocker was the first FDA approved treatment for ALS; however, there are several limitations that prevent it from being an effective standard of care therapy. The exact average of ALS patients in the United States taking Riluzole (Rilutek®) is widely variable between reports, ranging between 50% to 75%. (1) Some patients cannot tolerate the known side effects (e.g., gastrointestinal disturbances, lethargy) or must discontinue use due to the drugs known hepatotoxicity effects. However, most patients opt not to take it because the added 3-5 months of life combined with the $6 daily cost even for the generic version makes it difficult for most patients to use. (13,14)

1.3.2 Edaravone (Radicava®)

In 2017, the FDA approved a repurposed stroke therapy from Japan, for use in all patients with ALS without requiring any clinical trials in the U.S. The data from Japan's phase 3 clinical trial faced outside criticism for enrolling ALS patients who were early on in their disease with overall better functionality. Additionally, the drug carries a hefty $148,000 price tag per year of treatment. Medicare and Veterans Administration offers coverages upwards of 80%, but public insurance programs do not provide any coverage. (15) There are also additional costs associated with drug administration staff resources, as well as, placing and maintaining a central venous catheter for the monthly infusions. Lastly, the treatment itself can be burdensome to patients; it requires monthly infusion cycles, administered over a 10-day period. Although home infusions are possible, remote clinic infusions are not; thus vacations, family time, and other social activities either decrease or halt to accommodate the cycles. Consequently, within the first year, less than 10% of Americans with ALS accessed Radicava and fewer still have continued treatment with it. (15)

Given the limited treatment options, the standard of care predominantly focuses on palliative care methods such as, non-invasive ventilation (NIV), percutaneous endoscopic gastrostomy (PEG) tube feeding, and assistive devices to aid patients as the disease progresses.

1.3.3 Respiratory Function

Maintaining respiratory function is of utmost importance in patients with ALS as it affects daily quality of life and overall disease outcome. Consequently, monitoring respiratory decline and initiating NIV such as BiPAP or Trilogy in a timely manner is key to minimizing prolonged respiratory distress. In comparison to tracheostomy-free ALS patients who never used NIV during the course of their disease, overall median survival benefits are as great as 13 months [HR=0.61; $p<0.001$], regardless of site of onset. (16) Bulbar-onset patients, for whom respiratory

decline doubles the monthly risk of mortality compared to limb-onset patients, experience survival benefits as high as 19 months [HR=0.50; p<0.001]. (16; 17) Despite the overall upper limit survival benefit almost three times that of Riluzole, many insurance companies in the United States will not approve NIV coverage until pulmonary function tests indicate severe respiratory restriction.

1.3.4 Dysphagia

PEG tubes allow for a safe and effective method of providing enteral feeding to the extent of the patient's dysphagia involvement (i.e., NPO, partial, medication administration). Since the placement procedure is done under general anesthesia, it must be done prior to respiratory impairment falling within the severe criterion. A post-mortem analysis of 83 patients in the U.S. revealed a significant survival benefit [HR=0.24; p<0.01] in the patients with a PEG, after adjusting for covariates (e.g., age, site of onset). (18) However, due to the lack of larger scale data to support it, the overall effect on survival remains a topic of debate. Regardless, alleviating the consequences of dysphagia cannot be underestimated.

1.3.5 Assistive Devices

As patients develop deficits to mobility and communication, assistive devices become crucial to support remaining motor function. Assistive devices include items such as manual or power wheelchairs, orthoses, home adaptations, and augmentation and alternative communication (AAC). (19) The procurement of these various modifiers depends on healthcare access, geographic location, and insurance approvals. One study followed almost 1500 patients across 12 ALS centers in Germany found that 54.8% of patients needed 5 or more assistive devices, but 29.8% of these devices were not procured. Like U.S. trends, the more complex and expensive the device, the less likely it was to be obtained. The procurement rates were lowest for

transfer systems like lifts and ramps (40.3%), AAC devices (38.8%), and power wheelchairs (38.5%). Even though patients report these devices as the ones that provide the highest satisfaction and usefulness (20), the primary cause of failed procurement was insurance rejection (50.9%), followed by patient noncomformity (29.5%), and finally patient death before procurement (19.6%). (21)

The ongoing clinical practice is to treat ALS as if the disease is a homogeneous disease; however, this approach fails to appreciate and investigate the broad spectrum of survival. The variability in survival between patients is best supported by addressing the heterogeneous nature of the disease, both in the phenotypic presentation and varying rates of functional decline. Recent studies based out of the United Kingdom have developed a model of predicting survival based on known factors linked to survival. Unfortunately, this model is restricted to patients of European ancestry and does not include any patient demographics beyond ALS traits. Considering the varying prognosis between patients, identifying predictors of survival based on an individual patient's demographics and ALS characteristics is key to providing more personalized care. Novel epidemiological studies have helped the neuromuscular community provide average prognoses to newly diagnosed patients and identify subgroup differences. Trials in rare diseases frequently have smaller sample sizes due to the limited pool of eligible patients. (22) The creation of large-scale databases complements the ongoing efforts of clinical trials in rare diseases like ALS.

METHODS

2.1 University of California, Irvine (UCI) Neuromuscular Center (NMC)

The study design planned for retrospective review of serial data collected from January 1, 2013 through January 1, 2018. Even though the UCI NMC database continues to collect prospective data as part of clinical care, the analysis for this study was restricted to the specified time-period to ensure enough longitudinal data points per subject. The retrospective study using UCI data was submitted to and approved by UCI's local Institutional Review Board (IRB) under Expedited Category 5: research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). UCI Health Enterprise Data & Analytics maintains and oversees the Enterprise Data Warehouse which integrates data from the EMR, Professional Billing, Hospital Billing, and other administrative systems. UCI Health's Honest Broker service runs Enterprise Data Warehouse queries using filters such as diagnosis codes and billing codes and returns de-identified results for IRB approved research use.

Patients were identified using the ninth (ICD-9) and tenth (ICD-10) revisions of the International Statistical Classification of Diseases and Related Health Problems diagnosis codes for ALS, 335.20 and G12.21, respectively.

2.2 Northeast Amyotrophic Lateral Sclerosis (NEALS) Consortium

As a melting pot country, the United States health system is posed with the challenge of multi-ethnic backgrounds and demographics that are likely not covered in the current body of literature. Despite its name, the NEALS consortium is composed of over 100 research centers across the country dedicated to translating scientific advances into new treatments and quality improvement projects. The Pew Research Center estimates that 11.1 million of the nation's

unauthorized immigrants live in just 20 major metropolitan areas, with California and Texas account for five and three areas, respectively. Figure 3 depicts the NEALS research centers superimposed with the most diverse metropolitan areas in America as well as those recorded as having the most unauthorized immigrants. (11; 12)

Figure 3. Map of NEALS Sites vs. Most Diverse Metro Areas vs. Most Unauthorized Immigrants

2.3 Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database

As a prominent clinical trial center, UCI NMC is a part of several neuromuscular collaborative research networks including the NEALS consortium. A partnership between NEALS, Prize4Life, Neurological Clinical Research Institute (NCRI) at MGH engendered the PRO-ACT database. The platform houses over 8500 ALS patient records from multiple completed clinical trials. The initiative merges data from existing publicly- and privately-conducted ALS clinical trials to provide those with an interest in moving ALS research forward quickly with a powerful tool.

PRO-ACT provides researchers with access to over 10,000 de-identified records for patients who took part in a clinical trial. The database is composed of data from 23 Phase II/III clinical trials that had placebo and treatment-arm data. Datasets are available for more than 10 million longitudinally collected data points including demographics, lab, medical and family history and other data elements. (23)

2.3.1 PRO-ACT Database Design

The initial database was composed of all phase II and III ALS clinical trials completed between 1990 and 2010 with at least 80 subjects enrolled. Key decision markers for each trial were contacted and asked to donate de-identified trial datasets. A common data structure was created for the data that was categorized as "common" among the eligible trials. The data went through extensive cleaning to become as cohesive as possible for the final database. The result was longitudinal data from 16 trials on 8635 people with ALS, including 11 distinct data categories totaling 8 million data points. (23) This large database allows researchers to utilize network models, machine learning algorithms for clustering, predicting and stratifying data that was otherwise not possible to explore in ALS research.

2.3.2 PRO-ACT Database Advantages

The first large-scale example of this was the 2012 DREAM-Phil Bowen ALS prediction Prize4Life challenge. The challenge was a collaboration between Prize4Life and The DREAM Project (Dialogue for Reverse Engineering Assessments and Methods) that invited solvers to build algorithms utilizing three months of data to predict disease progression nine months later. Over 1000 registrants from 64 countries took part in the challenge. The resulting algorithms not only identified new potential predictors of ALS progression, but has the potential to reduce the required sample size for clinical trials by at least 20%. (24)

As mentioned before, ALS epidemiology studies heavily rely on death certificates and registry data because there is no clinical test to determine if a person has the disease. Given this limitation, ALS is often misdiagnosed and the validity of epidemiological conclusions using mortality data is questionable. A study in South Carolina inspected the medical records of patients identified in the state's morbidity data with the ALS ICD-10, G12.2, that 85% had supporting diagnostic documentation in their charts, but only 65% of death certificates were coded with an ALS linking cause of death; 18% had an 'alternative neurological diagnosis' as the cause of death. (25) The retrospective study was able to circumvent this problem because all cases come from the PRO-ACT database where the patients have been confirmed by an expert neurologist as having the disease.

2.4 Outcome Measures

The progressive symptoms of ALS and functional decline are measured by way of the ALS Functional Rating Scale revised [ALSFRSr] (Figure 4), which measures gross and fine motor function, bulbar function, and respiratory function. In the clinic setting, patients complete this patient reported outcome (PRO) with a certified evaluator, as well as forced vital capacity (FVC) tests with a licensed respiratory therapist. The FVC is a measurement of lung size (in liters) and represents the volume of air in the lungs that can be exhaled following a deep inhalation (Figure 5). The results, presented in liters, are compared to what is expected for someone of the same sex, age and height; the resulting calculation is the percent vital capacity. Lower percentages are indicative of diaphragmatic weakness while seated and/or supine.

Both the ALSFRSr and FVC commonly serve as the primary or secondary endpoint in ALS clinical trials. They also serve as valuable red flags for initiating NIV, PEG tube placement, and obtaining orthotics and other adaptive equipment for patients as they progress.

Figure 4. Amyotrophic Lateral Sclerosis Functional Rating Score - revised (ALSFRSr)

Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R

SPEECH
4 Normal speech processes
3 Detectable speech disturbance
2 Intelligible with repeating
1 Speech combined with nonvocal communication
0 Loss of useful speech

SALIVATION
4 Normal
3 Slight but definite excess of saliva in mouth; may have nighttime drooling
2 Moderately excessive saliva; may have minimal drooling
1 Marked excess of saliva with some drooling
0 Marked drooling; requires constant tissue or handkerchief

SWALLOWING
4 Normal eating habits
3 Early eating problems – occasional choking
2 Dietary consistency changes
1 Needs supplemental tube feeding
0 NPO (exclusively parenteral or enteral feeding)

HANDWRITING (with dominant hand)
4 Normal
3 Slow or sloppy; all words legible
2 Not all words legible
1 Able to grip pen but unable to write
0 Unable to write

CUTTING FOOD/HANDLING UTENSILS (patients without gastrostomy)
4 Normal
3 Somewhat slow and clumsy, but no help needed
2 Can cut most foods, although clumsy and slow; some help needed
1 Food must be cut by someone, but can still feed slowly
0 Needs to be fed

CUTTING FOOD/HANDLING UTENSILS (patients with gastrostomy)
4 Normal
3 Clumsy but able to perform all manipulations independently
2 Some help needed with closures and fasteners
1 Provides minimal assistance to caregiver
0 Unable to perform any aspect of task

DRESSING & HYGIENE
4 Normal function
3 Independent and complete self-care with effort or decreased efficiency
2 Intermittent assistance or substitute methods
1 Needs attendant for self-care
0 Total dependence

TURNING IN BED AND ADJUSTING BED CLOTHES
4 Normal
3 Somewhat slow and clumsy, but no help needed
2 Can turn alone or adjust sheets, but with great difficulty
1 Can initiate, but not turn or adjust sheets alone
0 Helpless

WALKING
4 Normal
3 Early ambulation difficulties
2 Walks with assistances (any assistive devices including AFOs)
1 Nonambulatory functional movement only
0 No purposeful leg movement

CLIMBING STAIRS
4 Normal
3 Slow
2 Mild unsteadiness or fatigue
1 Needs assistance (including handrail)
0 Cannot do

DYSPNEA
4 None
3 Occurs when walking
2 Occurs with one or more of the following: eating, bathing, or dressing
1 Occurs at rest, difficulty breathing when either sitting or lying
0 Significant difficulty, considering using mechanical respiratory support

ORTHOPNEA
4 None
3 Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
2 Needs extra pillow in order to sleep (more than two)
1 Can only sleep sitting up
0 Unable to sleep without mechanical assistance

RESPIRATORY INSUFFICIENCY
4 None
3 Intermittent use of NIPPV
2 Continuous use of NIPPV during the night
1 Continuous use of NIPPV during the night and day
0 Invasive mechanical ventilation by intubation or tracheostomy

Total: _____/48

Source: J Neurol Sci. Oct 1999.

Figure 5. Forced Vital Capacity (FVC)

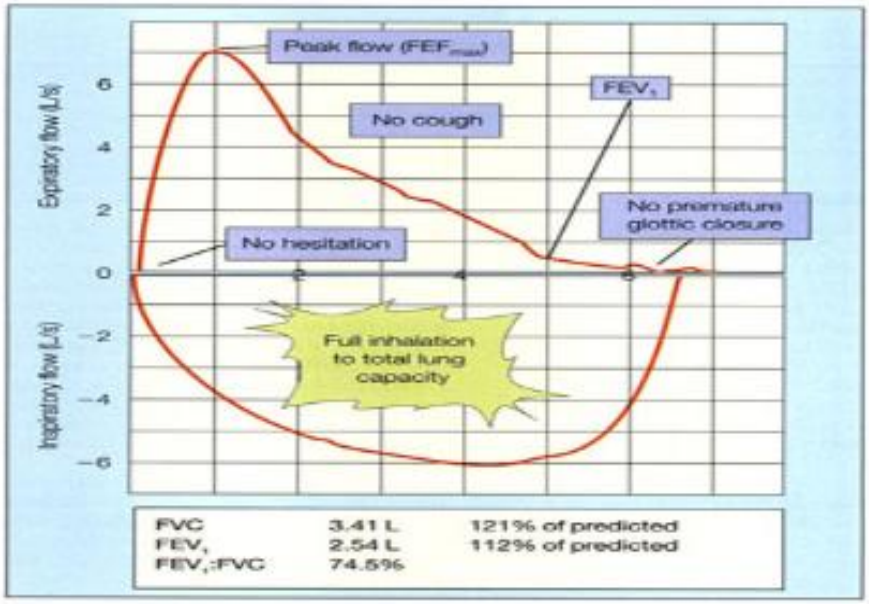


*Figure 1 – **A normal flow-volume loop** is evident in this composite graph of the expiratory flow-volume loop and the forced inspiratory vital capacity loop. The positions of forced expiratory volume in 1 second (FEV_1), peak flow (maximal forced expiratory flow [FEF_{max}]), and forced vital capacity (FVC) are identified. There is no evidence of hesitation, cough, premature glottic closure, or other common causes of technical problems.*

2.5 Retrospective Data Collection

The following data was targeted for data abstraction from the UCI NMC database and PRO-ACT database:

- Age
- Smoking status
- Comorbidities restricting lung function
- Time since diagnosis
- Time since symptom onset
- Time to NIV initiation
- Time to death, if applicable
- ALSFRSr scores
- Seated %FVC scores

2.6 Study Endpoints

Since the average life expectancy of a person with ALS averages about two to five years from the time of diagnosis, identifying links that are predictors of survival may help clinicians in initiating the palliative care previously discussed. As such, the following study endpoints were set under the premise of viable data from the UCI and PRO-ACT databases:

- ALSFRSr slope of decline over time stratified within groups by site of onset (limb vs. bulbar)
- FVC (%) slope of decline over time stratified within groups by site of onset (limb vs bulbar)

2.7 Methods of Analysis

Since this was a retrospective review of data, power and sample size calculations were not necessary to analyze the data. Statistical analysis was conducted using SPSS version 25.0 (IBM, Inc., Armonk NY) and SAS version 9.4 (SAS Institute Inc., Cary NC) software. Descriptive statistics were used to determine the distribution between the following patient characteristics: age, sex, site of onset (limb or bulbar), race, ethnicity, and time to death. Additional descriptive statistics were used to observe the distribution of site of onset within sex, Caucasian race, and ethnicity. Bivariate correlations were used to test for significant correlation between disease-specific variables and age, sex, and race/ethnicity. Independent samples t-tests were used to determine the relationships between Riluzole use or site of onset against time to death. Univariate regression was employed to determine the average ALSFRSr score among the subjects.

RESULTS

3.1 UCI NMC Dataset

The Honest Broker query identified 192 patients, but data abstraction was prematurely terminated because of access provisioning issues. Consequently, a total of 54 patients were reviewed and 25 met the inclusion criteria requiring a confirmed diagnosis and ≥ 3 visits. The primary reason for exclusion was diagnosis misidentification in query's target. (Figure 6, Figure 7)

Figure 6. UCI NMC: Excluded Cases

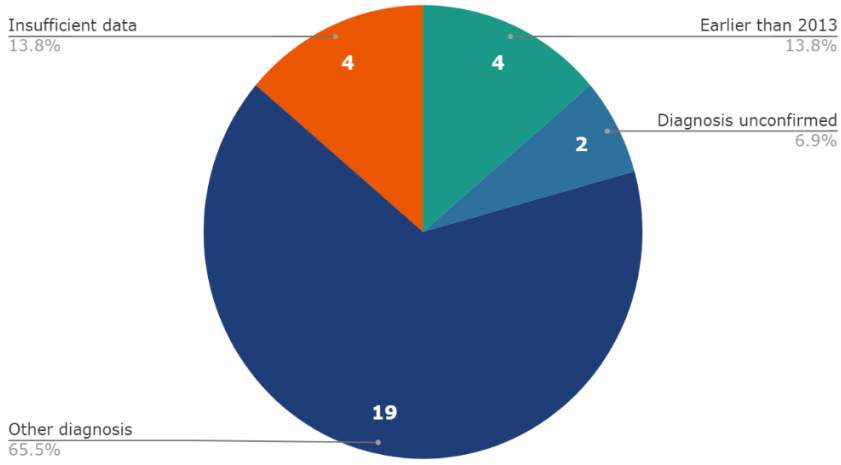
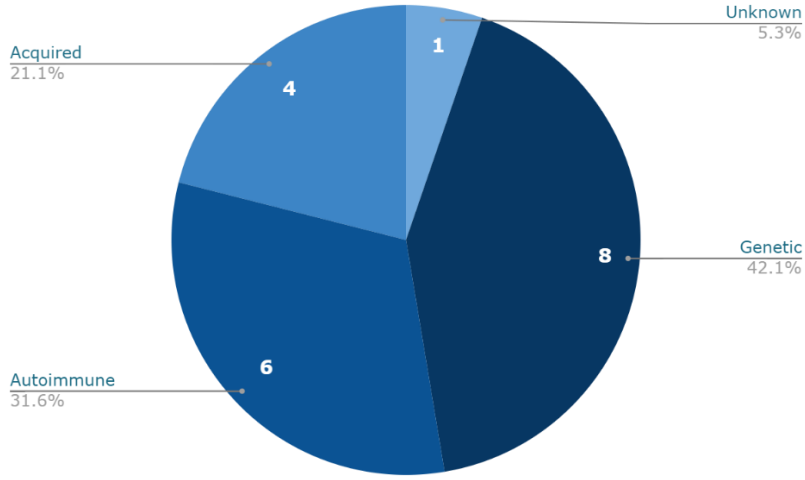
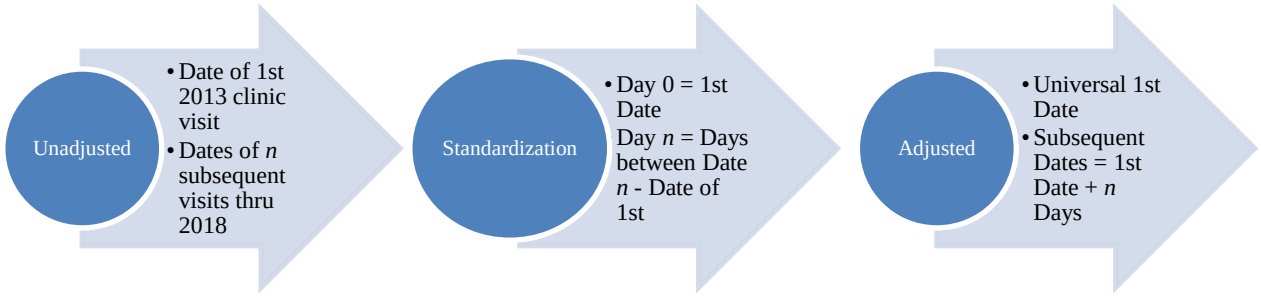


Figure 7. UCI NMC: Excluded Cases - Other Diagnoses



The data abstracted for included patients were as follows: site of onset, date of clinic visits, ALSFRSr scores, %FVC seated, race/ethnicity, symptom onset date, diagnosis date, age at diagnosis, and date of first documented NIV and/or PEG use (if applicable). The intervals between clinic visits varied between patients since appointments are dependent on patient and clinician availability, as well as insurance approval. To easily compare between subgroups, visit dates were adjusted (Figure 8) and a new variable was created to calculate the diagnostic delay which was defined as the difference, in days, from date of diagnosis to date of symptom onset.

Figure 8. UCI NMC: Visit Date Adjustment



During the data abstraction phase, it was evident that the inconsistent recording of ALSFRSr scores would be a limiting factor in the overall data analysis. Among the 25 patients, only 55% of the expected ALSFRSr counts were present. The imputation method was considered as that is the most commonly used missing data method in ALS trials. However, since the sample size was smaller than anticipated, the analytical plan was modified to be predominantly focused on reporting observations.

3.1.1 Demographics

The average patient age was approximately 61 years (range: 35-83). In this random sampling of 25 patients, the ratio of bulbar- to limb-onset ALS was 1:1.3. Approximately 68% of patients had race or ethnicity documented in their records. (Table 1) Additionally, 48% had documented NIV use and 36% had documented PEG placement data with 100% of PEG patients using NIV.

Table 1. UCI NMC: Demographics

Race/Ethnicity	***n* (%)**
Caucasian	11 (64.7)
Pacific Islander	1 (5.9)
Asian	2 (11.8)
Hispanic or Latino*	3 (17.6)

Table entries are sample size (%) out of 17; *unknown race

3.1.2 Site of Onset

The average age of bulbar-onset patients was 65.2 years (range: 48-83), whereas the limb-onset patients were 58.9 years (range: 35-79). Patients with bulbar-onset ALS on average had a longer diagnostic delay than limb-onset ALS patients by approximately 129 days. Although this value was not statistically significant (p=.376), a 3-month difference is clinically relevant given the faster rate of decline usually seen in patients with bulbar-onset ALS. This difference was demonstrated by the faster time in the 17% lower mean FVC score (Figure 9) and faster time to NIV initiation and PEG placement from time of diagnosis. (Table 2)

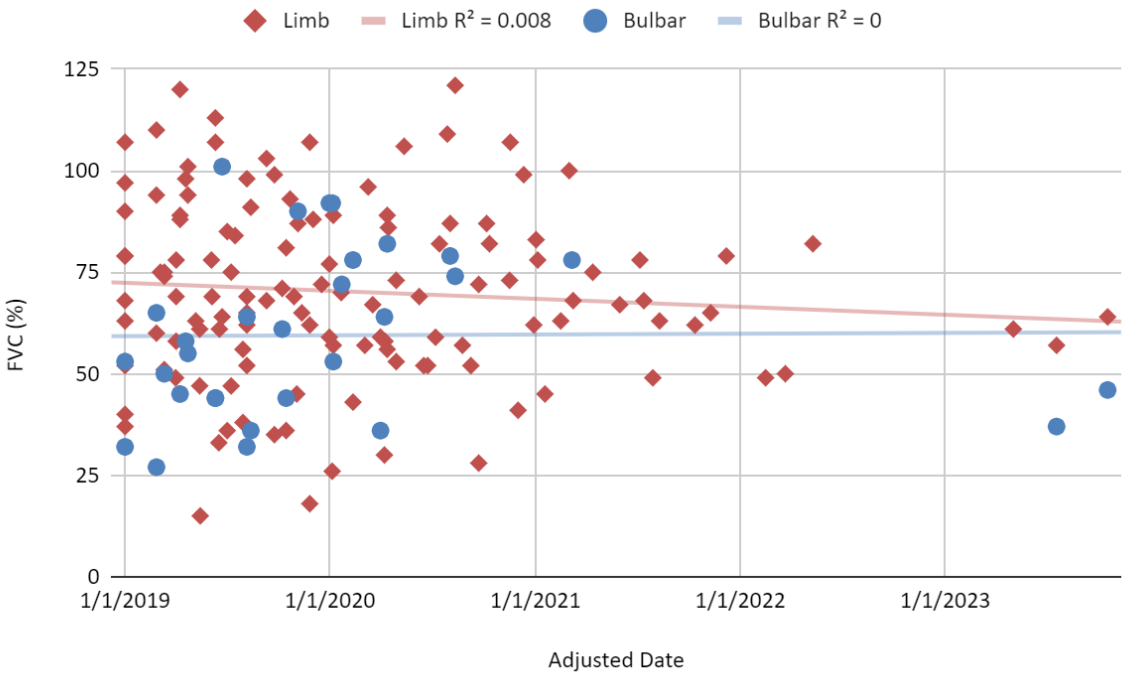
Table 2. UCI NMC: Mean Values by Site of Onset

	Bulbar	Limb	p
FVC (%)	70.1	87.1	.072
NIV Initiation (days)	193	421	.302
PEG Placement (days)	183	740	.224

Table entries are mean; p-values computed using independent samples t-test

On average, limb onset patients had a higher average FVC score and more documented FVC trials than bulbar onset patients. A total of 12 patients, 6 bulbar and 6 limb onset patients initiated NIV, but only half of the limb onset group went on to have PEG tubes placed.

Figure 9. UCI NMC: FVC Decline by Site of Onset



3.2 PRO-ACT Dataset Cleaning

Although there were over 12,000 subjects in the PRO-ACT dataset, initial review of the various files that compose the database revealed large amounts of missing data per subject. The target subjects for inclusion in the final analysis required a robust dataset with as minimal missing values as possible.

Prior to 1999, the ALSFRS scale only had one question related to respiratory function, thus giving disproportionate weight to limb and bulbar dysfunction. The ALSFRSr incorporated additional assessments of dyspnea, orthopnea, and the need for ventilatory support. Given the importance of respiratory function in ALS, it was important to have subjects that were

administered the ALSFRSr instead of the ALSFRS. Subjects with ALSFRSr data and three or more visits in the PRO-ACT dataset were extracted; the resulting aggregate file revealed 3374 viable cases with 30,978 data points.

As mentioned before, FVC is an objective measure of respiratory function and its decline is indicative of diaphragmatic weakness. It serves as a key clinical tool for initiating NIV earlier on during the disease when the survival benefit is higher. The aggregate data extrapolation for all subjects with more than three visits revealed 5014 cases for use.

After preparing both aggregate ALSFRSr and FVC files, the two datasets were compared to identify match cases. Match cases were defined as subjects that had ALSFRSr data, FVC data, and more than three visits for analysis. The resulting PRO-ACT Matched Cases file identified 375 subjects that met the inclusion criteria. However, it was at this point that the FVC inclusion parameter was re-visited. In addition to the absence of respiratory-restricting comorbidity data, there was a significant amount of missing data points within each case which risked compromising the integrity of conclusions drawn from the analyses. (Table 3) Consequently, the analytical plan was amended to forgo FVC analysis and proceed solely with the cases identified in the ALSFRSr aggregate file. Figure 10 details the datasets selected for these subjects that were merged into one file for the full analysis. The variables were compared against the 'Subject ID' variable to identify the extent of missing data; the 'Diagnostic Delay' variable was calculated using the absolute value of the difference between the 'Symptom Onset to Trial Start' and 'Diagnosis to Trial Start' variables, in days.

Figure 10. PRO-ACT: Dataset Variables

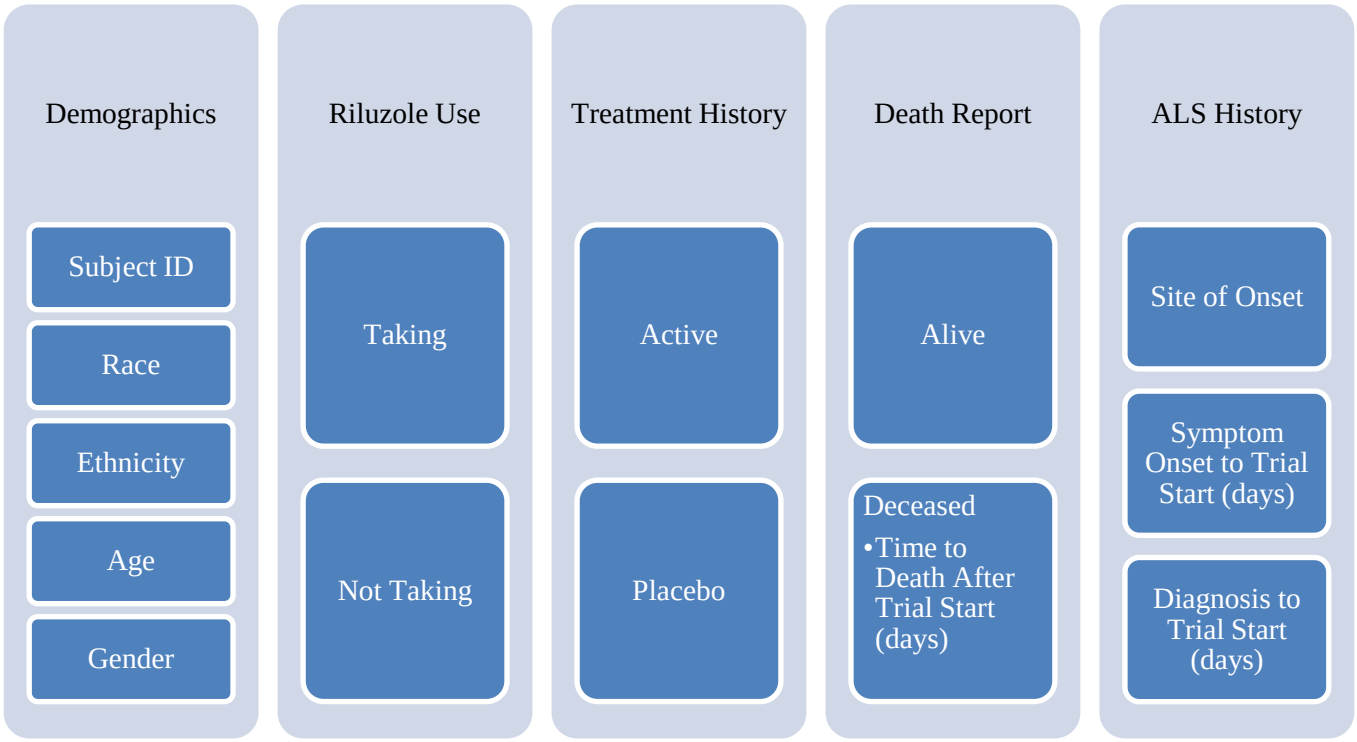


Table 3. PRO-ACT: Missing Data

Variable	***n***
Site of Onset	444 (13.2)
Diagnostic Delay	1380 (40.9)
Age	678 (20.1)
Gender	0 (0.0)
Riluzole Use	619 (18.4)
Ethnicity	1806 (53.5)
Race	1720 (51.0)
Death Report	1796 (53.2)

Table entries are sample size (%) missing out of 3374 patients

3.2.1 Demographics

The average age of the participants was approximately 56 years (range: 18-82) with a 1.7:1 male to female ratio. Of the 3374 subjects, only 2930 (86.4%) had data recorded for site of

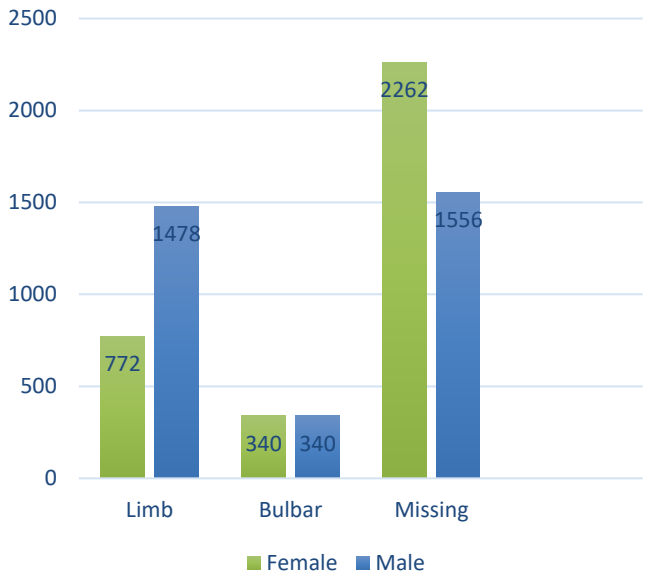
symptom onset. Within this group, 30.5% of the 1112 females had bulbar-onset ALS; whereas among 1818 males, only 18.7% had bulbar-onset ALS. (Figure 11) Approximately 50% of the 3374 subjects did not have race recorded. Among the 1671 subjects with race recorded, 94.6% were categorized as Caucasian, leaving 3.6% as either Black/African American or Asian; the remaining 1.8% were categorized as unknown. (Table 4) The reporting of Hispanic/Latino ethnicity was missing in over 50% of the included cases. The frequency of Hispanic/Latino ethnicity, regardless of race, was reported as 4.7% Hispanic/Latino and 95.3% non-Hispanic/Latino. Given the large disparity between Caucasian and non-Caucasian races in this dataset, the analysis was conducted once more without any ALSFRSr and minimum number of visit restrictions. By removing these restrictions, Caucasians comprised 62.6% of the total PRO-ACT database, while Black/African American and Asian subjects made up 16.5%; the remaining 20.9% fell under other or unknown. The same was done for the ethnicity data which revealed that 81.7% of the PRO-ACT database was either unknown or missing ethnicity data.

Table 4. PRO-ACT: Demographics

Variable	n (%)	Mean
Age (years)		
Female	990 (29.3)	57.8
Male	1706 (50.6)	54.5
Race		
American Indian/Alaska Native	0	-
Asian	17 (0.5)	-
Black/African American	28 (0.8)	-
Hawaiian/Pacific Islander	15 (0.4)	-
Unknown	30 (0.9)	-
Caucasian	1581 (46.8)	-
Ethnicity		
Hispanic or Latino	74 (2.2)	-
Non-Hispanic or Latino	1494 (44.3)	-

Table entries are sample size (%) out of 3374 patients

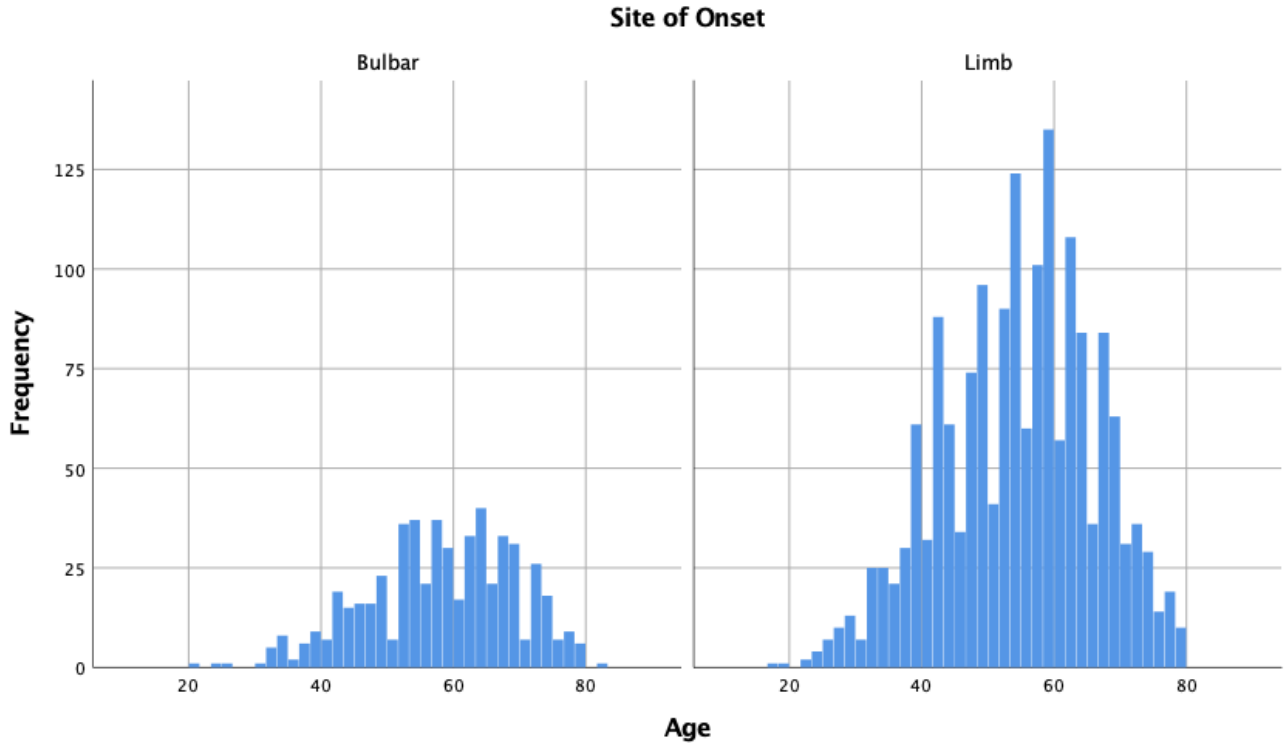
Figure 11. PRO-ACT: Site of Onset by Gender



3.2.2 Enrollment Age

Compared to the bulbar-onset patients where the average age was 58.3 years (CI: 57.4-59.2), the limb-onset patients had a younger average age of 54.8 years (CI: 54.2-55.3). (Figure 12)

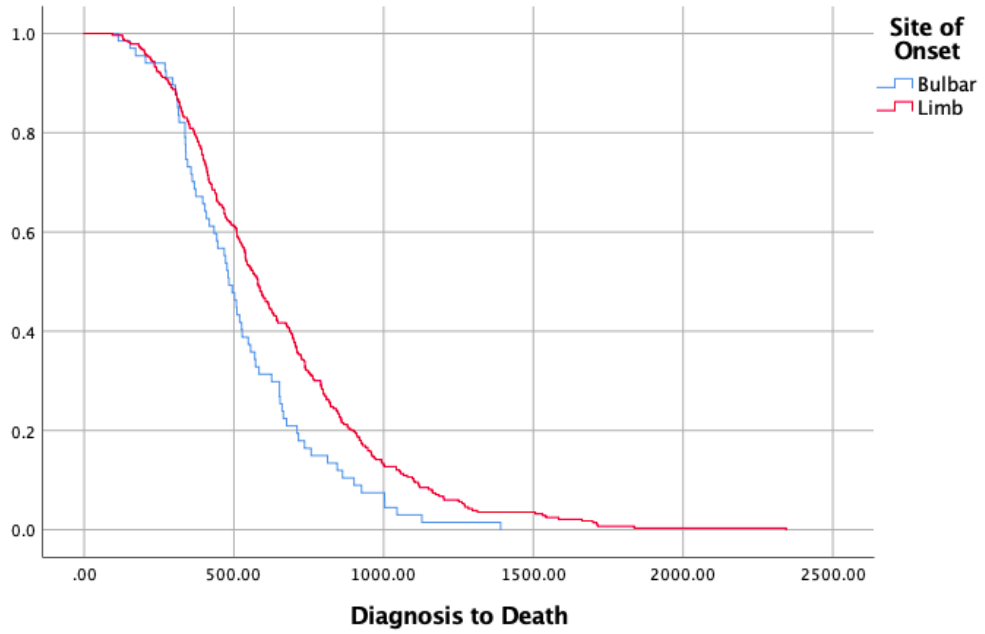
Figure 12. Site of Onset vs Age



3.2.3 Gender

An inter-gender comparison, stratified by site of onset, of the mean survival times from diagnosis to death revealed that bulbar- and limb-onset females lived longer than males by 77 (p=.097) and 20 days (p=.544), respectively. The intra-gender comparison demonstrated that limb-onset patients, regardless of gender, lived longer on average. However, there was a significant mean difference in time from diagnosis to death for males by approximately 115 days (p=.003). (Figure 13)

Figure 13. PRO-ACT: Kaplan-Meier Survival Curve for Males



3.2.4 ALSFRSr

The average first and last documented ALSFRSr scores for all patients in the dataset were 37.8 and 26.4, respectively. Among the 3374 patients, the average length of study participation was 377 days corresponding with a 13-point overall rate of decline on the 48-point scale. Upon examination, 24 patients were identified as unusual cases because they did not have any change in ALSFRSr scores. The first 6 were grouped as probable early terminations who were not in a study long enough, only 37-95 days, for the outcome measure to detect functional change. The other 18 patients were in a study for at least 109 days and at most 739 days; the average ALSFRSr score in this group was 44 without any change in 327 days. An adjusted analysis was done excluding the latter 18 patients and retaining the former 6 patients. The adjusted average length of study participation was 114 days corresponding with a 6-point overall rate of decline. (Figure 14, Figure 15)

Figure 14. PRO-ACT: ALSFRSr Score Over Time in Limb-Onset ALS

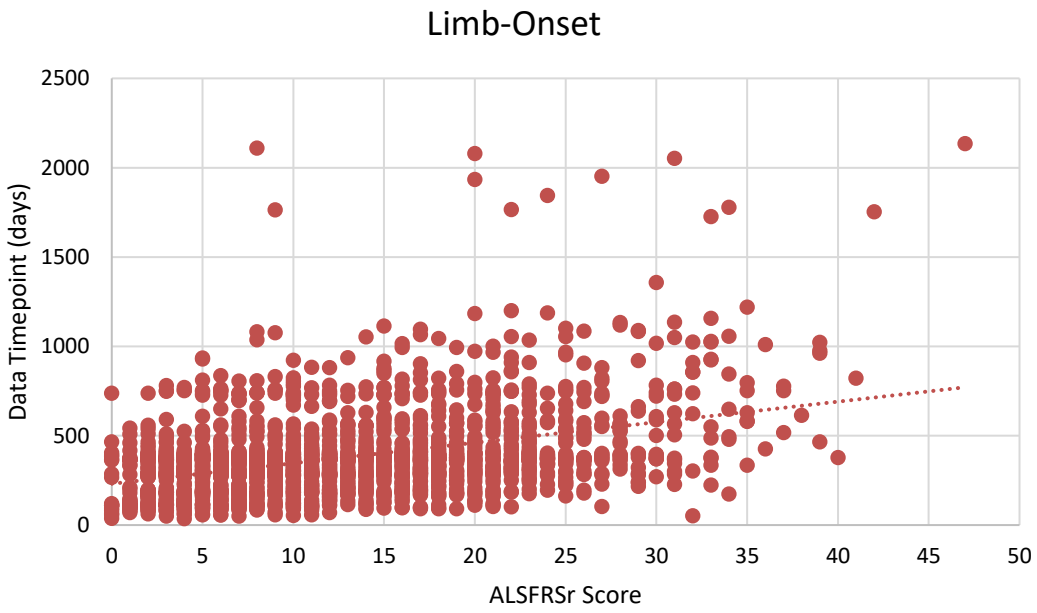
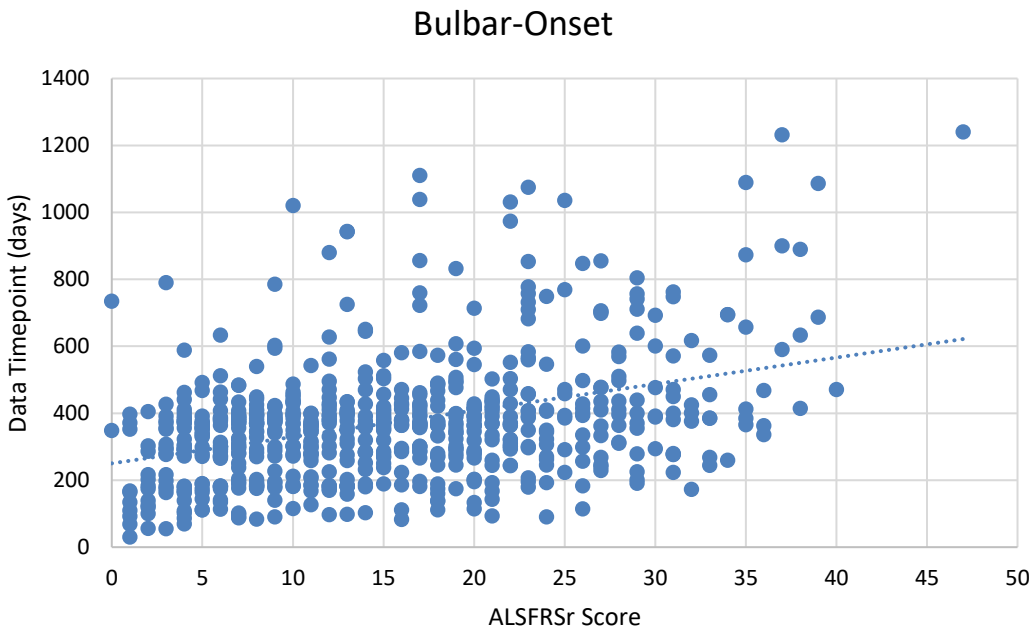


Figure 15. PRO-ACT: ALSFRSr Score Over Time in Bulbar-Onset ALS



3.2.5 Mortality

Vital status was reported for 1578 patients, 728 of whom passed away during or shortly after study participation. Based on the 598 patients with more specific death data available, the

average time to death was 2.6 years (IQR: 1.8-3.2) after disease onset. Despite the increased mortality risk associated with bulbar-onset ALS, only 17.2% of the bulbar-onset subjects died compared to the 82.8% documented as limb-onset. As expected, the average time to death for subjects with limb-onset compared to bulbar-onset ALS was significantly longer. However, the diagnostic delay was not significantly different between the two groups. (Table 5) It is possible that there were more deaths in the bulbar-onset group that was not captured as it should have been, or these subjects withdrew from the study beforehand in which case it would not be part of this database.

Table 5. PRO-ACT: Time to Death Stratified by Site of Onset

	Limb-Onset (N=441)	Bulbar-Onset (N=145)	p
Diagnostic Delay	315	286	.122
Symptom Onset to Death	970	860	.001
Diagnosis to Death	655	575	.004

Table entries are mean, in days; p-values computed using independent samples t-test

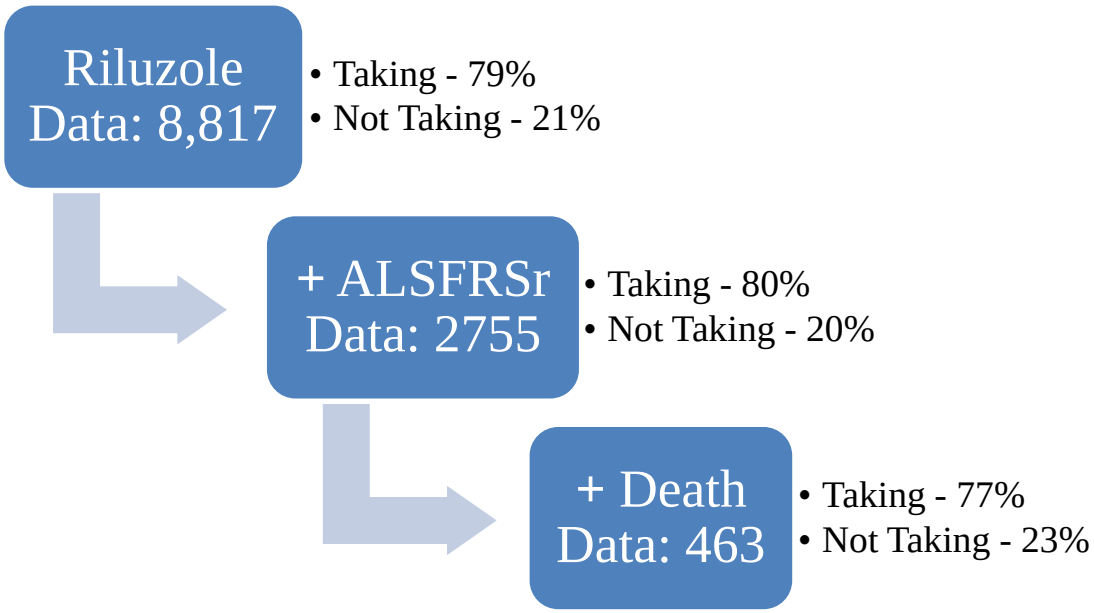
3.2.6 Study Treatment Group

Since the PRO-ACT database contains data points from subjects that participated in a clinical trial, the potential effects of study treatment assignments were explored. Independent samples t-test was used to identify mean difference in survival between the active and placebo groups across the 23 clinical trials that composed the dataset. Equal variances were assumed between the two groups which showed the subjects who were in the placebo group had a mean difference in time to death of 214 days compared to the active group whose median time to death was 824 days [CI: -412 to -15, p=.036].

3.2.7 Riluzole

Although there was a great deal of missing data, the use of Riluzole was one of the most robust variables in the PRO-ACT database. Riluzole use was collected for 92.4% of the 10,723 subjects in the database. Since most ALS clinical trials include inclusion criterion requiring a stable Riluzole status (taking or not taking) for at least 30 days prior to study screening, an independent samples t-test was conducted for all subjects with both Riluzole and death data that had at least 3 study visits to detect possible effect on time to death. The ratio between the two subgroups stayed consistent as the sample size narrowed. (Figure 16) The average time to death (in days) for subjects using Riluzole was approximately 408 days compared to 450 days [CI: -4 to 88] for those who were not taking it. The mean difference in time to death was not statistically significant (p=.073).

Figure 16. PRO-ACT: Riluzole Use



3.3 Prospective Online ALS Questionnaire

A total of 32 respondents completed the online questionnaire, which was available for 30 days. There were 10 respondents who required assistance from a caregiver to input their responses on their behalf.

3.3.1 Demographics

The average age was 66 years (range: 45-95) for both men (n=17) and women (n=15). Women reported a slightly higher diagnostic delay (10.8 months) than men did (8.1 months). Respondents were asked to provide their race by selecting all of the following that applied: European, Middle Eastern, North African, Black or African American, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Native Hawaiian or Other Pacific Islander, Cuban, Mexican, Puerto Rican, South or Central American, American Indian or Alaska Native. The responses received fell into six distinct categories, two of which were biracial. (Table 6)

3.3.2 Site of Onset

After recalling their first symptom(s), 10 cited 'difficulty speaking' or 'difficulty breathing' as the main symptom that lead them to seek out a physician's evaluation. (Figure 17) These 10 were categorized as bulbar-onset ALS, while the 22 respondents who cited 'foot drop', 'muscle twitching' or 'muscle weakness' as the main symptom were categorized as limb-onset ALS. The gender ratio as equal in the bulbar-onset group, but 1:1.75 in the limb-onset group with higher male prevalence. (Table 6)

Figure 17. Online Questionnaire: Reported First Symptom(s)

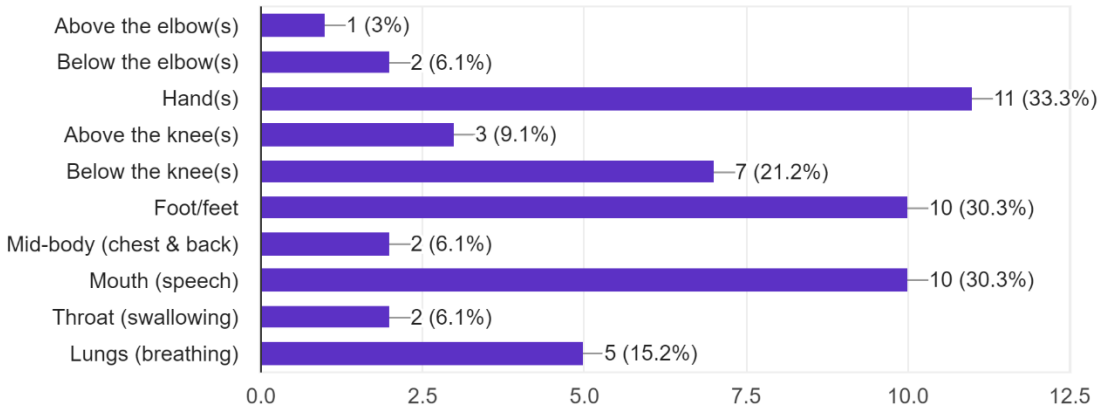


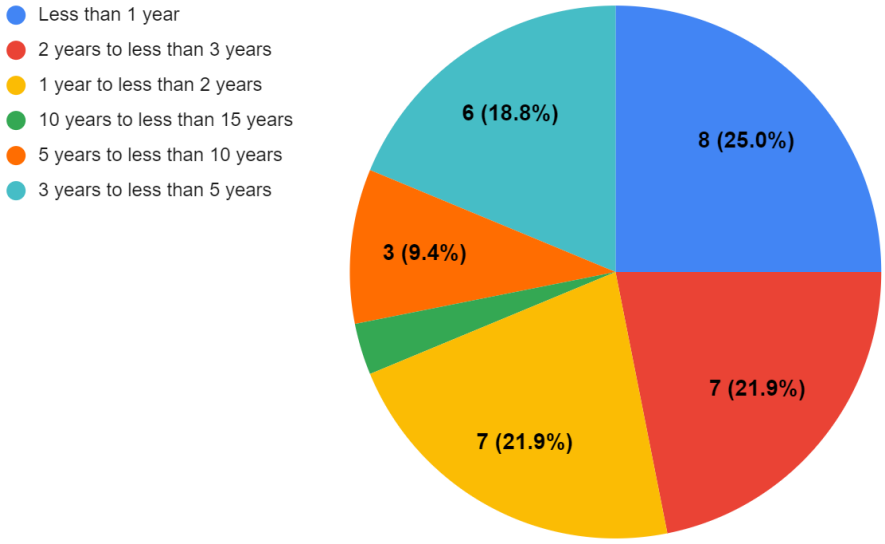
Table 6. Online Questionnaire: Race Distribution by Site of Onset with Gender Ratio

	Limb-Onset	Bulbar-Onset	Male: Female
European	15	8	12:11
Black or African American	1	0	1:0
Mexican	3	0	1:2
South or Central American	1	1	1:1
Chinese & Native Hawaiian or Other Pacific Islander	1	0	1:0
European & American Indian or Alaska Native	1	1	2:0

3.3.3 Diagnostic Journey

A quarter of the respondents reported themselves as diagnosed less than one year ago, while 12% reported they were diagnosed upwards of five years ago. (Figure 18) Prior to getting diagnosed, 54% of respondents were misdiagnosed and managed for another disease at least once; 16% were misdiagnosed more than two times.

Figure 18. Online Questionnaire: ALS Diagnosis Duration



DISCUSSION

4.1 The Comparison to National Averages

The average age in the PRO-ACT database aligns with the current national average of 55 years and less than 50% of the 3,374 patients survived past five years from symptom onset. However, there was a higher incidence of males with ALS and the racial prevalence aligns with the study conducted at MGH which observed higher rates of ALS among Caucasians compared to other racial groups. The concurrence between that study and this one is to be expected given the disproportionate ratio of Caucasian subjects to non-Caucasian subjects. As demonstrated by Rochon et al, representation of minorities in clinical trials remains wanting. Their data indicated that approximately 82% of randomized control trials participants were "White (non-Hispanic)" relative to 72% who reported to be "White" in the 1999 U.S. Census Bureau. By contrast, about 27% of the 1999 US population reported as "Black (non-Hispanic), Asian and Pacific Islander, and Hispanic", but only 13% reported as trials participants. (26)

Comparatively, within the UCI dataset and the Online Questionnaire respondents, the mean age was higher than the national average by 6 and 11 years, respectively. Although the Caucasian prevalence was not as high as what was reported in the PRO-ACT database, it was still the most prevalent group. It is difficult to rule out the effect of the small sample sizes from the UCI dataset and Online Questionnaire dataset, 25 and 32, respectively. In general, minorities have less access to healthcare and mistrust in the medical system. Consequently, they are less likely to participate in clinical trials due to a lack of awareness, misperceptions about them, and overall lack of knowledge to make an informed decision to participate in one. Additionally, unlike the PRO-ACT dataset, the former two datasets had a relatively equal incidence of ALS between genders.

4.2 The Role of Patient Characteristics

Although the PRO-ACT analyses demonstrated an increased incidence of ALS in non-minorities, a reliable conclusion regarding the rate of incidence and mortality between racial/ethnic groups was not possible because of the small group of minorities in the database. The gap was narrowed in the UCI and Online Questionnaire datasets, but vital status was often out-of-date in the clinic dataset and not applicable in the live patient sampling.

4.3 The Value of Prospective Data Collection

Overall, the Online Questionnaire dataset successfully demonstrated a decreased mean diagnostic delay compared to the PRO-ACT dataset and comparative studies as well as a primarily Caucasian prevalence.

4.3.1 Redefining Caucasian Terminology

Currently the FDA guidelines define Caucasian as a person having origins in any of the original peoples of Europe, the Middle East, or North Africa. (27) The environmental factors (e.g., political, geographic, economic) are drastically different between these regions, but for statistical inferences they are always grouped together. More sensitive race/ethnicity results may be acquired with the use of more specific Caucasian terms.

4.4 The Significance of Missing Data

Clinical trial designs are robust to generate data that effectively proves or disproves the hypothesis. Nonetheless despite best efforts to minimize it, missing data happens for several reasons: duration of trial, outcome assessment difficulty, study protocol adherence, poor communication with study subjects. (28) Throughout the analyses, the biggest limitation was missing data points within the datasets which limited the availability of cases for evaluation. Often these cases were missing values within an outcome. For example, the standard FVC test

result is the highest FVC percent of three attempts. An overwhelming number of tests were missing values for individual attempts, predicted normal, and/or percent predicted.

Missing data was not unique to the PRO-ACT database. While conducting the review of the patients within the UCI NMC database, missing death data was one of the most frequent findings. Checking the National Death Index (NDI) is a possible means for acquiring a more accurate and robust report of deaths; however, as the subjects in the PRO-ACT database were part of clinical trials, all data was de-identified. In the past few years, capturing Hispanic/Latino ethnicity has been emphasized more; however, in both databases, it was infrequently recorded. In the PRO-ACT database, the lack of decline among 18 patients makes it probable that the imputation method is used for the ALSFRSr database. Although the UCI NMC database had missing FVC data, the imputation method was not used in the analysis to avoid impacting the results as was the case with the PRO-ACT database until the 18 patients were extracted.

Missing data corrupts studies, introduces bias, invalidates conclusions, and alters the original statistical plan. However, patients with missing data cannot be completely excluded either because it affects the study power and ignores potential outlier values that narrow the confidence interval. Missing data can be classified into three recognized types:

1) Missing completely at random (MCAR): there are no systematic differences between the missing values and the observed values, e.g., FVC values are missing because the spirometer was not working
2) Missing at random (MAR): the systematic difference between the missing values and the observed values can be explained by differences in observed data, e.g., missing FVC values are missing because the patient refused to do the assessment after initiating NIV

3) Missing not at random (MNAR): even after differences in observed data are considered, the systematic differences remain between missing and observed values, e.g., patients with low FVC values are more likely to miss visits because they are more disabled by the disease

A crucial part of a study's design is how missing data will be addressed. MCAR or MAR type data are less likely to occur and can be ignored; however, MNAR provides a critical look into the population being studied as well as insight for future studies. There are many methods to take care of missing data, each with their own merits and draw backs.

The combination of electronic medical records and historical clinical trial repositories present a wealth of data that is otherwise nearly impossible to come by in the rare disease setting. Using these data banks may engender future clinical trials with more robust analytical plans powered by smaller sample sizes. However, the validity of any conclusions drawn utilizing such methods are questionable if a corrective action plan is not implemented to address the missing data and prevent future oversight. There are several strategies to reduce missing data, including: increasing structured data documentation, reducing data input errors, and utilization of natural language processing (NLP). (25) The same missing data mitigation strategy can be employed for both EMR and clinical trials.

4.5 The Effect of Investigational Products

In the past 20 years, over 50 clinical trials have been conducted to investigate 60 molecules, but the overwhelming majority have failed to demonstrate clinical efficacy. (29) Of these 50 trials, 23 of them contributed data to the PRO-ACT database.

Although the trials failed, the tested compounds were not directly associated with contributing to disease progression. Yet, there is a statistically significant difference in the time

to death between the active drug and placebo groups with survival favoring the placebo group. A possible explanation could be experiencing side effects associated with the active investigational product diminishing the overall quality of life, which in turn contributed to disease progression.

Another possible explanation to take into consider is the placebo response: the physiological response to the inactive arm. (30) One of the contributors for this effect are therapeutic interactions with staff members during the study. Clinical trial subjects receive more face-to-face interaction with clinicians and other multidisciplinary members, as well as encouragement and support from study staff. Another contributor is the increased expectation/hope of treatment benefit that patients experience. Patient expectations about trial outcomes have shown to be an important mediator of the placebo effect. (31) This is even more pronounced in trials with competitive enrollment, like most ALS trials, where clinicians feel somewhat compelled to make the study more attractive to potential participants by highlighting the potential benefits of participation. Prior systematic reviews have also identified placebo response to be higher in studies with outcomes based on questionnaires instead of clinical biomarkers. (32) Of the 23 drugs that advanced into further clinical development, 11 of them used the ALSFRSr as the primary endpoint. Placebo response is notably more pronounced in trials where outcomes are measured by patient reported outcomes to those assessed by clinicians. (33)

4.6 The Importance of Unavailable Data

There were several data points that are collected as part of ALS clinical trials, including the ones that are in the PRO-ACT database, but were not available for analysis. The most notable data points were ‘smoking status’, ‘comorbidities restricting lung function’, and ‘NIV initiation

timepoint.' Understandably, not all medical history points can be included within the database. However, these variables impact the accuracy of disease progression predictive modeling.

Since the mortality risk for bulbar-onset ALS patients is adjusted with the monthly survival benefit from non-invasive ventilation (NIV), it would have been beneficial to be able to factor in NIV use as well. Unfortunately, this key variable was not captured and thus could not be analyzed. Previous studies estimate a 3.5-fold survival benefit with the use of NIV across all ALS patients, which is of importance in bulbar-onset ALS since it has twice the monthly mortality rate once the respiratory system is affected by the disease. (17)

4.7 The Complexities of Late-Stage Clinical Trials

Roughly 50% of investigational drugs fail in late-stage clinical development due to inadequate efficacy and/or safety concerns. (34) In an assessment of 640 phase 3 trials, the factors most often associated with likelihood of FDA approval were orphan designation, cancer drugs, and larger sponsor size (annual gross revenues $\geq$ $1 billion USD). The 1983 Orphan Drug Designation Act is a fast-track distinction for novel therapies created by the FDA to promote medical advancement for rare disease populations.

Compared to nonorphan drugs, orphan drugs are more likely to be approved based on small, single-arm trials which attempt to mitigate the enrollment challenge with rare diseases. In 2009, Mitsumoto *et al* compared drugs with and without orphan indications and identified the elements of clinical trials that received FDA approvals of drugs within neurological indications. The group found that all groups without an orphan indication included at least two randomized, double-blind, placebo-controlled trials. In contrast, only 32% of orphan indications had at least two similar trials but conducted 33 pivotal trials for the 19 drugs approved with orphan indication. Of the 33 trials, 33% did not have a placebo control, 27% were not double-blind, and

12% were not randomized at all. Comparatively, drugs approved without orphan indication had more pivotal trials and a larger mean trial size. (35)

Small, single-arm trials increase the chance for false-positive results and bypasses an opportunity for in-depth understanding of the drug in development. This is especially true in diseases such as ALS where the variability in disease course poses a complication in trial design. Since time is used as a proxy for disease progression, the power to detect treatment effect can be reduced by the patients that are slow progressors who will have little change during participation. Consequently, most ALS trials now have inclusion criteria that exclude this subset thus foregoing the effect of a proposed investigational drug in a real-world setting. Rather than excluding based on disease variability, disease staging provides an alternate approach for measure disease progression regardless of its nature in any one individual.

One of the most widely used ALS staging systems is King's clinical stages which can be derived from standard clinical observations and estimated from the revised ALSFRS-r. It ranges from 1 (early disease) to 4 (late disease), with stage 5 being death. The high correspondence between the ALSFRSr and actual clinical stage based on examination findings make King's stage useful for retrospective analyses. The clinical trial for Riluzole, which received FDA approval in 1995, demonstrated a 35% reduction in mortality at a dose of 100 mg per day. In 2018, King's staging was used to retrospectively analyze the results from the original dose-ranging study to understand the relationship between the survival benefit of Riluzole and disease stage. The study found that the survival benefit of Riluzole is achieved by extending stage 4, not by prolonging stages 2 or 3, or overall slowing the disease. (36) Stage 4 is last living stage of the disease with the highest disability. Although it could be argued that NIV and PEG are also used at stage 4 and prolong this stage, both provide functional benefit by alleviating respiratory

discomfort and nutritional failure, respectively. In contrast, the Riluzole trial failed to show an overall effect on function. Ultimately patients should be counselled with this information because it affects their quality of life to make a fully informed decision.

The push for pharmaceutical innovation has opened the door for smaller-scale trials and abbreviated late stage testing. However, robust drug development is the key to preventing widespread use of ineffective, or even harmful drugs. The shift should be directed at improving methods of validity that serve as the bridge between preclinical to clinical. (34) This is of importance in rare diseases, like ALS, where time is crucial leaving patients vulnerable to rushing healthcare decisions.

False or incomplete data is the root of uninformed or misinformed decisions. However, the technology behind modern big data analytics has reduced this inherent risk that accompanies working with data thus allowing for confidence in more accurate data. Although large clinical trial data repositories are valuable, in the setting of rare diseases, natural history databanks may be more appropriate for big data analysis. Natural history studies allow researchers to gain a better understanding of a disease's progression, how it is managed by clinicians, and what unmet needs exist. These studies may also help identify environmental factors, biomarkers, and other previously unknown risk factors that can guide which drugs are targeted to prevent or slow the disease. Relevant data points need to be agreed upon among the ALS community of researchers, physicians, and community experts (i.e., patients and support); starting the conversation already raises much needed awareness for the ALS community. Ideally, every ALS patient who is seen at an ALS center of excellence should be consented to contribute relevant de-identified data at every clinic visit throughout their disease course. A standardized natural history databank can allow for calculated prevalence that is more inclusive of minorities and may help establish good

standards in disease management. Furthermore, if natural history data is comparable with data from a clinical trial, then the placebo group can be smaller or eliminated entirely. It not only reduces the costs associated with conducting clinical trials, but can ameliorate the time to study enrollment completion. Ultimately, big data can lead clinical researchers to substantial breakthroughs and empower key decision-makers (e.g., patients, clinicians) to making decisions with more certainty.

REFERENCES

1. "Amyotrophic Lateral Sclerosis (ALS) Fact Sheet", NINDS, Publication date June 2013. NIH Publication No. 16-916
2. Paganoni S, Macklin EA, Lee A, et al. Diagnostic timelines and delays in diagnosing amyotrophic lateral sclerosis (ALS). *Amyotroph Lateral Scler Frontotemporal Degener*. 2014;15(5-6):453–456. doi:10.3109/21678421.2014.903974
3. Kasarskis E. http://web.alsa.org/site/PageServer?pagename=ALSA_Ask_Dec2011. Published 2017. Accessed 2018.
4. Swinnen B, Robberecht W. The phenotypic variability of amyotrophic lateral sclerosis. Nature News. https://www.nature.com/articles/nrneurol.2014.184. Published October 14, 2014.
5. Rechtman L, Wagner L, Kaye W, Villanacci J. Updated Prevalence and Demographic Characteristics for ALS Cases in Texas, 2009–2011. *Southern medical journal*. 2015;108(8):483-486. doi:10.14423/SMJ.0000000000000324.
6. Marin B, Boumédiene F, Logroscino G, et al. Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. *International Journal of Epidemiology*. 2017;46(1):57-74. doi:10.1093/ije/dyw061.
7. National Amyotrophic Lateral Sclerosis (ALS) Registry. Centers for Disease Control and Prevention. https://www.cdc.gov/als/ALSFAQ.html. Published April 25, 2017. Accessed May 25, 2018.
8. Computer and Internet Use in the United States: 2015. September 2017. Available at https://www.census.gov/content/dam/Census/library/publications/2017/acs/acs-37.pdf.
9. Roberts AL, Johnson NJ, Chen JT, Cudkowicz ME, Weisskopf MG. Race/ethnicity, socioeconomic status, and ALS mortality in the United States. Neurology. 2016;87(22): 2300-2308.doi:10.1212/WNL.0000000000003298.
10. National ALS Registry Releases Updated Prevalence Estimates. Centers for Disease Control and Prevention. https://www.cdc.gov/media/releases/2016/p0804-als-registry.html. Published August 4, 2016. Accessed May 2018.
11. Passel JS, Cohn DV. 20 metro areas are home to six-in-ten unauthorized immigrants in U.S. Pew Research Center. http://www.pewresearch.org/fact-tank/2017/02/09/us-metro-areas-unauthorized-immigrants/. Published February 9, 2017. Accessed June 1, 2018.
12. Trulia. America's Most Diverse Neighborhoods And Metros. Forbes. https://www.forbes.com/sites/trulia/2012/11/13/finding-diversity-in-america/#398727204b89. Published November 13, 2012. Accessed June 2, 2018.
13. Bensimon G, Lacomblez L, Meininger V. A Controlled Trial of Riluzole in Amyotrophic Lateral Sclerosis. New England Journal of Medicine. 1994;330(9):585-591. doi:10.1056/nejm199403033300901.
14. Rilutek (riluzole). ALS Worldwide. http://alsworldwide.org/research-and-trials/article/rilutek-riluzole. Published February 2, 2015. Accessed August 2018.
15. Goldstein R. One Year in and 2500 People on Edaravone. ALS Therapy Development Institute. https://www.als.net/news/one-year-in-and-2000-people-on-edaravone/. Published May 7, 2018. Accessed 2018.
16. J. Neurol. Neurosurg. Psychiatr. 2016 Mar 01;87(3)280-286, DJ Berlowitz, ME Howard, JF Fiore, S Vander Hoorn, FJ O'Donoghue, J Westlake, A Smith, F Beer, S Mathers, P Talman.

17. Knibb JA, Keren N, Kulka A, et al. J Neurol Neurosurg Psychiatry Published Online First: July 26, 2016. doi:10.1136/jnnp2015-312908.
18. Burkhardt C, Neuwirth C, Sommacal A, Andersen PM, Weber M (2017) Is survival improved by the use of NIV and PEG in amyotrophic lateral sclerosis (ALS)? A post-mortem study of 80 ALS patients. PLoS ONE 12(5): e0177555. https://doi.org/10.1371/journal.pone.0177555
19. Brownlee A. Assistive Technology Program. Assistive Technology Program. https://www.alsphiladelphia.org/sslpage.aspx?pid=934. Published 2005. Accessed 2018.
20. Gruis KL, Wren PA, Huggins JE. Amyotrophic lateral sclerosis patients' self-reported satisfaction with assistive technology. *Muscle Nerve*. 2011;43(5):643-7.
21. Andreas Funke, Susanne Spittel, Torsten Grehl, Julian Grosskreutz, Dagmar Kettemann, Susanne Petri, Ute Weyen, Patrick Weydt, Johannes Dorst, Albert C. Ludolph, Petra Baum, Moritz Oberstadt, Berit Jordan, Andreas Hermann, Joachim Wolf, Matthias Boentert, Bertram Walter, Nadine Gajewski, André Maier, Christoph Münch & Thomas Meyer (2018) Provision of assistive technology devices among people with ALS in Germany: a platform-case management approach, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 19:5-6, 342-350, DOI: 10.1080/21678421.2018.1431786
22. Bell SA, Tudur Smith C. A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials.gov. *Orphanet J Rare Dis*. 2014;9:170. Published 2014 Nov 26. doi:10.1186/s13023-014-0170-0
23. Atassi N, Berry J, Shui A, et al. The PRO-ACT database: design, initial analyses, and predictive features. *Neurology*. 2014;83(19):1719–1725. doi:10.1212/WNL.0000000000000951
24. Küffner, R et al. Crowdsourced analysis of clinical trial data to predict amyotrophic lateral sclerosis progression. Nature News. https://www.nature.com/articles/nbt.3051. Published November 2, 2014. Accessed June 12, 2019.
25. Wells BJ, Chagin KM, Nowacki AS, Kattan MW. Strategies for handling missing data in electronic health record derived data. *EGEMS (Wash DC)*. 2013;1(3):1035. Published 2013 Dec 17. doi:10.13063/2327-9214.1035.
26. Rochon PA, Mashari A, Cohen A, Misra A, Laxer D, Streiner DL, et al. The inclusion of minority groups in clinical trials: problems of under representation and under reporting of data. Account Res. 2004;11:215–223. doi: 10.1080/08989620490891412.
27. Office of Minority Health. Collection of Race and Ethnicity Data in Clinical Trials.; 2016.https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf
28. Kaushal S. Missing data in clinical trials: Pitfalls and remedies. *Int J Appl Basic Med Res*. 2014;4(Suppl 1):S6–S7.
29. Petrov D, Mansfield C, Moussy A, Hermine O. ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment?. *Front Aging Neurosci*. 2017;9:68. Published 2017 Mar 22. doi:10.3389/fnagi.2017.00068.
30. Fava et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychother Psychosom. 2003 May-Jun;72(3):115-27.
31. Hrobjartsson A, Goetzsche PC. Placebo interventions for all clinical conditions Cochrane Database Syst Rev. 2010 Jan 20; (1).
32. Rutherford BR et al. Patient Expectancy as a Mediator of Placebo Effects in Antidepressant Clinical Trials. Am J Psychiatry. 2017 Feb 1;174(2):135-142.

33. Rief, W. et al. Meta-analysis of the placebo response in antidepressant trials. J. Affect. Disord. 118, 1–8 (2009).
34. Hwang TJ, Carpenter D, Lauffenburger JC, Wang B, Franklin JM, Kesselheim AS. Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results. *JAMA Intern Med.*2016;176(12):1826–1833. doi:10.1001/jamainternmed.2016.6008
35. Mitsumoto J, Dorsey ER, Beck CA, Kieburtz K, Griggs RC. Pivotal studies of orphan drugs approved for neurological diseases. *Ann Neurol*. 2009;66(2):184–190. doi:10.1002/ana.21676
36. Fang T, Bensimon G. Stage at Which Riluzole Treatment Prolongs Survival in Patients with Amyotrophic Lateral Sclerosis: a Retrospective Analysis of Data from a Dose-Ranging Study. *The Lancet Neurology*, 1 May 2018, doi.org/10.1016/S1474-4422(18)30054-1.