

**AN ANALYSIS OF QUALITY OF LIFE (QOL) AND SURVIVAL
IMPACT IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)
PATIENTS**

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Presented to
The Academic Faculty

by

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In Partial Fulfillment
of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering in the
School of Engineering

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Date Approved: December 4, 2017

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This thesis is dedicated first and foremost to my family whose support and love is unwavering.

To Tyler Colling who keeps me going everyday with his endless outpouring of love.

To every teacher who has shaped my love for learning and encouraged my endless curiosity, especially Mark Donahue, without whom I could have never dreamed of the achievements I have experienced to date.

To every mentor who has shared their knowledge and experience with me over the years, especially Cassie Mitchell, Grant Coan, Dominic Giuliano, and Adam Carroll.

And finally, to every person who has lost their life to Amyotrophic Lateral Sclerosis and to those who continue to fight.

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LIST OF SYMBOLS AND ABBREVIATIONS

ADI	Assessment of depression index
ALS	Amyotrophic Lateral Sclerosis
CI	Confidence interval
CIM	Clinic impression of mood
FVC	Forced vital capacity
GLM	General linear model
QOL	Quality of life

SUMMARY

In neurodegenerative diseases, such as Amyotrophic Lateral Sclerosis (ALS), quality of life (QOL) – a patient’s ability and desire to lead a fulfilling life – is an important measure to determine disease evolution and treatment plan options. A comprehensive QOL assessment, however is challenging to gather in a clinical setting and relies on survey results convoluted with bias. Current research of QOL metrics in ALS are inadequate and limited to small, cross-sectional studies relying often on depression as the sole measure of QOL. This study proposes a new metric for QOL analysis gathered from qualitative physician remarks on patient mood in the clinical setting, referred to as clinic impression of mood (CIM). A meta-analysis of fifty-one factors gathered from over a thousand ALS patients who have visited the Emory ALS Center was performed to analyze the validity of CIM as a QOL measure. These factors are compared against CIM and depression scorings based on the revised clinical Assessment of Depression Index (ADI-12). A chi-square test was used to compare binary factors and a linear regression model was used for continuous metric analysis. The results of this study demonstrate a strong relationship between CIM and survival duration. Further research into the relationship between CIM, depression, physical health, and survival will allow for more accurate disease progression predictions and thus more suitable treatment plans that center around a patient’s QOL.

CHAPTER 1

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurological disease that currently has no cure. ALS is characterized by the progressive decline in muscle strength and control resulting in spasticity, paralysis, and ultimately complete respiratory failure. Disease progression is rapid providing most with life expectancy of 2-5 years after onset. Despite this bleak prognosis, arguments exist that quality of life (QOL), a measurement of an individual's perceived happiness, does not diminish with disease progression meaning that as a person's health declines, they retain a positive outlook on life.

QOL is an important measure for clinical understanding of the psychological effects of ALS. The findings of past studies have disagreed as to whether or not there is a correlation between physical decline and a decreased QOL. Miglioretti et al suggests that quality of life (QOL) and mental function are independent factors (Miglioretti et al., 2008). His conclusion states that the Common Sense Model holds for ALS patients. This means that QOL is codependent on physical function and illness progression. In particular, this study shows, respiratory function and QOL appear to be most closely related. Robbins and Simmons disagree with Miglioretti arguing that QOL is not related to physical decline (Robbins et al., 2001; Simmons et al., 2000; Simmons, 2015).

A thorough investigation of QOL factors and their relationships to physical and mental decline, is needed to improve clinical management and to better assess the impact of non-curative interventions. This research is imperative to the decision-making processes and affects choices like selecting treatment options. For example, if it can be shown that using specific non-invasive breathing therapies, such as bi-level positive airway pressure

(bi-pap), correlates with a higher QOL, patients might be more likely to use said options. Ultimately, patients need to properly understand the risks and rewards treatment options, etiological or palliative, offer for their projected QOL. Understanding these factors could also play a role in clinical treatment of ALS. Alternatively, if it can be shown that there is insufficient QOL data being collected in ALS clinics, it could allow for a push to include comprehensive surveys in annual treatment. Finally, these QOL factors play a key role in insurance coverage decisions and deeper research in this field could allow for key changes to improve patient treatment and intervention access.

Disagreements among individual studies that have examined ALS QOL call for a more comprehensive assessment of QOL to assess existing and generate new hypotheses. To this end, this project utilizes a meta-analysis to examine QOL factors, including metrics of QOL and correlations of QOL with disease outcomes. A mass binary factor assessment can provide evidence for correlations between physical and mental health and the overall quality of life that ALS patients experience. Understanding these connections is key for optimizing future ALS clinical patient management and assessing potential therapies.

CHAPTER 2

LITERATURE REVIEW

ALS is an incurable and aggressive neuromuscular disease that affects an estimated 20,000 to 30,000 people in the United States, with over 6,000 new diagnoses per year (Malik et al., 2014). The general life expectancy from the time of diagnosis is approximately two to five years. While researching potential cures for ALS is important for long term eradication of the disease, these efforts will not aid patients who are currently battling ALS or who will receive their diagnosis before a cure can be found. For these people, quality of life (QOL) research has a more immediate benefit. QOL research centers on relationships between physical, mental, and social wellbeing and the overall satisfaction of persons affected by ALS. This research however is limited and varies widely across the field. Researchers have failed to agree on the relationships between ALS progression and factors such as physical ability, mental stability, and emotional or spiritual connectedness.

Robbins, for example, argues that QOL is independent of physical health. Robbins' study ventures outside of physical health correlations in quality of life (QOL) of ALS patients (Robbins et al., 2001). He also considers non-medical factors such as how religious or spiritual beliefs are altered by disease progression. Several QOL scales are used throughout this study including the McGill Quality of Life questionnaire (MQOL), Sickness Impact Profile (SIP), ALS Functional Rating Scale (ALSFRS), and the Idler Index of Religiosity (IIR). These four rating scales were used to perform two-way repeated measures multivariate analysis of variance tests. The general conclusion of this study is that QOL in ALS is independent of physical function. However spiritual, religious, and psychological factors varied based on physical abilities and progression.

Simmons hoped to show similar results as Robbins in regards to physical capabilities and QOL (Simmons et al., 2000). Simmons' focused on the usability McGill Quality of Life questionnaire (MQOL) for the assessment of mental health. This rating scale has been validated in studies involving HIV and cancer patients, but is not used in ALS clinics. Contrary to Robbins, Simmons' results were inconclusive, between physical decline and QOL. He did however validate the MQOL as a useful tool in ALS progression mapping.

Miglioretti suggests that QOL and mental function are independent factors. His conclusion stands that the Common Sense Model holds for ALS patients (Miglioretti et al., 2008). This means that QOL is codependent on physical function and illness progression. It is noteworthy that respiratory function and QOL appear to be most closely related based on the results of his study. By considering mood and life quality as independent, Miglioretti is able to gain differing results than the previously outlined studies.

Pizzimenti also followed this thinking and found more concrete results arguing that depression and pain are closely related to QOL (Pizzimenti et al., 2013). An increase in pain correlated to a significant decrease in QOL as did an increase in depression. Pizzimenti argues that these two factors should be closely monitored by doctors and taken into consideration when prescribing medications. Lou agree with Pizzimenti's finding about depression and includes that fatigue is also associated with a decline in QOL (Jau-Shin Lou, 2003).

Lo Coco and Gauthier demonstrate a unique cross sectional study involving patients with ALS as well as their primary caregivers (Gauthier et al., 2007; Lo Coco et al., 2005). This allows for a unique perspective of the QOL of caregivers which surprisingly doesn't follow the predicted progression. Lo Coco's study indicates that caregivers reporting the

lowest QOL are not the same caregivers responsible for the most physically impaired patients. The study did indicate however that the patients QOL decreases with decreased physical function. Both of these studies provide great insights into the QOL of entire family units when someone is suffering from ALS. It is of note that Lo Coco's study agrees with Miglioretti in that QOL and physical health have some correlations, thus refuting Robbins and Simmons (Robbins et al., 2001; Simmons et al., 2000). Gauthier however demonstrated that patient QOL was not related to physical health and rather only caregiver QOL depended on physical health factors.

This disagreement among former studies gives rise to concern and can be misleading to patients researching their diagnosis. The primary issues with these studies are their sample sizes and data collection methods. Most ALS QOL studies are limited to extremely small groups of patients who are monitored using multiple complex QOL surveys taken on a regular basis. These QOL surveys are not currently in use at ALS clinics around the country. Most ALS patients never see one of these surveys and, if they do, the data is not passed from the clinic to researchers for analysis, making these surveys rather useless for clinical QOL tracking.

A meta-analysis of clinical informatics could provide insight into the relationships between mental and physical decline and QOL in ALS. By analyzing measurable factors of physical health and interpreting doctor notes on mood and sleeping habits, an analysis of QOL can be performed from a different perspective than the perspective of the surveys typically used in these small studies. A meta-analysis will also allow for an exponentially larger sample size for data analysis which could allow for a more concrete conclusion.

An argument may be sustained that using clinical notes and medication usage rather than QOL surveys could weaken the integrity of the data. However, this is the best measure available from ALS clinics around the country. If the conclusion of this study finds that this clinic data is insufficient for analysis of QOL, it would demonstrate the need for stricter standardization of QOL surveys in clinical settings. Several studies have been performed over the course of decades that demonstrate the need for more compact QOL surveys in clinical settings (McGuire et al., 1997; Simmons et al., 2000; Simmons et al., 2006).

Having a detailed understanding of patient and doctor perceived quality of life is imperative for ALS treatment plans and progression tracking as has been shown by Chio (Chio et al., 2004). They demonstrated that the health factors gathered in the clinical setting are not adequate for determining QOL and that measures that can be captured by various surveys need to be obtained to form an effective QOL study. Patients need a clear understanding of how certain treatment decisions and physiological factors could impact their projected QOL. Current studies are not sufficient to aid in these decisions, leaving room in this field for a detailed meta-analysis of clinical factors.

The current study utilizes a comprehensive binary collection of de-identified patient data from the Emory ALS Center in Atlanta, Georgia. Statistical correlations between physical health factors and QOL factors are analyzed in order to draw a more thorough conclusion than the aforementioned studies. The goal is to use a far more expansive sample size and easily measurable clinical health factors to conclude if physical decline contributes to a lower QOL.

CHAPTER 3

METHODS

3.1 Data Translation

This study aims to define the relationships between physical health, mental health, and survival duration in ALS. To achieve this, data from patient appointments at the Emory ALS Center was transcribed into a relational database using the lab's published biocuration protocol (Mitchell, 2015 J Undergrad Neurosci Educ), which includes independent quality control assessment to insure >98.8% transcription accuracy. All patient data for the present study was de-identified and anonymized. Forty-seven of the physical health and mental health indicators were translated from text-based physician charts into binary values. The remaining six physical health factors were numerical measure taken from the charts. These factors are defined in Table 1.

Each physical health indicator is additionally categorized based on the specific field it encompasses. For example, forced vital capacity (FVC) is further categorized as a respiratory health indicator as it is the measure of the amount of air that can be forced out of the lungs during testing.

Table 1. Physical and mental health factors and categorizations

Factor	Data Type	Category
Forced vital capacity (FVC)	Continuous	Respiratory
Percent predict	Continuous	Respiratory
Negative inspiratory force (NIF)	Continuous	Respiratory
Oxygen saturation	Continuous	Respiratory
ALSFRS-r respiratory	Continuous	Respiratory
General pain present	Binary	Pain
Level of disability	Binary	Disability
ALSFRS-R	Binary	Disability
Paraplegia	Binary	Disability
Quadriplegia	Binary	Disability
Hemiparesis	Binary	Disability
Head drop	Binary	Muscle control
Jaw jerk	Binary	Muscle control
Toe walk	Binary	Muscle control
Atrophy	Binary	Muscle control
Moderate to severe atrophy	Binary	Muscle control
Fasciculation	Binary	Muscle control
Atrophy	Binary	Muscle control
Moderate to severe atrophy	Binary	Muscle control
Swallowing problems	Binary	Oral muscle control
Moderate to severe swallowing problems	Binary	Oral muscle control
Drooling	Binary	Oral muscle control
Moderate to severe drooling	Binary	Oral muscle control
Tongue atrophy	Binary	Oral muscle control
Moderate to severe tongue atrophy	Binary	Oral muscle control
Tongue fasciculation	Binary	Oral muscle control
Dysarthria	Binary	Vocal control
Moderate to severe dysarthria	Binary	Vocal control
Dysphasia	Binary	Vocal control
Moderate to severe dysphasia	Binary	Vocal control
PEG tube placed	Binary	Gastrointestinal
PEG tube nutrition use	Binary	Gastrointestinal
PEG tube as main source of nutrition	Binary	Gastrointestinal
Assistive device	Binary	Therapy
Cough assist use	Binary	Therapy
Suction use	Binary	Therapy
Bi-pap usage	Binary	Therapy
Antidepressant usage	Binary	Medication and Depression
Drooling medication usage	Binary	Medication and Oral muscle control
Non-opioid pain medication usage	Binary	Medication and Pain
Opioid pain medication usage	Binary	Medication and Pain
NSAID medication usage	Binary	Medication and Pain
Sleeping medication usage	Binary	Medication and Sleeping problems
Muscle related medication usage	Binary	Medication and Muscle control
Accompaniment to appointment	Binary	Lifestyle
Family support	Binary	Lifestyle
Hospice care	Binary	Lifestyle
Issues in home reported	Binary	Lifestyle
Reported change in behavior	Binary	Lifestyle
Sleeping problems reported	Binary	Sleeping problems

These factors were compared against two indicators of patient mental health: tertiary clinic impression of mood and depression. Clinic impression of mood is patient mood as recorded by a physician during a visit to the Emory ALS Center. Depression was measured using the revised, clinical assessment of depression index (ADI-12). Several therapy factors were considered as well, including bi-pap usage, antidepressant usage, and pain medication usage.

In addition to comparing clinic impression of mood and depression against the factors listed in Table 1, duration of disease was compared from three different times to all previously mentioned factors. The three times analyzed include duration from diagnosis, duration from first appointment, and duration from symptom onset. The goal of this analysis was to determine if any of the fifty factors or depression are strongly correlated with duration of survival in ALS.

The foremost anticipated correlation is between respiratory ability and depression. However, this study also aims to show relationships between mental health and antidepressant usage, pain medication usage, and muscle control loss. In addition to the overall aim of this study, the binary data generated could be used to perform several future studies. Correlations between the prevalence of any number of physical health indicators and participation in therapeutic interventions could be analyzed using this data.

3.2 Clinic Impression of Mood Metric Development

The newly developed measure of clinic impression of mood was derived from patient electronic health records from the Emory ALS Center. Qualitative physician notes relating to mood changes or general mood observations were translated into a binary measure herein referred to as clinic impression of mood (CIM). Patients were assigned a

zero for CIM at a given appointment if records of their mood indicated a “positive” or “neutral” mood. Patients were alternatively assigned a one for CIM if their mood was disturbed negatively. Each patient was evaluated on an individual basis throughout their appointment history. Consideration was given to their baseline mood at their first appointment and their mood changes were tracked from the first to their last appointment at the clinic. If there were no notes provided on mood at an appointment, the appointment was excluded.

The database utilized in this study included categories for “Mood”, explicitly, as well as a category for “Other Visit Information”. Both categories were probed using specific keyword searches included in Table 2 below. If these categories were left blank or did not contain relevant information, a CIM score was not assigned for the appointment.

Table 2. Keyword searches and corresponding clinic impression of mood (CIM) score determinations

Keyword	CIM Score
Anxious	1
Appropriate	0
Cheerful	0
Crying	**
Decreased	*
Depressed	1
Down	*
Dysthymic	1
Emotional	1
Euthymic	0
Fair	0
Flat	1
Frustrated	1
Good	0
Increased	*
Irritable	1
Laughing	**
Liable	1
Normal	0
Not good	1
Pleasant	0
Sad	1
Stable	*
Struggling	1
Tearful	**
Unclear	Not assigned
Unstable	1
Up	*
Volatile	1
* Requires probing of mood at previous appointment	
** Requires probing patient record mention of pseudobulbar affect (PBA), if confirmed, then crying or laughing is not considered as an indicator of mood	

3.3 Patient Inclusion and Exclusion Criteria

Patients must have visited the Emory ALS Center at least once to have completed a preliminary appointment. Patients who were diagnosed with any disease other than ALS were excluded. Additionally, if a clear determination about factor application to a specific

appointment could not be determined, no data was entered for said factor on that appointment. The sample size varies between groups being analyzed but must be over 20 appointments to be considered in this study. A total of 1,258 patients were included in the binary data generation, although not every patient was considered in every factor analysis. If the patient did not have a value for a factor area in an appointment, the factor was not considered for that appointment. Hence the variance in group sample sizes.

3.4 Statistical Methods

Statistical analysis was performed in Matlab. A chi-square test was used to compare two factors against each other to determine goodness of fit if both factors included exclusively binary data. A generalized linear model (GLM) was used for the continuous metric comparisons. A significant p-value was accepted as $p < 0.05$ and a confidence interval of 95% was used for comparison of significance.

CHAPTER 4

RESULTS

4.1 Clinic Impression of Mood (CIM) shows strong correlations to physical health

Of the fifty categories analyzed, twelve were shown to be good predictors of clinic impression of mood (Table 2). In particular, clinic impression of mood (CIM) showed a high level of correlated decline with decreased respiratory function, as measured by percent predict and forced vital capacity (FVC). High level correlations are also present between CIM and some factors of muscle control, general pain, and cough assist usage. Lower level correlations with CIM exist with bi-pap usage, some additional muscle control factors, family support, and ALSFRS-R scores.

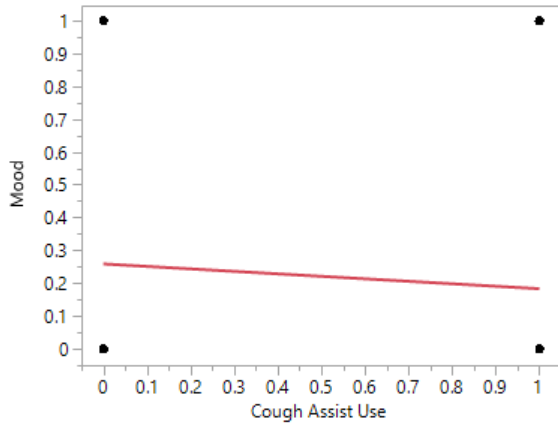
Table 3. Clinic impression of mood significant factors

Factor	Sample size	p-value
Cough assist**	1,484	0.000622
Bi-pap usage**	1,979	0.000012
Jaw jerk**	2,112	0.000183
Toe walk*	142	0.017957
Swallowing problems*	840	0.014395
Moderate to severe swallowing problems*	200	0.002729
Drooling**	2,702	0.000745
General pain**	671	0.000518
Family support*	4,175	0.041075
ALSFRS-R*	848	0.041246
Percent predict**	1,300	0.000977
Forced vital capacity (FVC)**	1,272	0.0000091

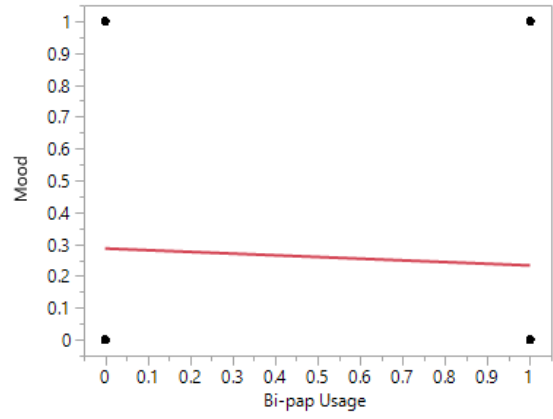
Table 2 shows significant factors compared to clinic impression of mood with their respective p-values and the number of appointments analyzed for each category.

*denotes $0.05 > p\text{-value} > 0.001$, ** denotes $p\text{-value} < 0.001$; CI 95%

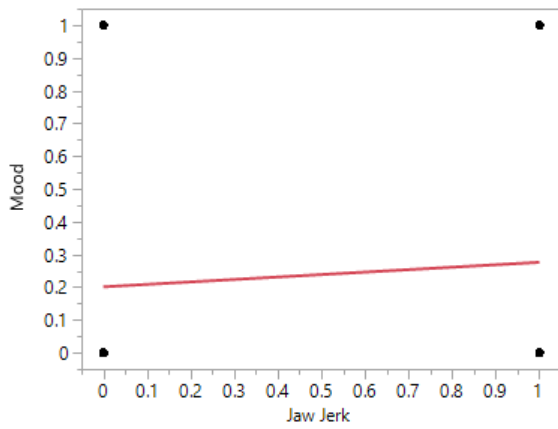
To determine how these significant factors impact clinic impression of mood, bivariate fit plots were produced for each factor (Figure 1). The sloping direction of the line of best fit can be used to determine the correlational relationship between the factor and clinic impression of mood.



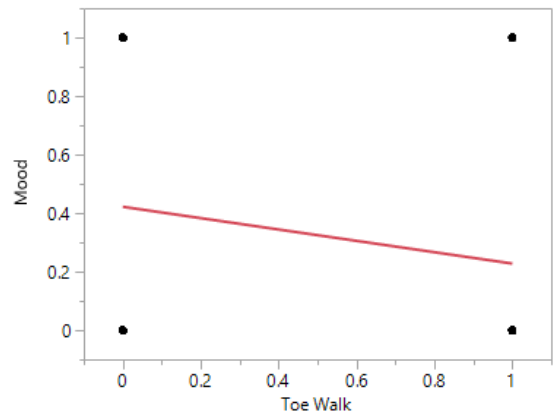
A



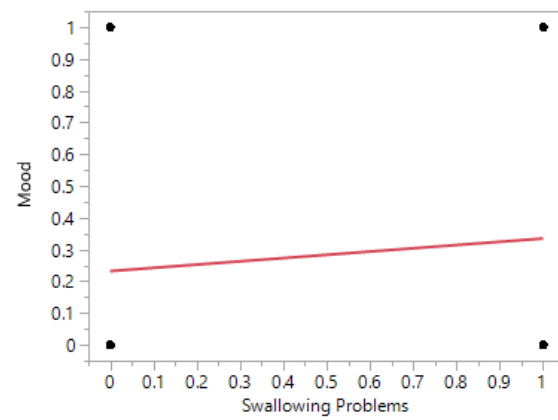
B



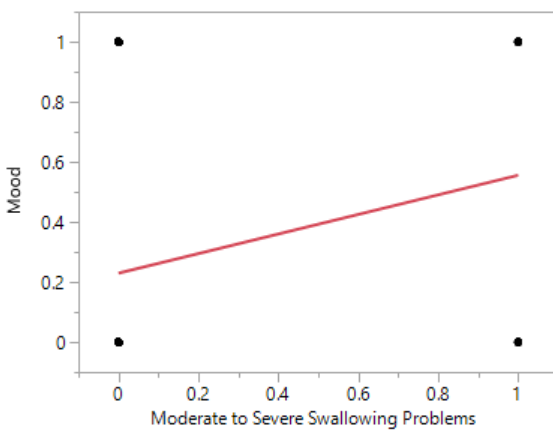
C



D



E



F

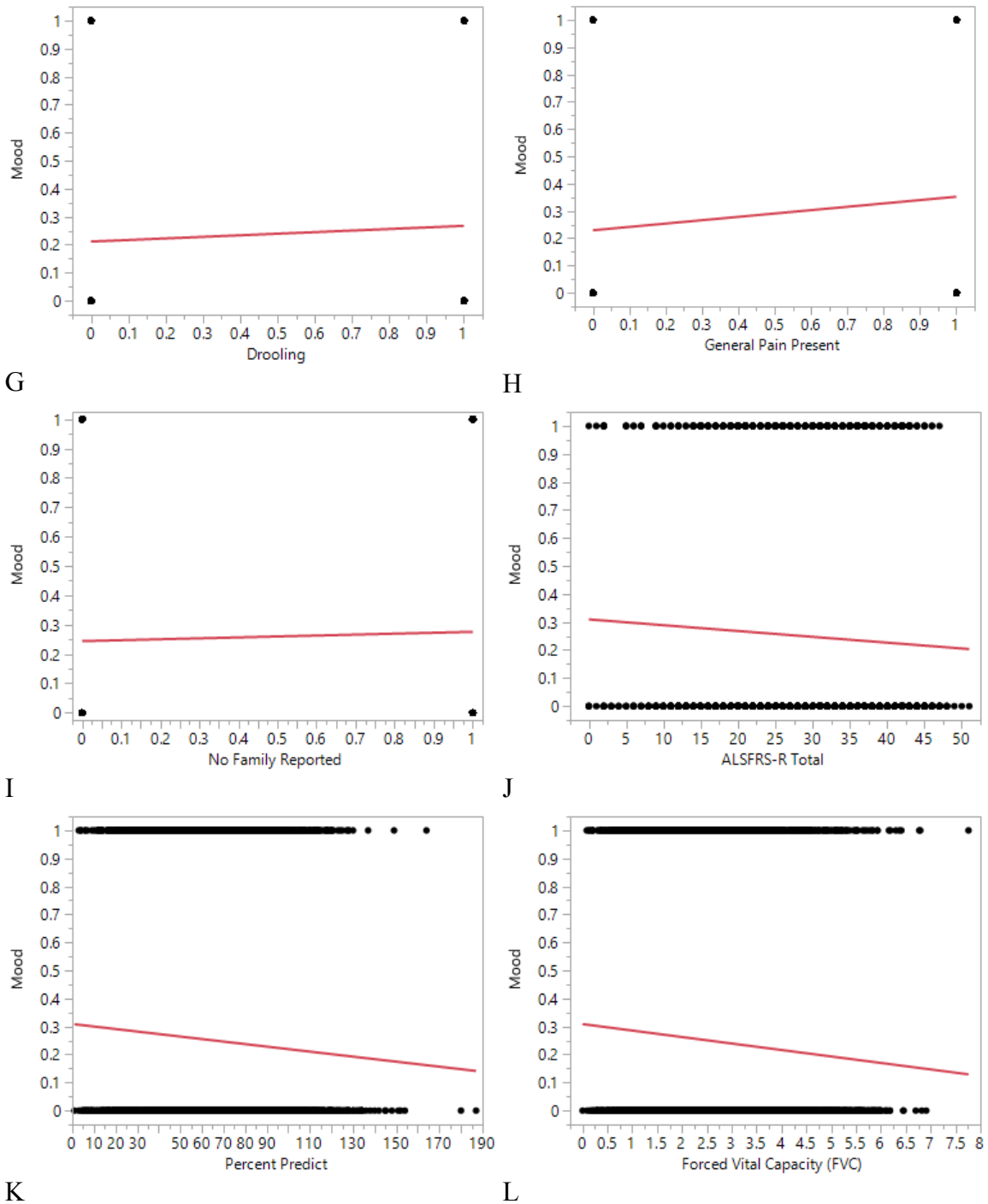


Figure 1. Bivariate fit of clinic impression of mood by significant factors. (A-G) Binary data for significant variables fit to CIM data using a logistical regression. **(H-J)** Continuous data for significant variables fit to CIM data using a linear regression.

4.2 Depression shows few correlations to physical health due to limited sample size

In order to compare the ADI-12 data to the fifty factors, three data sets were formed. Two binary sets of data were developed from the ADI total scores. The first group is categorized as depressed which includes all appointments where the patient scored a 23 or higher on the ADI-12 assessment (Hammer et al., 2008). The second group is categorized as majorly depressed and includes patients who scored a 30 or higher on the ADI-12 assessment. The final group contains the raw ADI-12 scores.

In the depression group, only the ALSFRS-R respiratory category was identified as a good predictor of depression. In the major depression group, the only statistically significant factor was clinic impression of mood. Finally, when comparing the raw ADI-12 scores to all fifty factors, only muscle related medications, was shown to be related to ADI-12 scores.

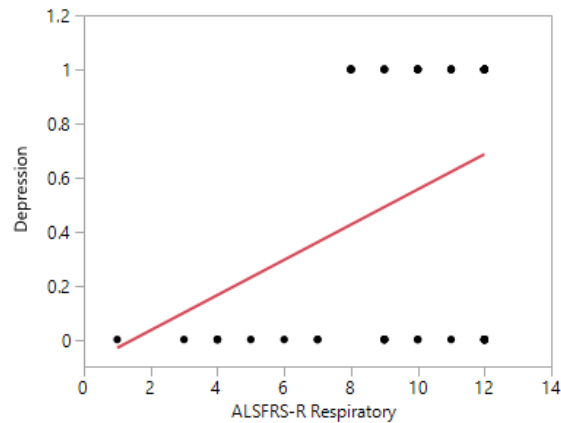


Figure 2. Bivariate fit of depression by ALSFRS-R respiratory scores
Continuous data for ALSFRS-R Respiratory sub-scores fit to Depression data using a logistical regression. p-value < 0.01; 95% CI.

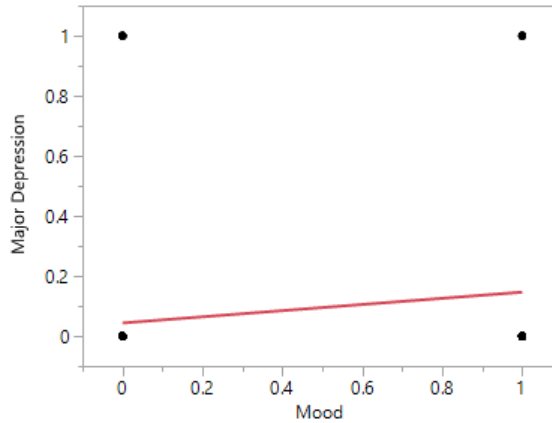


Figure 3. Bivariate fit of major depression by clinic impression of mood
 Binary data for Clinic Impression of Mood (CIM) fit to Major Depression data using a logistical regression. p-value < 0.05; 95% CI.

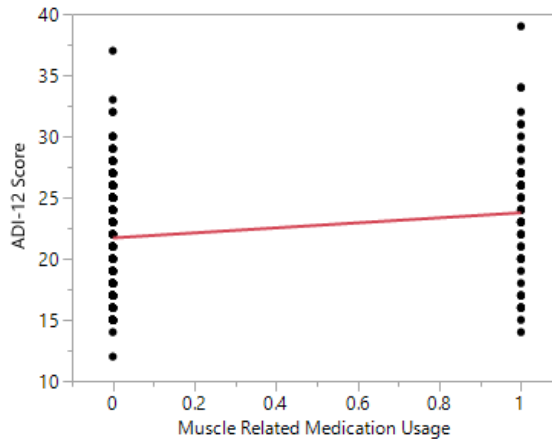


Figure 4. Bivariate fit of ADI-12 scores by muscle related medications
 Binary data for Muscle Related Medication Usage fit to continuous ADI-12 scores using a logistical regression. p-value < 0.01; 95%

4.3 Survival shows strong correlations to physical health and QOL factors

Duration of survival was collected in three groups for each patient: duration from onset, first visit, and diagnosis. Several predictive factors were identified in each survival duration group (Table 4-6).

Table 4. Duration from onset significant factors

Factor
Moderate to severe disability**
Cough assist**
Bi-pap use**
Moderate to severe atrophy*
Fasciculations present**
Jaw jerk present *
Swallowing problems**
Moderate to severe swallowing problems*
Drooling**
Moderate to severe drooling*
Tongue atrophy*
Dysarthria**
Moderate to severe dysarthria**
Clinic impression of mood**
General pain**
Not accompanied to appointment**
No family reported*
No friend support*
ALSFRS-R**
Forced vital capacity (FVC)**
ALSFRS-r respiratory*

*denotes $0.05 > p\text{-value} > 0.001$, ** denotes $p\text{-value} < 0.001$

Level of disability, respiratory therapies, CIM, pain, ALSFRS-R, and FVC all had a highly significant relationship when compared to survival from onset. Certain social factors were also predictive of survival: lack of accompaniment to an appointment at a high level and no friend support system or family identified at a low level. Finally, muscle control factors varied between low and high levels of significance. At a high level were reported fasciculation, swallowing problems, drooling, and dysarthria. At a low level were atrophy, jaw jerk, moderate to severe swallowing problems and drooling, and tongue atrophy.

Table 5. Duration from first appointment significant factors

Factor
Moderate to severe disability**
Cough assist**
Suction use*
Bi-pap use**
Moderate to severe atrophy**
Fasciculations present**
Head drop present*
Jaw jerk present**
Swallowing problems*
Moderate to severe swallowing problems*
Tongue atrophy*
Tongue fasciculations**
Dysarthria**
Moderate to severe dysarthria**
Clinic impression of mood**
General pain**
Sleeping problems*
Not accompanied to appointment**
No family reported*
No friend support*
ALSFRS-R**
Percent predict**
Forced vital capacity (FVC)**
Negative inspiratory force (NIF)**
ALSFRS-r respiratory**

*denotes $0.05 > p\text{-value} > 0.01$, ** denotes $p\text{-value} < 0.001$

Level of disability, respiratory therapies, CIM, pain, ALSFRS-R, ALSFRS-r respiratory and all four respiratory measures had a highly significant relationship when compared to survival duration from first appointment at the Emory ALS Center. Certain social factors and reported sleeping problems were also predictive of survival at a low level of significance. Finally, muscle control factors varied between low and high levels of significance. At a high level were moderate to severe atrophy, dysarthria, reported

fasciculation, jaw jerk, tongue fasciculations. At a low level of significance were head drop, swallowing problems, and tongue atrophy.

Table 6. Duration from diagnosis significant factors

Factor
Moderate to severe disability**
Cough assist**
Suction use*
Bi-pap use**
Moderate to severe atrophy**
Fasciculations present**
Jaw jerk present*
Toe walk*
Swallowing problems**
Moderate to severe swallowing problems*
Moderate to severe drooling*
Moderate to severe tongue atrophy*
Tongue fasciculations**
Dysarthria**
Moderate to severe dysarthria**
Moderate to severe dysphasia*
Clinic impression of mood**
General pain*
Not accompanied to appointment**
ALSFRS-R**
Percent predict*
Forced vital capacity (FVC)**
Negative inspiratory force (NIF)**
ALSFRS-r respiratory*

*denotes $0.05 > p\text{-value} > 0.01$, ** denotes $p\text{-value} < 0.001$

Level of disability, respiratory therapies, CIM, ALSFRS-R, FVC, and NIF had a highly significant relationship when compared to survival duration from ALS diagnosis. Reported pain, ALSFRS-r respiratory, percent predict, and appointment accompaniment were also predictive of survival at a low level of significance. Again, muscle control factors varied between low and high levels of significance. At a high level were moderate to severe atrophy, swallowing problems, dysarthria, reported fasciculation, jaw jerk, tongue

fasciculations. At a low level of significance were moderate to severe swallowing problems, drooling, tongue atrophy, and dysphasia, in addition to jaw jerk, toe walk, swallowing problems, and tongue atrophy. It should be noted that while clinic impression of mood was determined to be a strong indicator of all three survival groups, neither the raw ADI-12 scores nor the binary depression categories from the ADI-12 data were found to be good predictors of survival.

CHAPTER 5

DISCUSSION

The objective of this study is to analyze the ability of a newly proposed QOL metric, clinic impression of mood (CIM), to predict survival duration in ALS. Additionally, the ability for physical health to predict CIM will be explored. Together, these analyses will help determine the validity of CIM as an impactful QOL measure. Additionally, the relationship between physical health and survival will be discussed in light of the study's findings. The final goal of this study is to answer whether QOL is dependent on physical health in ALS. The discussion of our findings will be presented in five sections that follow.

5.1 ALSFRS-R Total scores are not significantly correlated with CIM or depression despite respiratory score correlation

ALSFRS scores have long been upheld in the ALS research community as a staple measure of disease progression and survival prediction (Cedarbaum et al., 1999). The ALSFRS-R total score was not a highly significant factor when compared with clinic impression of mood whereas percent predict and FVC respiratory measures were highly significant (Table 2, Figure 1). Additionally, ALSFRS-R total scores showed no significance in ADI-12 depression scoring categories.

Because ALSFRS scores are often used as a stand-in metric for survival, the analysis of ALSFRS-R total scores and respiratory sub-scores compared to survival duration was a key component of this work. While ALSFRS-R total scores showed high levels of significance, this is largely due to the linear regression model which is commonly employed in the analysis of ALSFRS scoring trends (Cedarbaum et al., 1999; Kimura et

al., 2006; Kollwe et al., 2008). Recent research on the validity of ALSFRS scores however has demonstrated concerns about the analysis of these scores using linear regression models and argues that these scores require a more robust analysis to avoid inaccurate interpretations of correlated variables (Franchignoni et al., 2013; Franchignoni et al., 2015; Mandrioli et al., 2015; Voustianiouk et al., 2008).

5.2 Respiratory Ability and Muscle Control loss correlate with better mood outlook

Examining factors individually, it is shown that percent predict and FVC as measures of respiratory function are negatively associated with CIM. Therefore, as respiratory ability decreases, we see patient mood impression follows this decreasing trend. Patients who reported using respiratory therapies, namely cough assist and bi-pap, suffered less declined CIM levels. This is a positive indicator that intervention with such therapies could support an improved QOL (Bourke et al., 2001; Simmons, 2005). While ventilation data was not available for this study, the finding that lower respiratory function scores correlate with higher mood ratings aligns with the findings of several ventilation QOL studies in the ALS field (Gelinas et al., 1998; Kaub-Wittemer et al., 2003; Mustfa et al., 2006).

The presence of certain oral muscle control problems, namely jaw jerk, swallowing problems (any as well as moderate to severe), and drooling correlated with the absence of mood abnormalities. This indicates that the loss of these controls does not negatively impact mood, but rather correlates with a normal mood. This finding is in contrast to many studies that demonstrate that as these basic muscle controls are lost, risk of depression increases (Gauthier et al., 2007; Lo Coco et al., 2005).

Together, decreased FVC and percent predict and decreased muscle control are common as ALS progresses. Interpreting these results on a high level, they appear to indicate that later in disease progression, there is a lower instance of mood problems observed by clinicians. This demonstrates the similar findings as Kübler who showed a negative relationship between depression severity and disease duration (Kübler et al., 2005).

5.3 Tertiary Clinic Impression of Mood may be a strongly predictive metric to be used in addition to depression indices

The lack of statistically significant results from the ADI-12 data is largely due to the limited sample size. This assessment was given to patients for a small window of time at the Emory ALS Center. Only 240 appointments out of 8,130 included completed ADI-12 data. The number of appointments with corresponding physical health measures further slimmed down the sample size available for analysis. While no concrete conclusions could be drawn from the ADI-12 collected data, further research into this viability of data from this assessment should be conducted.

An ongoing issue in the field of depression assessment is the use of surveys to retrieve information from patients. Recall bias has been shown to affect the depression statistics gained from surveying and must be considered when analyzing survey results (Coughlin, 1990; Kruijshaar et al., 2005; Patten, 2003). An easier metric to gather could be clinic impression of mood as interpreted by staff handling a patient in real time. Using this metric could alleviate the argument of recall bias and would be easier for physicians to gather during clinic visits. The goal of recording CIM is not necessarily to diagnose

depression, as physicians have proved less than successful at making this diagnosis from clinic visits, but rather to track variabilities in patient mood expression (Cepoiu et al., 2007; Cepoiu et al., 2008; Coventry et al., 2011; Mitchell et al., 2009; Rettew et al., 2009). CIM has shown viability in other epidemiological fields although caution has been given that a standard system of rating patient mood should be created (Balestrieri et al., 2002; Cepoiu et al., 2008; McDonald et al., 1999).

Beyond future work on the ADI-12 depression relationship to physical health, more work should be conducted on the relationship between QOL and physical health as a whole. More regimented practices in ALS clinical setting could help researchers collect more usable data for this type of analysis. The type of records kept by the Emory ALS Center vary between appointments. Sometimes respiratory measures are recorded along with detailed notes on the patients' general wellbeing and physical health as it is being impacted by ALS. Other times, there is very little data recorded about the patients' health. More systematic practices in clinical settings could progress this field of research.

Through this study, we have demonstrated the predictive power of clinic impression of mood (CIM) as a new QOL factor in ALS disease monitoring. Depression is a heavily relied on measure to describe mood incongruences in ALS patients however, we have demonstrated the need for a better metric for mood analysis and have provided an easily obtainable alternative to depression surveying in the clinical setting.

5.4 As physical health declines so too does survival duration

As previously discussed, many studies rely on ALSFRS-R scores to measure progression and to predict survival (Atassi et al., 2014; Kimura et al., 2006; Zach et al.,

2015). Our study however uses three distinct survival timelines based on the survival duration of patients from three different benchmarks: the first time they recall an onset symptom of ALS, their first appointment at the clinic, and their official diagnosis date. Our findings agree that ALSFRS-R scores are a strong indicator of survival durations in ALS.

Respiratory factors, FVC and percent predict, were found to be strong predictors of survival duration. This finding agrees with many survival studies in the field on FVC's predictive power which all agree that sustaining a higher FVC score correlates with prolonged survival (Baumann et al., 2010; Czaplinski et al., 2006; Stambler et al., 1998). Cedarbaum and Gordon argue that using FVC as a predictor of survival requires researchers to ignore complex factors at play such as the impacts of respiratory therapies such as non-invasive ventilation (NIV) and differences between therapies and procedure clinic to clinic (Cedarbaum and Stambler, 2001; Gordon et al., 2009). The findings of this study agree with many others that respiratory therapies such as bi-pap, a form of NIV, impact respiratory ability and therefore help prolong survival (Hardiman, 2011; Kleopa et al., 1999; Lechtzin et al., 2004; Lechtzin et al., 2007; Vrijsen et al., 2013; Vrijsen et al., 2016). Hardiman's research also takes into consideration how respiratory functioning impact QOL and he reports that intervening with NIV to preserve FVC correlates with an increased QOL through the prolonged survival duration. Our findings are in clear agreement.

Our findings support that experiencing fasciculations is strongly correlated with a decreased duration of survival which is in agreement with other fasciculation studies in ALS (de Carvalho and Swash, 1998; Shimizu et al., 2014). There is little research on the

impact of muscle control loss on survival in ALS however. For this study, muscle control loss is indicated by reported or clinically observed atrophy of various muscles, increased drooling, and difficulty controlling oral muscles. Our findings support that as muscle control is reportedly decreased, survival duration also significantly decreases (Table 3-5).

5.5 Positive mood outlook shows correlation with increased survival duration

Our findings additionally suggest that lacking interpersonal relationships correlates with an increased survival duration. This may be due to the perception of burden on caregivers and friends throughout ALS progression (Chio et al., 2005; Galvin et al., 2016; Pagnini et al., 2010). Lacking these relationships may alleviate the stress associated with having loved ones watch or experience the deteriorating process of ALS on the body. This impact of interpersonal relationships on survival are largely speculative and social interaction is better analyzed in relation to QOL. While ALS patients often feel as though they are a burden on those around them, research shows that interpersonal relationships still assist in increasing patient QOL (Young and McNicoll, 1998). The directionality of this correlation was confirmed in our analysis however it was not found to be statistically significant.

Clinic impression of mood (CIM) was found to be strongly correlated with survival duration in ALS. Patients who exhibited mood disturbances during their clinic visits survived for a significantly shorter duration from onset, first appointment, and diagnosis. This key finding lends support to the argument that QOL is maintained independent from physical health (Robbins et al., 2001; Simmons et al., 2000).

5.6 Recommendations

Through this meta-analysis, a need has been demonstrated for further research in several key areas. First, further consideration should be given to the comparative value of binary CIM scores to continuous ADI-12 depression scores. A suitable sample size for this analysis could not be obtained through the Emory ALS Center database. A more robust statistical method should also be used to draw more concrete conclusion about the relationship between ALSFRS-R scores and survival duration. Finally, confirmation or rejection of the usability of CIM measures must be accomplished through further studies.

CHAPTER 6

CONCLUSIONS

Quality of life (QOL) has developed into a more highly researched aspect of ALS care in the last 20 years, however researchers have failed to agree on whether QOL is independent of a patient's physical health. Our study has found that survival duration in ALS is impacted by several factors of physical health factors and by clinic impression of mood (CIM), which is a newly recommended measure for QOL. Furthermore, CIM was found to be predicted by several physical health factors. So, while the survival duration analysis seems to lend support to the notion that QOL is independent of physical health, the ability to predict CIM based on several physical health factors refutes this claim. This study agrees with the findings of Lo Coco and Miglioretti who claim that QOL is impacted by physical health. CIM has proved a strong predictive factor of survival duration in ALS and should be further researched as an indicator of QOL.

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