Survival and multidisciplinary amyotrophic lateral sclerosis clinic care at a United States Veterans Affairs medical center

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ABSTRACT

Introduction/Aims: The purpose of this work was to investigate survival outcomes in patients with amyotrophic lateral sclerosis (ALS) at our Veteran's Affairs Medical Center multidisciplinary ALS clinic and compare this to relevant data from several European studies.

Methods: Our sample consisted of 56 total Veterans (n=56; 54 males, 2 females) who had been seen between June 24, 2013 and February 1, 2021 at our multidisciplinary ALS clinic.

Results: The median survival time of our Veterans from symptom onset was 40.96 months (95% CI of 32.17, 76.07), and the median survival time from diagnosis was 23.77 months (95% CI of 18.64, 38.58). This was consistent with the literature. Further consistent with the literature is that multidisciplinary clinics, including ours, have survival advantage over general neurology clinics. Analyzing factors that contributed to this survival, we found a significant protective effect on survival from Edaravone use (HR = 0.32, p = 0.036). Otherwise, there was no significant effect on survival noted from use of percutaneous endoscopic gastrostomy (PEG), non-invasive ventilation (NIV), or Riluzole.

Conclusion: We found no significant difference in survival rates between our U.S. Veterans in our multidisciplinary ALS clinic and European multidisciplinary ALS clinics, and both are better than general neurology clinics. We also found that Edaravone use may provide some benefit to survival in this patient population.

Keywords: ALS, multidisciplinary, PEG, NIV, Edaravone, survival

1 Background

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder characterized by progressive loss of upper and lower motor neurons. There is currently no cure for ALS, and treatment options are limited and focus on slowing disease progression and improving quality of life. Until the recent approval of sodium phenylbutyrate and taurursodiol in September 2022, pharmacological therapy has been restricted to two FDA-approved drugs, Riluzole and Edaravone, which have shown modest benefit in survival time or benefit in delaying functional decline.[1,2] Symptom-based palliative care that includes use of non-invasive ventilation (NIV), percutaneous endoscopic gastrostomy (PEG), and assistive equipment has also been shown to positively modify outcomes in affected patients.[3,4]

Guidelines from professional societies in the United States (American Academy of Neurology [AAN])[5] and Europe (European Federation of the Neurological Societies [EFNS])[6] recommend ALS multidisciplinary clinics (MDCs) for managing patients with ALS to optimize healthcare delivery and prolong survival. This recommendation has Level B ("Probably effective") evidence, based primarily on two European studies from Ireland[7] and Italy[8] which showed an increase in time of survival from symptom onset and from diagnosis compared to similar patients managed in general neurology clinics (GNC). A single study from Italy[9] did not show a survival benefit from MDC care. MDC care is also recommended for improving quality of life in patients with ALS, based on a study from the Netherlands[10] with Level C ("Possibly effective") evidence. No similar studies have been done in the United States or with U.S. Veterans as the study population.

U.S. Veterans are at increased risk of developing ALS. In 2008, the U.S. Institute of Medicine released a report that determined that there was evidence of a relationship between military service and later development of ALS.[11] The evidence from reviewing 30 studies was too limited, however, and found "no strong evidence that any particular military exposure is associated with ALS etiology".[12] Persistent exposures to neurotoxicants that accumulate in the central nervous system, as well as service-linked trauma, are thought to contribute to ALS pathogenesis.[13]

In September 2008, the VA established ALS as a service-connected disability for Veterans who served 90 days consecutive active duty and who later were diagnosed with ALS.[14] In January 2012, the VA determined that the service-connection for ALS would automatically be rated as 100% disabling.[15] This service-connected disability status entitles Veterans with ALS to a substantial package of financial and healthcare benefits that includes providing free medical care, equipment, transportation, monthly compensation for work lost, and nursing home coverage.

In 2013, our VA Healthcare System developed an ALS multidisciplinary clinic (MDC). The multidisciplinary team

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Table 1. Results for VA MDC together with relevant results from comparison studies. VA = Veterans Affairs medical center; PEG = percutaneous endoscopic gastrostomy; NIV = noninvasive ventilation; MDC = multidisciplinary clinic; GNC = general neurology clinic; N/A = not applicable; * *Respiratory subtype also included generalized onset disease causing relatively large number*

	Traynor et. al. 2003 [7]	Chio et. al. 2006 [8]	Zocollela et. al. 2007 [9]	Paipa et. al. 2019 [16]	Aridegbe et. al. 2012 [17]	Martin et. Al. 2017 [19]	VA MDC
Total number of patients (n) included in each cohort	82	221	84	344	254	330	56
Mean age at symptom onset (years)	59.0	60.8	63.5	62	62.6	58.1	64.9
Mean age at diagnosis (years)	60.1	N/A	64.2	N/A	N/A	N/A	66.5
Delay to diagnosis from symptom onset (months)	13.0	N/A	N/A	10	16.6	12.0	16.5
Mean age at death (years)	61.95	N/A	65.7	N/A	N/A	N/A	71.4
Percent limb onset	58.5% (N=48)	N/A	75% (N=63)	66.65% (N=229)	73% (N=185)	73.6% (N=243)	60.7% (N=34)
Percent bulbar onset	34.1% (N=28)	N/A	19% (N=16)	29.9% (N=103)	27% (N=69)	25.5% (N=84)	17.9% (N=10)
Percent bulbar *p* value vs. VA	0.0515	N/A	>0.9999	0.0776	0.1765	0.2428	Reference
Percent respiratory onset	7.4% (N=6)	N/A	6% (N=5)	3.5% (N=12)	N/A	N/A	21.4% (N=12)*
Percent PEG tube use	N/A	32% (N=unknown)	6% (N=5)	32.3% (N=111)	26% (N=66)	N/A	46.4% (N=26)
Percent PEG *p* value vs. VA	N/A	N/A	<0.0001	0.0480	0.0035	N/A	Reference
Percent NIV use	6.1% (N=5)	15.4% (N=unknown)	2.5% (N=2)	48.8% (N=168)	29% (N=73)	13.3% (N=44)	80.4% (N=45)
Percent NIV *p* value vs. VA	<0.0001	N/A	<0.0001	<0.0001	<0.0001	<0.0001	Reference
Percent use of Riluzole	98.8% (N=80)	N/A	66% (N=55)	88.7% (N=305)	89% (N=222)	60.9% (N=201)	44.6% (N=25) (53.6% used a medication)
Riluzole *p* value vs. VA	<0.0001	N/A	0.0144	<0.0001	<0.0001	0.0275	Reference
Median time of survival from symptom onset in MDC	N/A	1080 days (35.5 months)	26 months	40 months	36.8 months	N/A	1239 days (40.96 months)
Median time of survival from symptom onset in GNC	N/A	775 days (25.5 months)	33.3 months	34 months	28 months	N/A	N/A
Median time of survival from diagnosis in MDC	677 days (22.2 months)	N/A	17.6 months	N/A	19 months	21.6 months	719 days (23.77 months)
Median time of survival from diagnosis in GNC	448 days (14.7 mos)	N/A	18 months	N/A	11 months	N/A	N/A

at our MDC includes a physiatrist, specialist nurse, social worker, dietitian, psychologist, occupational therapist, physical therapist, speech and language pathologist, pulmonologist and respiratory therapist, and a palliative care physician. (Table A.1 in supplement)

In this retrospective chart review, we evaluated data from the ALS MDC at our VA medical center as it more closely resembles that of the European model in terms of access to and financial coverage of care compared to private practices in the United States. Outcomes regarding survival time, medication use, and symptom-based treatments of patients treated in MDCs were compared to those reported in prior studies.

2 Methods

2.1 Study Design

The previously mentioned studies on which current ALS multidisciplinary clinic recommendations from the AAN and EFNS are based were retrieved electronically using PubMed.gov.[7-10] By reviewing the references of these papers; searching PubMed using keywords "amyotrophic lateral sclerosis," "motor neuron disease," "ALS," and "multidisciplinary"; and using editorial suggestions, we also identified four newer studies from Paipa et al.[16], Aridegbe et al.[17], Rooney et. al.[18], and Martin et. al.[19]. Survival, intervention use, and type of ALS onset data reported for the multidisciplinary clinics in these studies is included in Table 1 except for the study by Rooney et. al. which did not include comprehensive survival data for the Irish multidisciplinary clinic studied. This data was recorded to be used for comparison with the corresponding data obtained from our VA MDC.

A list of VA MDC attendees from June 24, 2013 to February 1, 2021 was obtained from VA records. This list included a total of 56 patients (n = 56) which is consistent with the rarity of ALS and catchment area of our VA medical center. 41 of these patients were deceased on or before February 1, 2021. A retrospective chart review was then performed on our 56-patient cohort to identify patient gender; age at symptom onset; age at diagnosis; age of death (if applicable); onset type (bulbar, limb, or respiratory/generalized onset); use of a PEG; use of NIV, including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), and/or average volume assured pressure support (AVAPS); use of Riluzole; and use of Edaravone. If only the month was noted for time of symptom onset or diagnosis, the first of the month was used as the date of symptom onset or diagnosis for age calculation. If only the year was noted for time of symptom onset or diagnosis, the first of the year was used as the date of symptom onset or diagnosis for age calculation. Of note, we defined the subtypes based on what the charts mentioned as the first symptom at onset.

2.2 Ethical Approval

This study was approved by the Institutional Review Board of our VA Medical Center (IRB # 202101656). A waiver of the requirement for informed consent was obtained because of the retrospective design of the study.

2.3 Statistical Analysis

For survival analysis, two patients with ALS in our sample were involved in the MDC from the beginning of the clinic and survived for the entire duration of the study. These observations were censored beginning on February 1, 2021, the last day that patients were monitored. A Kaplan-Meier survival curve was constructed to find the distribution of the survival times of the patients in our study. The median survival time for our study was determined, along with its corresponding 95% confidence interval (CI), and this was compared with the median survival estimates from the other studies of interest.

Pairwise differences for PEG and NIV use rates between our MDC and each of the other relevant studies with sufficient data were assessed using Fisher's exact test. To account for multiple comparisons, a Bonferroni correction was employed for the PEG and NIV rate comparisons, such that the alpha threshold for the PEG comparisons was $0.05/3 = 0.0167$, and the alpha threshold for the NIV, bulbar, and Riluzole comparisons was $0.05/4 = 0.0125$.

The impact of Edaravone on survival times was assessed using Cox proportional hazards models to determine a hazard ratio (HR). A multivariate model was constructed for both survival time from symptom onset and survival time from diagnosis, in which Edaravone was assessed, along with the effects of age and gender. Schoenfeld residuals were also obtained to ensure that the Cox model was appropriate for the analysis.

Results

3.1 Demographics

Our cohort was comprised of 56 Veterans (n = 56). There were two females (4%), which is consistent with our VA population.[20,21] Our results, together with results from the literature, are presented in Table 1.

3.2 Survival from Time of Symptom Onset and Time of Diagnosis

The median survival time from symptom onset and from diagnosis in our VA MDC was 40.96 months (95% CI of 32.17, 76.07) and 23.77 months (95% CI of 18.64, 38.58) respectively. The survival probability is plotted as a function of time from symptom onset in Figure 1.

Figure 1. Survival probability as a function of days from symptom onset and diagnosis

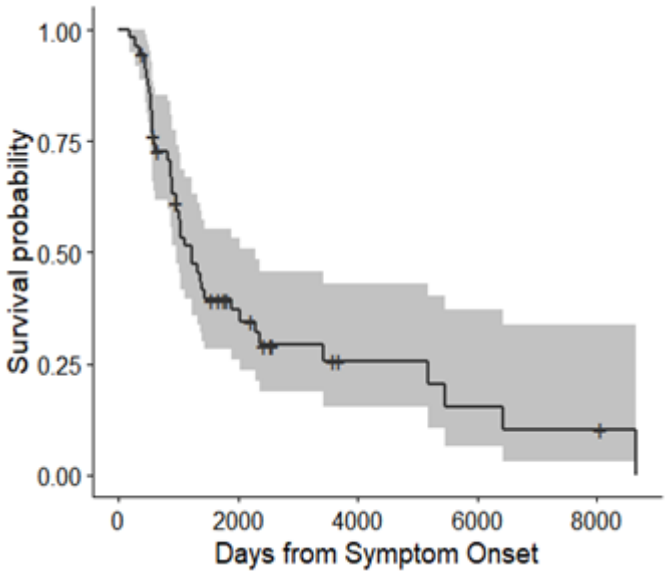

Figure 1a. Survival probability as a function of days from symptom onset

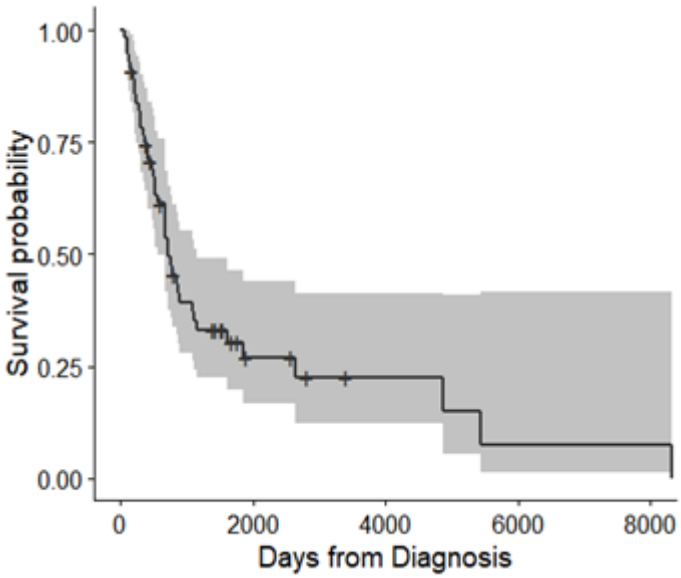

Figure 1b. Survival probability as a function of days from diagnosis.

3.3 Effect of Age and Gender on Survival

Using time to death from symptom onset as the outcome, and after adjusting for gender and Edaravone use, our model found age at symptom onset (Age_SO) to be a substantial risk factor (HR = 1.06, $p < 0.001$; Table 2). The Age_SO HR is interpreted as follows: at any given timepoint, the likelihood of a patient dying is 6% greater than that of a patient who is one year younger. This model found no noteworthy effect related to gender after adjusting for Edaravone use and age (HR = 0.79, $p = 0.80$; Table 2).

Table 2. Effect of age at symptom onset on survival, controlling for gender and Edaravone use

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.32	0.11, 0.93	**0.036**
Age at Symptom Onset	1.06	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.79	0.18, 3.40	0.8

[1]HR = Hazard Ratio, CI = Confidence Interval

3.4 Survival by ALS Subtype

The Cox proportional hazards model demonstrated that the location of symptom onset had an effect on patient survival from symptom onset. Specifically, patients who had limb onset subtype had greater lengths of survival from time of symptom onset relative to those with bulbar onset (HR = 0.26, $p = 0.002$). This effect remained significant after adjusting for Edaravone use, gender, and age at symptom onset (HR = 0.34, $p = 0.020$; Figure 2a; Table A.2a in appendix).

Similarly, survival from time of diagnosis was also longer in limb onset vs. bulbar onset. The results of the unadjusted effect of limb onset type on patient survival time from diagnosis, relative to bulbar onset were statistically significant (HR = 0.34, $p = 0.010$). When the model accounted for the effects of Edaravone usage, gender, and age at diagnosis, the effect of limb onset was similar, but no longer statistically significant (HR = 0.46, $p = 0.071$; Figure 2b; Table A.2b in appendix).

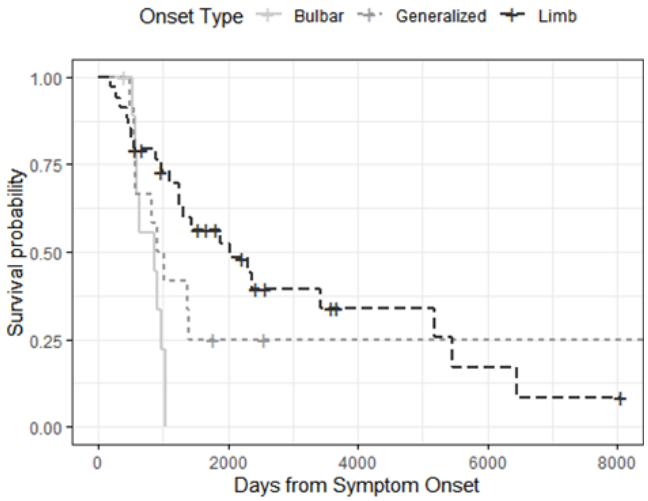

Figure 2a. Survival probability as a function of time from symptom onset by ALS subtype

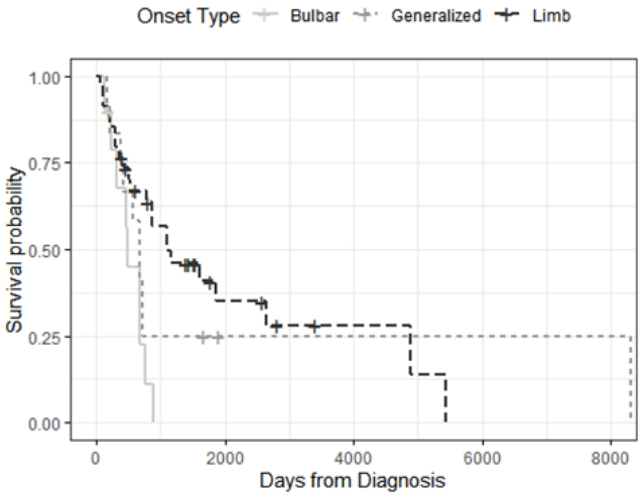

Figure 2b. Survival probability as a function of time from diagnosis by ALS subtype

3.5 Use of Equipment: PEG or NIV

The PEG use rate among patients in our study was 46.4%. If it was noted in a patient's chart that PEG had not been used yet, the data were analyzed as PEG not being used, although PEG might have been used at a later date. Figure A.3a and Table A.3a show the effect of PEG use on survival from symptom onset, and Figure A.3b and Table A.3b show survival from time of diagnosis (see appendix). In both univariate and multivariate (aka adjusted) models, we did not detect a relationship between PEG use and survival times from symptom onset (Table A.3c; see appendix) or diagnosis time (Table A.3d; see appendix).

80.4% of the patients in our study used NIV. In both univariate and multivariate (aka adjusted) models, we did not detect a relationship between NIV use and survival times from symptom onset (Table A.3e; see appendix) or diagnosis time (Table A.3f; see appendix).

3.6 Use of Riluzole

Riluzole was prescribed in 44.6% of our patients. We investigated a multivariate model (controlling for age and subtype), and the effect of Riluzole was not statistically significant in both survival from symptom onset (p = 0.8) and survival from diagnosis (p = 0.6); similarly, the univariate model also was not significant. (Figure A.4a-A.4b and Table A.4a-A.4b; see appendix).

3.7 Edaravone Effect on Survival

Fourteen of our patients (25% of our sample) were using Edaravone. When investigating the survival time from symptom onset, the Cox proportional hazards model found that Edaravone had a significant protective effect on our patient population (HR = 0.32, p = 0.036). The global Schoenfeld test of this model resulted in a p value of 0.9948, implying that the use of the Cox model is justified.

Using the Cox proportional hazards model to predict survival time from diagnosis, results were similar to those of survival from symptom onset. Edaravone is found to have a protective effect on the survival of our patient population (HR = 0.29, p = 0.023), while age at diagnosis was shown to be a risk factor (HR = 1.07, $p < 0.001$), and gender was not found to influence survival times (HR = 0.94, $p > 0.9$). The global Schoenfeld test of this model resulted in a p value of 0.9994, implying that the use of the Cox model is justified. Additionally, univariate Cox proportional hazards models were used to predict the survival time of patients with ALS from symptom onset (Table A.5a; see appendix) and diagnosis (Table A.5b; see appendix). In both instances, Edaravone usage is shown to increase survival times.

The effect of Edaravone on survival from symptom onset and diagnosis while controlling for age and gender of the patient is presented in Figure 3 and Tables 2 and 3.

Figure 3. Survival from Symptom Onset (SO) and diagnosis in patients on Edaravone vs patients not using it

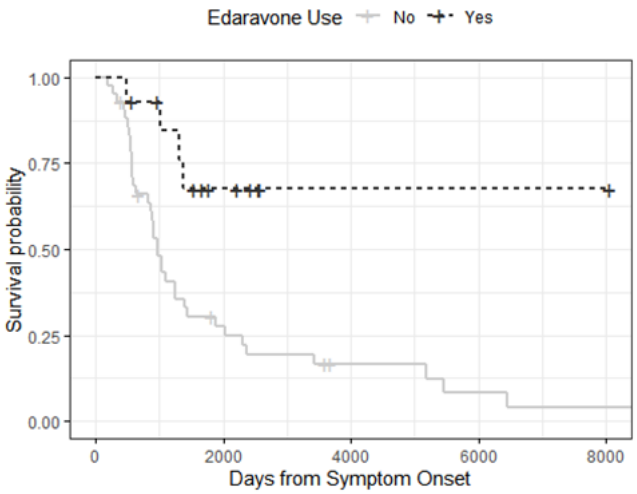

Figure 3a. Survival from Symptoms Onset in patients on edaravone vs patients not using it

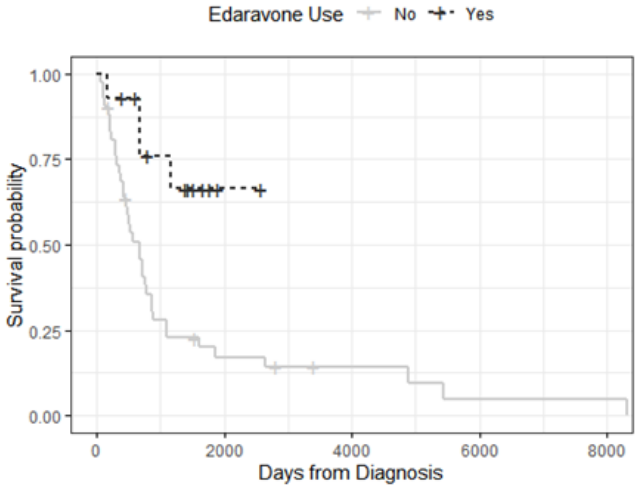

Figure 3b. Survival from diagnosis in patients using edaravone vs. patients not using it

Table 3. Effect of Edaravone on survival from time of diagnosis, controlling for age and gender

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.29	0.10, 0.84	**0.023**
Age at Diagnosis	1.07	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.94	0.22, 4.01	>0.9

[1]HR = Hazard Ratio, CI = Confidence Interval

4 Discussion

The median survival time of Veterans in our MDC from symptom onset was significantly greater than the median estimate provided in Zocollela et al.[9], whereas no significant difference is shown between the median survival time from symptom onset and the estimates provided in other similar studies.[7,8,16,17,19] Similarly, the median survival from time of diagnosis is significantly greater than the median estimate provided in Zocollela et al.[9] Apart from the Zocollela study,[9] all the other studies[7,8,16,17,19] showed that their MDC improved survival compared to the care provided at a general neurology clinic (GNC). The Zocollela study is one of the oldest studies (recruited in the 1990s), so it is possible their MDC did not provide the same level of care that is provided in MDCs more recently, such as fewer medications and less equipment support (Table 1). In the study by Chio,[8] their MDC used more NIV and PEG than what was used in their GNC; the MDC in Paipa[16] also used more PEG, NIV, and Riluzole vs. GNC; and similarly, the MDC studied by Traynor[7] used more NIV and Riluzole. Use of PEG, NIV, and Riluzole have all shown some benefit on survival,[22-24] but it is possible that the combination of these treatments, along with daily psychosocial support, contribute to improved survival in MDC clinics, with up to an additional 9-10 months in some cases.[7,8,23] Furthermore, quality of life was improved in patients with ALS in MDC clinics independent of the use of aids and appliances.[10,23]

Our results also agree with the hypothesis that MDC care improves median survival relative to GNC care. The 95% confidence intervals for our survival times were 32.17–76.07 for time of survival from symptom onset and 18.64–38.58 for time of survival from diagnosis. Comparing the time of survival seen in our study with that reported by GNCs in the included studies (data summarized in Table 1), our survival values fall outside of the range for survival from symptom onset reported for GNCs in Chio and Aridegbe[8,17] and outside of the range for survival from diagnosis reported for GNCs in Traynor, Zocollela, and Aridegbe.[7,9,17] The time of diagnosis is a more definite starting point than symptom onset and therefore possibly more likely to accurately reflect a difference.

4. 1 Survival by ALS Subtype

We found that Veterans who had limb onset ALS survived longer from time of symptom onset or time of diagnosis relative to those with bulbar onset ALS. This remained true even after controlling for Edaravone usage, gender, and age. Our findings are consistent with the literature where bulbar onset ALS is thought to have a poorer prognosis than spinal onset ALS (recorded as limb or respiratory/generalized onset in Table 1), although this can be variable.[25] Furthermore, we found no statistically significant difference in the number of bulbar onset cases in

our study versus all five relevant studies from which this was reported suggesting that our sample make up is consistent with the literature.

4. 2 Survival by Age and Gender

Our model found that age at symptom onset is a substantial risk factor and that at any given time point, the likelihood of a patient dying is 6% greater than that of a patient who is one year younger. This is consistent with the literature.[26] This model also found no noteworthy effect of survival based on gender. This is consistent with the literature, where most studies did not find a role for gender in the prognosis.[26]

4.3 Equipment Use

The rate of PEG use in our study was significantly greater than that of patients in the study from Zocollela et al. ($p < 0.0001$) and from Aridegbe et al. ($p = 0.0035$).[9,17] No significant difference was detected between PEG use rates from our study and the study from Paipa et al. ($p = 0.0480$).[16] Chio et al. and Martin et al. did not report the percentage PEG use.[8,19] We did not find that PEG use added survival advantage. Burkhardt et al.[27]found that PEG ($p < 0.01$) had a significant impact on survival. They initially did not find benefit for PEG use, but after adjustments for diagnostic delay, region of onset, predicted ALS-FRS (ALS-functional rating scale), gender, age at diagnosis, and BMI loss, they found significant benefit. We repeated a similar analysis but did not find a survival advantage. Although PEG use is widely accepted in ALS care to prevent starvation and dehydration and to improve quality of life, survival benefit of PEG is not universally demonstrated.[26]

The reason for increased PEG use in the VA MDC is not clear. In the VA MDC, PEG use is discussed early but generally, patients are not referred for the procedure until they have significant weight loss (>10%), dysphagia, aspiration, or fatigue with eating which is in accordance with AAN guidelines.[27] All patients are seen quarterly by nutrition, speech pathology, and pulmonology. Weights, pulmonary function tests, and bedside swallows are monitored quarterly. Video swallows are done when deemed indicated by speech pathology. Patients are referred to gastroenterology for consultation if/when they want to proceed with a PEG and they perform the procedure if they feel it is indicated. If patients choose a PEG, the procedure is performed when FVC is still >50%.

The percentage of our patients using NIV was greater than the percentage of NIV use in any of the other studies ($p < 0.0001$ for each comparison), but we did not find a survival advantage. This is consistent with the literature, where survival advantage was found in some studies,[28-32] but not universally.[33] It is possible that this result was confounded by NIV use for non-ALS purposes such as obstructive sleep apnea. Overall, there is a higher use of CPAP and BiPAP in the U.S., possibly due to a higher prevalence of sleep apnea in the U.S. vs. Europe. Therefore, we hypothesize that the percentage of NIV use in our sample is diluted by patients using NIV for other reasons, though we did not perform an analysis of who was started on NIV initially for alternative reasons and did not require adjustments based on weakness due to ALS progression.

4.4 Medication Use: Riluzole

Significant differences were detected in Riluzole use rates between our VA MDC and the studies performed by Traynor, Paipa, and Aridegbe et. al.[7,16,17] The difference between Riluzole use rates of our VA MDC and the studies performed by Zocolella and Martin et. al. was marginally significant,[9,19] but not statistically significant, after applying the Bonferroni correction for multiple comparisons.

This difference in Riluzole use is most likelyrelated to patient preference. All patients at the VA MDC are offered medications unless they have a contraindication to use. Since ALS care is palliative by nature, it is not unreasonable for a patient concerned about quality of life to decline Riluzole use given minimal clinical benefit. Some VA MDC patients used both Riluzole and Edaravone; 30 of 56 patients used either one or both medications (53.6%). Because our Riluzole use was very low, we could not detect survival advantage.

4.5 Medication Use: Edaravone

Our Cox proportional hazards model found that Edaravone had a significant protective effect on our patient population and improved survival from symptom onset, as well as from time of diagnosis (HR = 0.29, $p = 0.023$). No other identified study has reported Edaravone use in MDC.

Edaravone is a relatively newly approved medication for ALS and therefore was not included as a variable in any of the European comparison studies. A clinical trial published in 2017 showed benefit in reducing the decline in the ALS-FRS in well-selected patients with ALS,[2] but survival advantage has not been well-established. Two recent studies with small cohorts of 45 and 57 patients, both conducted in Japan, demonstrated evidence for improvement in survival with Edaravone use.[34,35] A larger retrospective review in the U.S. also showed survival benefit,[36] while a study conducted in Germany showed no survival benefit or slowing of clinical decline.[37] Twenty-five percent of our cohort used Edaravone and we were able to show a statistically significant increase in life expectancy in the patients that had used Edaravone relative to those who had not, though we did not record dosage or dosing frequency amongst these patients. We did not perform an analysis on comorbidities, other medication use, or personal opinions in the patients who opted to take Edaravone, though it seems possible that those patients who chose to take this medication preferred a maximum treatment approach as opposed to a comfort-focused approach. While this philosophy may confer survival benefit, it is beyond the scope of this retrospective review. Our data

may still contribute to recent findings that Edaravone may in fact prolong life in ALS patients.

Limitations

There are several limitations in our research. First, the diagnosis of ALS is clinical, often with the assistance of electromyography (EMG) to help support the diagnosis. The El Escorial criteria, which provide a unified set of ALS diagnostic criteria, were first published by the World Federation of Neurology in 1994.[38] These criteria remain a standard of diagnosis for ALS. Unfortunately, we do not know what criteria were used to make a diagnosis of ALS for the patients in our study, because most patients in the VA MDC were not diagnosed at the VA hospital but were initially seen by a non-VA neurologist. While all of the VA MDC referrals came from neurologists, making proper criteria usage more likely, we cannot say whether the patients in our cohort would be defined as having definite, probable, or possible ALS based on El Escorial criteria. A misdiagnosis could certainly affect survival data and should be mentioned. The most recent Gold Coast criteria has simplified the ALS diagnostic categories and would be used moving forward.[39]

Second, we lacked the exact date for onset of symptoms for most patients given that this date is generally subjective and based on patient history. We suspect this is not unique to our study since ALS is insidious.

Third, our clinic is a relatively small ALS clinic with less than 8 new patients added per year. It is not a typical multidisciplinary ALS center, and the findings might not be applicable to larger, much busier clinics as the amount of time available to each patient would be significantly higher in our clinic.

Finally, we did not compare our results to a local GNC, because the veterans with ALS in our study were enrolled only in the VA MDC. In the future, as veterans have options to go to community neurologists, our study will provide a basis against which to compare survival of veterans in VA MDCs vs. GNCs.

In conclusion, we found that Veterans enrolled in a US-based multidisciplinary ALS clinic had similar survival to those cared for at European MDCs, and both have survival advantage over those cared for by general neurologists reported in the literature. This becomes relevant if more Veterans choose to seek care outside the VA, in locations where only general neurologists exist. Fortunately, according to the recent Veterans Health Administration Directive 1101.07, Amyotrophic Lateral Sclerosis (ALS) System of Care, released on August 30, 2021, "Community care referrals will include approval for interdisciplinary ALS care".[40] Future research should compare ALS care at VA MDC versus that at academic center MDC and private general neurologists. We also showed agreement with recent literature suggesting that Edaravone was associated with a prolonged life expectancy.

Disclosure of conflict of interest

None of the authors has any conflict of interest to disclose.

Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Data availability statement

Any data not published within the article will be available upon request.

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Appendix

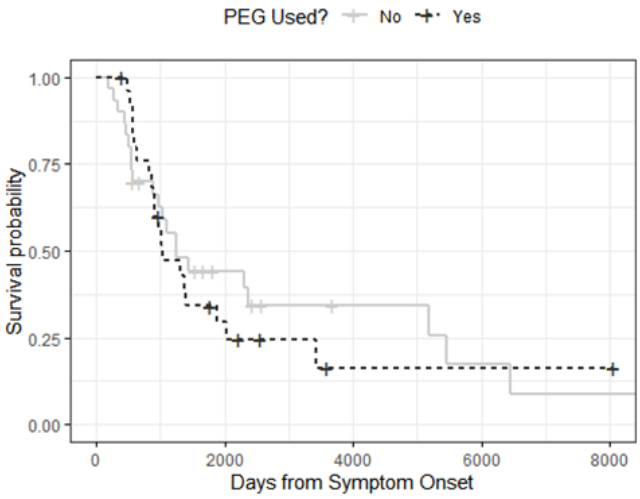

Figure A.3a. Survival probability as a function of time from symptom onset by PEG tube use

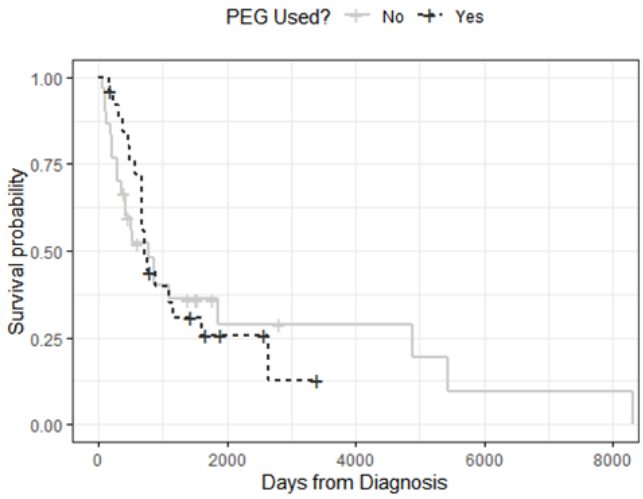

Figure A.3b. Survival probability as a function of time from diagnosis by PEG tube use

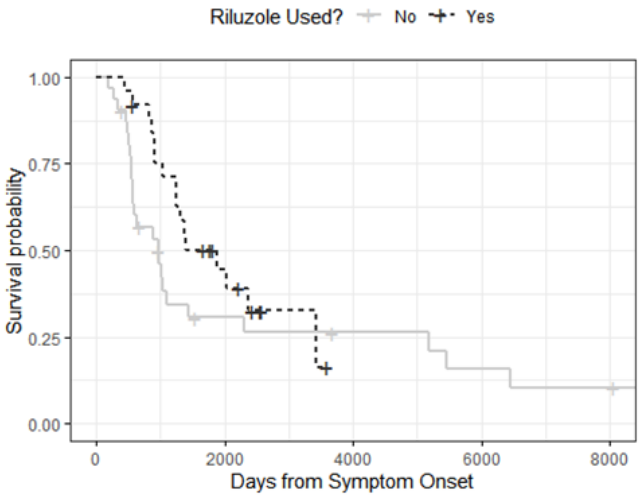

Figure A.4a. Survival from diagnosis in patients using riluzole vs. patients not using it

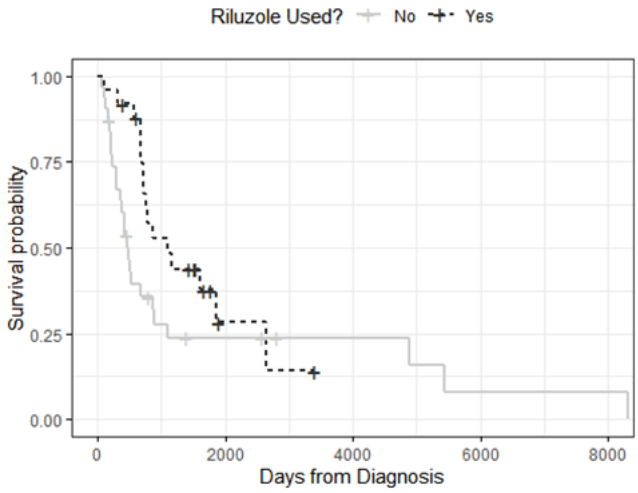

Figure A.4b. Survival from diagnosis in patients using riluzole vs. patients not using it

Table A1. ALS clinic roles

ALS Clinic team member	**Role**
RN Case Manager	Pre-clinic check-in call to complete ALS FRS-R; rooming veterans, vitals
Respiratory Therapist	Complete respiratory testing at the start of the clinic day
Physiatrist/PA	Medical management; medication management
Social Worker	Assists with support system and VA/community benefits & resources
Dietitian	Diet and nutritional assessment; feeding tube formulas management
Psychologist	Adjustment/grief/loss support; brief counseling support
Occupational Therapist	Strategies/tools/equipment for managing ADL/IADLs
Physical Therapist	Home and community mobility support; transfers; wheelchair assessments
Speech and language pathologist	Swallowing changes; augmentative and alternative communication (AAC) strategies for managing speech changes
Pulmonologist	Management of neuromuscular respiratory failure
Palliative care physician	Ongoing palliative care support, care planning, and hospice coordination

Table A.2a. Model for survival from symptom onset by ALS subtype

Full model: This table provides our estimates for the effect of onset type on survival time from symptom onset after adjusting for the potential confounders of edaravone usage, age at symptom onset, and gender.

Characteristic	HR[1]	95% CI[1]	*p* value
Edaravone usage	0.32	0.11, 0.96	**0.042**
Age at Symptom Onset	1.06	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.62	0.14, 2.75	0.5
Onset Type			
Bulbar	—	—	
Generalized	0.63	0.22, 1.75	0.4
Limb	0.34	0.14, 0.85	**0.020**

[1]HR = Hazard Ratio, CI = Confidence Interval

Unadjusted model: This table provides our estimates for the effect of Onset Type on survival time from symptom onset without adjusting for patient age, gender, or edaravone usage

Characteristic	HR[1]	95% CI[1]	*p* value
Onset Type			
Bulbar	—	—	
Generalized	0.39	0.15, 1.04	0.059
Limb	0.26	0.11, 0.62	**0.002**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.2b. Model for Survival from time of diagnosis by ALS subtype

Full model: This table provides our estimates for the effect of onset type on survival time from diagnosis after adjusting for the potential confounders of edaravone usage, age at diagnosis, and gender.

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.30	0.10, 0.88	**0.028**
Age at Diagnosis	1.06	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.76	0.17, 3.35	0.7
Onset Type			
Bulbar	—	—	
Generalized	0.79	0.29, 2.12	0.6
Limb	0.46	0.19, 1.07	0.071

[1]HR = Hazard Ratio, CI = Confidence Interval

Unadjusted Model: This table provides our estimates for the effect of Onset Type on survival time from diagnosis without adjusting for a patient's age, gender, or edaravone intake.

Characteristic	HR[1]	95% CI[1]	p-value
Onset Type			
Bulbar	—	—	
Generalized	0.46	0.18, 1.19	0.11
Limb	0.34	0.15, 0.77	**0.010**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3a. PEG and survival from symptom onset

Characteristic	HR[1]	95% CI[1]	p-value
PEG	1.38	0.71, 2.66	0.3
Age_SO	1.07	1.04, 1.11	<**0.001**
Gender			
F	—	—	
M	0.72	0.16, 3.18	0.7

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3b. PEG use and survival from time of diagnosis

Characteristic	HR[1]	95% CI[1]	p-value
PEG	1.14	0.59, 2.21	0.7
Age_Diag	1.07	1.04, 1.11	<**0.001**
Gender			
F	—	—	
M	0.76	0.17, 3.33	0.7

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3c. Model: PEG use and survival from symptom onset

Characteristic	HR[1]	95% CI[1]	p-value
PEG	0.90	0.36, 2.23	0.8
Age_SO	1.06	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.52	0.10, 2.59	0.4
Onset_type			
Bulbar	—	—	
Generalized	0.41	0.15, 1.14	0.086
Limb	0.32	0.10, 1.02	0.054
Delay to Diagnosis	1.00	1.00, 1.00	0.10

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3d. Model: PEG use and survival from time of diagnosis

Characteristic	HR[1]	95% CI[1]	p-value
PEG	0.56	0.21, 1.50	0.3
Age_Diag	1.07	1.03, 1.10	<**0.001**
Gender			
F	—	—	
M	0.41	0.08, 2.07	0.3
onset_type			
Bulbar	—	—	
Generalized	0.45	0.16, 1.26	0.13
Limb	0.23	0.07, 0.82	**0.023**
Delay to Diagnosis	1.00	1.00, 1.00	>0.9

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3e. Survival from symptom onset model and NIV use

Characteristic	HR[1]	95% CI[1]	p-value
NIV	1.50	0.58, 3.83	0.4
Age_SO	1.07	1.03, 1.11	<**0.001**
Gender			
F	—	—	
M	0.62	0.14, 2.78	0.5
Onset_type			
Bulbar	—	—	
Generalized	0.37	0.13, 1.04	0.060
Limb	0.34	0.14, 0.84	**0.020**
Delay to Diagnosis	1.00	1.00, 1.00	0.12

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.3f. Survival from symptom onset model and NIV use

Characteristic	HR[1]	95% CI[1]	p-value
NIV	1.30	0.50, 3.36	0.6
Age_Diag	1.07	1.03, 1.12	<**0.001**
Gender			
F	—	—	
M	0.64	0.14, 2.89	0.6
Onset_type			
Bulbar	—	—	
Generalized	0.50	0.18, 1.34	0.2
Limb	0.39	0.16, 0.93	**0.035**
Delay to Diagnosis	1.00	1.00, 1.00	0.8

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.4a. Effect of riluzole on survival from symptom onset, controlling for age and gender

Characteristic	HR[1]	95% CI[1]	p-value
Riluzole	0.89	0.44, 1.82	0.8
Age at Symptom Onset	1.06	1.03, 1.10	<**0.001**
Onset_type			
Bulbar	—	—	
Generalized	0.43	0.16, 1.15	0.092
Limb	0.30	0.12, 0.75	**0.010**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.4b. Effect of riluzole on survival from time of diagnosis, controlling for age and gender

Characteristic	HR[1]	95% CI[1]	p-value
Riluzole	0.82	0.40, 1.67	0.6
Age at Diagnosis	1.06	1.03, 1.10	<**0.001**
Onset_type			
Bulbar	—	—	
Generalized	0.54	0.20, 1.41	0.2
Limb	0.39	0.17, 0.90	**0.028**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.5a. Model demonstrating that edaravone is a preventative factor against death from ALS from symptom onset

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.24	0.09, 0.68	**0.007**

[1]HR = Hazard Ratio, CI = Confidence Interval

Table A.5b. Model demonstrating that edaravone is a preventative factor against death from ALS from diagnosis

Characteristic	HR[1]	95% CI[1]	p-value
Edaravone	0.25	0.09, 0.70	**0.009**

[1]HR = Hazard Ratio, CI = Confidence Interval