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Analysis of Mortality Causes and Locations in Veterans with ALS: A Decade Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Amyotrophic lateral sclerosis (ALS) is a motor neuron disease that leads to rapid degeneration of nerves in the brain and spinal cord, with eventual loss of voluntary movements, including breathing. This retrospective study of medical record data from 105 US veterans diagnosed with ALS at the Oklahoma City VA Medical Center between 2010 and 2021 aimed to identify patient demographics, and the causes and places of death for these veterans.

Material/Methods: Data from 105 US veterans diagnosed with ALS by the El Escorial criteria and supported by neurophysiology testing was reviewed. The information about the place and cause of death was obtained from each patient's care provider and death certificate. Crude mortality rates (per 100 person-years) and standardized mortality ratios (SMRs) were calculated for the causes of death, by sex, age group, and location of death.

Results: During the 11-year follow-up period, 80 (76.2%) veterans with ALS died. The mean (SD) follow-up time was 4.53 (4.55) years. Most of the deaths were due to respiratory failure and pneumonia (n=43, mortality rate=9.21 per 100 person-years). Most patients died at home (n=71, 88.7%). The annual crude mortality rate was 16.7 and the all-cause death SMR was 25.63 (95% CI, 20.32-31.55).

Conclusions: This study's findings are that in veterans with ALS, the main cause of death is respiratory disease (failure). The main location of death was the home, with their family members. The all-cause mortality rate among veterans with ALS was 26 times greater than for the general Oklahoma population.

Keywords: Veterans • Amyotrophic Lateral Sclerosis • Mortality • Caregiver Burden

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Introduction

Amyotrophic lateral sclerosis (ALS) is a rare, fatal, progressive neurodegenerative disease, with a worldwide incidence of 1.6 cases per 100 000 people, in which there is a loss of motor neurons in the brain, brainstem, and spinal cord [1]. It presents as painless voluntary muscle wasting with fasciculations and weakness from lower motor neuron involvement (amyotrophy); and upper motor neuron findings of hyperreflexia and spasticity from axonal loss involving the corticospinal tracts in the lateral spinal cord columns (lateral sclerosis) [1-3]. ALS is a clinical diagnosis based on the revised El Escorial criteria. These criteria require the presence of i) clinical, electrophysical, or neuropathologic evidence of lower motor neuron degeneration; ii) clinical, electrophysical, or neuropathologic evidence of upper motor neuron degeneration; and iii) evidence of progressive spread of symptoms and signs within a region or to other regions. Electrophysiological findings include fibrillation and positive sharp waves (suggesting acute denervation), long-duration complex motor unit action potential (cMUAP; suggesting chronic denervation), and large amplitude cMUAP (suggesting re-innervation) in the presence of normal sensory action potentials. Pharmacological treatment, which includes riluzole, edaravone, and Relyvrio, has had a modest effect on survival. Symptomatic management as recommended by a multidisciplinary ALS team is the main treatment option in patients with ALS [4].

Death in patients with ALS is mainly from respiratory failure within 2 to 5 years of disease onset [5]. The quality of clinical care and life in patients with ALS has recently improved by addressing their nutritional status through earlier use of gastrostomy tube (PEG), earlier use of noninvasive ventilation (NIV) for respiratory support, cough assist and suction devices to prevent aspiration pneumonia, better communication devices, and provision of mobility devices to help achieve independence in their environment [4]. Gil et al [6] in their study of 305 patients with ALS, reported that the leading cause of death was respiratory failure (in 77% of cases), followed by cardiac failure (in 3.4%), suicide (in 1.3%), and sudden death (in 0.7%). They could not ascertain the cause of death in 13% of the cases. Sixty-three percent of patients in their study died in the hospital. Corcia et al studied autopsies of 100 patients with ALS, and found that respiratory disorder was the main cause of death in 71% of cases, and cardiac failure was the main cause of death in 10% of cases [7].

Most of the studies on ALS have been conducted in the general population and few in the veteran population, who make up 7% (22 million) of the US population [8,9]. Therefore, this retrospective study of medical record data from 105 US veterans diagnosed with ALS at the Oklahoma City VA Medical Center between 2010 and 2021 aimed to identify patient demographics, and the cause and place of death. The information collected will help improve acute and end-of-life (palliative and hospice) care provisions. Determining the location of death (ie, within or outside a medical facility) for veterans with ALS will help us allocate the resources needed for highly specialized care, in different care settings such as hospice and nursing homes.

Material and Methods

Ethics Statement

This study was approved by the local Human Research Ethics Committee (IRB # 10358) and was exempt from veteran informed consent because of the retrospective review of the electronic medical records of veterans still being followed clinically. Furthermore, most of the veterans with ALS had died.

Study Design

This single-center, retrospective, longitudinal, observational study collected electronic data for veterans clinically diagnosed with definite/probable ALS by the El Escorial criteria [10] and supported by neurophysiology testing on their initial clinical evaluation. They were all prescribed riluzole and vitamin D, and were advised regarding NIV and PEG placement when indicated. This study protocol is identical to our recently published study of the mortality prediction model in veterans with ALS [11]. In brief, veterans followed periodically every 4 months at the Oklahoma City VA Medical Center (OKC VAMC) from 1/1/2010 to 12/31/2021 were enrolled. The OKC VAMC ALS clinic is a Regional Center of Excellence that provides ALS specialty care as a continuum in the acute, chronic, and long-term phases of the disorder following the Veterans Health Administration policies. The ALS clinic set-up involves the veterans with ALS meeting in a room simultaneously with other multidisciplinary team members comprising a neurologist, respiratory physician, physician assistant, occupational therapist, physical therapist, speech therapist, respiratory therapist, dietician, psychologist, palliative care specialist, prosthetic specialist, social worker, and clinical coordinator [12-14].

Eligibility Criteria

The inclusion criteria for this study were complete electronic medical records for those veterans who were regularly followed in our ALS clinic including the causes and locations of death. The exclusion criteria were incomplete electronic medical records, including a lack of documentation of causes and locations of death.

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Data Collection

The demographic and clinical variables collected were the age of symptom onset, age at initial evaluation, survival (from symptom onset to death), sex, race/ethnicity, site of onset (limb/appendicular, bulbar, and respiratory), body mass index (BMI), initial ALS functional-related score-revised (ALSFRS-R) [15], total functional independence measure scores [16-19], and initial forced vital capacity [20]. The presence of co-morbidities known to influence mortality in the general population, such as hypertension, hyperlipidemia, diabetes mellitus, current smoking habit, presence of ALS-related complications such as depression, and interventions (riluzole, gastrostomy, NIV, tracheostomy) shown to prolong survival were recorded [3].

Assessment of Mortality

All veterans with ALS who died over the 11-year study period at any time were ascertained as to their dates, causes, and locations of death (home, long-term care facility, or hospital). This information was provided by the patient's care provider or next of kin to our clinic coordinator or social worker or obtained from death certificates filed with the Oklahoma State Department of Health. The causes of death were categorized into disease-related groups: (1) respiratory, (2) cardiovascular, (3) nutritional, (4) urinary system, (5) digestive system, (6) musculoskeletal or connective tissue, (7) nervous system, and (8) cancer.

This study meets the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and the information required is reported accordingly (see the Supplementary Checklist).

Statistical Analysis

Standardized mortality ratios (SMRs) were calculated based on the ratio of the observed to the expected number of deaths within a year. The death calculations were based on the age and sex-specific mortality statistics of Oklahoma State from 2010 to 2020. SMRs and crude mortality rates (per 100 person-years) were calculated for 3 subgroups: sex, cause(s) of death, and age group (35-44, 45-65, or 65+ years). The crude mortality rate calculation was done using the "person-years-at-risk" method for the total follow-up period. The annual incidence in Oklahoma State between 2010 and 2021 was calculated using the mid-interval population of Oklahoma State, which was curated by usafacts.org and the Census Bureau (https://www2.census.gov/programs-surveys/popest/). All cases were traced from the first ALS diagnosis date till December 2021. Statistical significance for all analyses was set at a *P*-value <0.05 (2-sided). Statistical analyses were performed using the R package (v3.5.3 Vienna, Austria).

Results

Analysis of Participants' Demographics

The clinical characteristics of our study sample of 105 veterans with ALS (on their first clinic visit and over the course of 11 years following their initial visit) are presented in **Table 1**. The mean age at symptom onset, confirmed diagnosis, and death (±SD, years) were 62.0 (11), 65 (11), and 67 (11), respectively. Of the 105 patients, 101 (96%) were men and 95 (91%) were non-Hispanic white. Sporadic ALS was observed in 81 veterans (77%). The number of veterans with ALS-onset types at presentation was appendicular (n=55, 52%), bulbar (n=45, 43%), and respiratory (n=5, 4.8%).

Of the 105 veterans with ALS, during the follow-up period, 80 (76.2%) died. The mean (±SD) duration of follow-up was 4.53 (4.55) years. Of the 80 patients with ALS who died, 77 were men and 3 were women (the men-to-women ratio was 25.67 to 1). The annual incidence was 2.67 (per 100 000) in the State of Oklahoma between 2010 and 2021. The annual crude mortality rate for our veterans with ALS (per 100 person-years) was 16.7.

Analysis of the Participants' Descriptive Characteristics with Respect to Causes of Death

Tables 2 and 3 present the causes of death by sex and age groups. Most of the deaths were from respiratory diseases (n=43, the mortality rate=9.21 per 100 person-years. Other causes of death were cardiovascular disease (n=7, cardiac arrest n=4, myocardial infarction n=3), malnutrition (n=3), urinary tract infection (n=2), and intracranial hemorrhage (n=1). The cause of death in the remaining 27 patients (33.75%) could not be identified. Veterans aged 65 years and older had the highest number of deaths (19.84%) followed by those aged 45-64 years (14%).

Analysis of the Participants' Descriptive Characteristics with Regard to Location of Death

Table 4 presents the locations of deaths: 71 (88.75%) occurred at home, 1 (1.25%) occurred in the acute hospital, and 7 (8.75%) occurred in nursing homes.

The all-cause death SMR was 25.63 (95% CI, 20.32-31.55); the SMR for women (40.18 95% CI, 7.58-98.53) was significantly greater than that for men (25.27 95% CI, 19.94-31.23) based on their 95% CIs. Among veterans with ALS, the prevalence of each cause of death was higher than among the general Oklahoma population, except for digestive system and cancer, because there were none of these causes of death in our cohort.

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Table 1. Clinical characteristics of veterans with ALS, based on the first clinic visit.

	Overall (N=105,%)
Age at symptom onset (years)	
Mean (SD)	62.3 (11.2)
Median [Min, Max]	65.0 [33.0, 87.0]
Age at diagnosis (years)	
Mean (SD)	64.6 (11.1)
Median [Min, Max]	66.0 [35.0, 88.0]
Age at death (years)	
Mean (SD)	66.9 (11.1)
Median [Min, Max]	68.0 [42.0, 89.0]
Onset to death (death-onset) (years)	
Mean (SD)	4.12 (3.87)
Median [Min, Max]	3.00 [1.00, 21.0]
Duration (present-onset) (years)	
Mean (SD)	2.62 (3.26)
Median [Min, Max]	2.00 [0, 21.0]
Sex	
Men	101 (96.2%)
Women	4 (3.8%)
Race	
Black	9 (8.6%)
Native American	1 (1.0%)
White	95 (90.5%)
Body mass index	
Mean (SD)	26.0 (5.97)
Median [Min, Max]	25.3 [15.5, 45.7]
Smoker	20 (19.0%)
Hypertension	58 (55.2%)
Diabetes mellitus	24 (22.9%)
Hyperlipidemia	49 (46.7%)
ALS type	
Appendicular	55 (52.4%)
Bulbar	45 (42.9%)
Respiratory	5 (4.8%)
Depression	30 (28.6%)
ALSFRS-R	
Mean (SD)	31.3 (8.34)
Median [Min, Max]	31.0 [14.0, 48.0]
Total functional independence measure	
Mean (SD)	90.9 (25.3)
Median [Min, Max]	99.0 [18.0, 123]
Forced vital capacity	
<50	14 (13.3%)
50-79	39 (37.1%)
≥80	38 (36.2%)
Percutaneous endoscopic gastrostomy	28 (26.7%)
NIV	36 (34.3%)
Riluzole	70 (66.7%)

ALS – amyotrophic lateral sclerosis; ALSFRS-R – Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; NIV – noninvasive ventilation.

Discussion

The main findings of this single-center, retrospective, observational study on the 11-year longitudinal collected data on veterans with ALS were as follows: First, respiratory diseases and respiratory failure were the most frequent cause of death (53.75%) followed by cardiovascular disease (8.75%), and malnutrition (3.75%). Second, most of the veterans with ALS died at home (88.75%) in the presence of their family members. Third, the annual crude mortality rate per 100 person-years for ALS was 16.7, and the SMR for all-cause death was 195 per 100 000 individuals.

First, the findings of respiratory failure and disease being responsible for most mortality in our study (53.75%) are similar to those from prior published reports [1,6,21]. In a study from Taiwan [22], the proportion of deaths from respiratory disease stemming from respiratory muscle weakness was 50.8%. However, in Italian (81.3%) [1], French (80%) [6], and Southwest Chinese (65.5%) [21] studies, the percentage of respiratory-related deaths

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Table 2. The cause of death by sex in veterans with ALS, 2010-2021.

The underlying cause of death	All		Men		Women	
	n	Mortality*	n	Mortality*	n	Mortality*
Respiratory diseases	43	9.21	41	9.01	2	16.67
Cardiovascular diseases or stroke	7	1.50	7	1.54	0	0.00
Metabolic diseases	3	0.64	3	0.66	0	0.00
ALS	20	4.28	19	4.18	1	8.33
Unknown	5	1.07	5	1.10	0	0.00
Total	78	16.70	75	16.49	3	25.00

* Per 100 person-years using the "person-years-at-risk" method; subjects without follow-up length info were excluded.
ALS – amyotrophic lateral sclerosis.

Table 3. The cause of death by age group in veterans with ALS, 2010-2021.

The underlying cause of death	Age at death							
	All		20-44 years		45-64 years		≥65 years	
	n	Mortality*	n	Mortality*	n	Mortality*	n	Mortality*
Respiratory diseases	43	9.21	2	6.06	15	7.81	26	10.74
Cardiovascular diseases or stroke	7	1.50	0	0.00	2	1.04	5	2.07
Metabolic diseases	3	0.64	0	0.00	1	0.52	2	0.83
ALS	20	4.28	0	0.00	9	4.69	11	4.55
Unknown	5	1.07	1	3.03	0	0.00	4	1.65
Total	78	16.70	3	9.09	27	14.06	48	19.84

* Per 100 person-years using the "person-years-at-risk" method, subjects without follow-up length info were excluded.
ALS – amyotrophic lateral sclerosis.

Table 4. The cause of death and location of death for each cause, in veterans with ALS, 2010-2021.

The underlying cause of death	Home		Nursing home		Hospital	
	n	%	n	%	n	%
Respiratory diseases	37	52.11	5	71.42	1	100.00
Cardiovascular diseases or stroke	6	8.45	1	14.29	0	0.00
Metabolic diseases	3	4.23	0	0.00	0	0.00
ALS	19	26.76	1	14.29	0	0.00
Unknown	6	8.45	0	0.0	0	0.00
Total	71	100.00	7	100.00	1	100.00

ALS – amyotrophic lateral sclerosis.

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was higher than in our study. Cardiovascular disease was the second most frequent cause of death in our study (8.75% of the cases), which was comparable to the 10.7% and 6% of cases reported in the Taiwan [22] and Italian [1] studies, respectively. Undernutrition was the third most frequent cause of death in our study (3.75% of the cases), which was much lower than the 25.9% reported in the southwest China study [21]. The proportion of veterans for whom the causes of death could not be ascertained was 33.75% of the cases in our study, compared with 13% in the Taiwanese [22] and French [6] studies. In the French study, the cause of death was ascertained directly from the patient's physicians. Our high percentage of cause of death that could not be ascertained was largely because we were unable to reach the deceased veteran's family members (even after repeated attempts and leaving telephone messages) and because we were unable to obtain their death certificates from the Oklahoma State Department of Health.

Second, most of the veterans with ALS died at home (88.75%) in the presence of their family members. Similar findings have been reported in Italian (85.2%) [1] and Southwest Chinese (82%) [21] studies of patients with ALS. Since 2003, an increasing number of patients have preferred to die at home and home now surpasses the hospital as the most common place to die in the United States [23]. This finding highlights the need to prioritize access to high-quality home-based care for veterans with serious illnesses.

Third, the annual crude mortality rate per 100 person-years for ALS was 16.7, and the SMR for all-cause death was 195 per 100 000 individuals. Compared with men, women had a significantly higher mortality rate. This could be explained by their small number (n=3) as it is expected the mortality rate among adult men with ALS to be higher than among the general population.

This study updates previously described information and adds new information about the causes and locations of death of American veterans with ALS.

The limitations of the present study are: First, the small sample size of 105 patients may bias the results as the power to detect associations is reduced. Second, the causes of death could not be ascertained in 27 (33.75%) cases in this study despite our best efforts. Third, the conclusions should be interpreted with caution and could be less generalizable to the general ALS patient population as this study primarily included veterans who were non-Hispanic white men (96%), and all veterans with ALS receive a higher standard of subsidized medical care through the Veteran Health System that may not be available to the general Oklahoma population.

The strength of this study is the completeness of data collected by the standardized ALS registry over 11 years with no loss on periodic follow-up. This completeness serves to provide a better understanding of ALS characteristics in veterans. Finally, this observational study represents real-world experience. With this study's findings, we re-emphasize to veterans with ALS the importance of the utilization of interventions such as NIV and PEG tubes when seen in the clinic. We also re-emphasize the importance of providing home delivery of essential medical equipment and specialized home-based care services, including appropriate caregiver support, so that neither the patient nor the care provider is overburdened with the veteran's care as the disease progressively worsens. We are now starting to collect data on what impact these interventions will have on the quality of life of the veterans with ALS we serve.

Conclusions

This study suggests that the most common cause of death among veterans with ALS in Oklahoma was respiratory disease/respiratory failure. The main location of death was at home among their family members. The all-cause death rate among veterans with ALS was 25.63 times greater than that among the general Oklahoma population.

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