

Background

Aside from age, sex, and certain genetic mutations, there are no clearly established risk factors for the development or progression of amyotrophic lateral sclerosis (ALS). Some studies have found slight differential risk of ALS across income brackets and racial and ethnic groups, suggesting greater relative risk of ALS in higher income quartiles and in non-Hispanic white patients. There have also been reported geospatial clusters of ALS, suggesting possible links with both socioeconomic status (SES) and environment. However, the independent roles of geography and socioeconomic factors in the development or progression of ALS remain to be determined.

Methods

In an ongoing retrospective chart review, this study is investigating time to significant clinical milestones (loss of speech, loss of ambulation, gastrostomy placement, tracheostomy placement, first use of non-invasive ventilation (NIV), and death) in four geographically distinct populations, specifically comparing patients with ALS treated at an urban, San Francisco-based clinic and satellite clinics in the agricultural and lower SES Central Valley region of California (combined cohort representing Fresno and Modesto), an intermediate SES tier (in Monterey and Santa Rosa), and patients seen entirely via telehealth.

Preliminary Results

	Total (N=82)		UCSF (N=40)		Video Only (N=8)		Santa Rosa (N=14)		Monterey (N=11)		Central Valley (N=9)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Male sex	43	(52.4)	21	(52.5)	5	(62.5)	5	(35.7)	7	(63.6)	5	(55.6)
Race												
Asian	2	(2.4)	1	(2.5)	1	(12.5)	0	-	0	-	0	-
Native Hawaiian or Pacific Islander	1	(1.2)	0	-	1	(12.5)	0	-	0	-	0	-
White	71	(86.6)	35	(87.5)	5	(62.5)	13	(92.9)	9	(81.8)	9	(100.0)
Other	4	(4.9)	2	(5.0)	0	-	1	(7.1)	1	(9.1)	0	-
Multiple	1	(1.2)	0		1	(12.5)	0		0	-	0	-
Ethnicity												
Hispanic or Latino	9	(11.0)	4	(10.0)	0	-	2	(14.3)	1	(9.1)	2	(22.2)
Not Hispanic or Latino	68	(82.9)	33	(82.5)	8	(100.0)	12	(85.7)	8	(72.7)	7	(77.8)
ADI (State decile) Median, (IQR)	3.5	(2, 7)	2	(1, 4)	2.5	(1.5, 5)	4.5	(3, 8)	3	(2, 5)	9	(8, 9)
Age at symptom onset, mean (SD)	61	(11.4)	61	(10.5)	63	(14.0)	65	(13.2)	65	(9.9)	53	(8.4)
Time from symptoms to diagnosis	21	(16.1)	20	(14.6)	14	(10.9)	21	(12.1)	20	(18)	29	(25.9)
Visit cadence (months), median (IQR)	2.2	(1.7, 3.0)	1.9	(1.6, 2.5)	1.8	(1.2, 2.8)	2.9	(2, 3.9)	2.4	(1.8, 3.0)	2.7	(1.0, 2.8)
% Video visits, median (IQR)	55	(22.6, 76.0)	55	(22.6, 76.0)	100	-	40	(25, 53.3)	60	(50, 66.7)	40	(38.5, 83.3)
Body region first affected												
Bulbar	16	(19.5)	9	(22.5)	3	(37.5)	1	(7.1)	2	(18.2)	1	(11.1)
Trunk	3	(3.7)	0	-	0	-	1	(7.1)	2	(18.2)	0	-
Respiratory	2	(2.4)	2	(5.0)	0	-	0	-	0	-	0	-
UE	25	(30.5)	12	(30.0)	2	(25.0)	3	(21.4)	2	(18.2)	6	(66.7)
LE	35	(42.7)	16	(40.0)	3	(37.5)	9	(64.3)	5	(45.5)	2	(22.2)
FTD	1	(1.2)	1	(2.5)	0	-	0	-	0	-	0	-
Family history of FTD/ALS												
Yes	8*	(9.8)	1	(2.5)	1	(12.5)	4	(28.6)	1	(9.1)	1	(11.1)
No	73	(89.0)	39	(97.5)	7	(87.5)	10	(71.4)	9	(81.8)	8	(88.9)

Table. Demographics and clinical characteristics of the patient cohorts. ADI: Area Deprivation Index; IQR: inter-quartile range; SD: standard deviation; VUS: variant of unknown significance; UE: upper extremities; LE: lower extremities; FTD: frontotemporal dementia. *Of the 8 patients with a family history of FTD/ALS, 5 were positive for C9ORF72 mutations, 1 had a VCP mutation, and 2 were tested without a genetic mutation found. Five additional patients had genetic mutations without a family history of FTD/ALS (1 with TDP-43, 1 with SQSTM1, 1 with VUS in NEK1, 1 with a variant of HEXA, and 1 with a variant of NEFH).

Figure (Right). Time-to-event analysis using Kaplan-Meier plots representing time in months from symptom onset to significant clinical milestones in the five patient cohorts (UCSF, Video Only, Santa Rosa, Monterey, and Central Valley). **A)** Time to loss of ambulation, **B)** Time to loss of speech, **C)** Time to Gastrostomy placement, **D)** Time to Tracheostomy, **E)** Time to first use of non-invasive ventilation (NIV), and **F)** Time to death. Three patients were excluded from the analysis of time to death as they opted to partake in physician-aid-in-dying.

Discussion

In a preliminary analysis of this ongoing study, we see small trends toward younger age at symptom onset in the Central Valley cohort, and more frequent clinic visits in the UCSF and Video Only cohorts, possibly suggesting differences in both disease presentation and healthcare access between cohorts. Our pilot study is limited by the small sample, the inability to directly test environmental factors including pollution and toxic exposures, limited chart review data on level of education and genetic testing (only 43% of our cohort underwent genetic testing), and under-representation of non-white races.

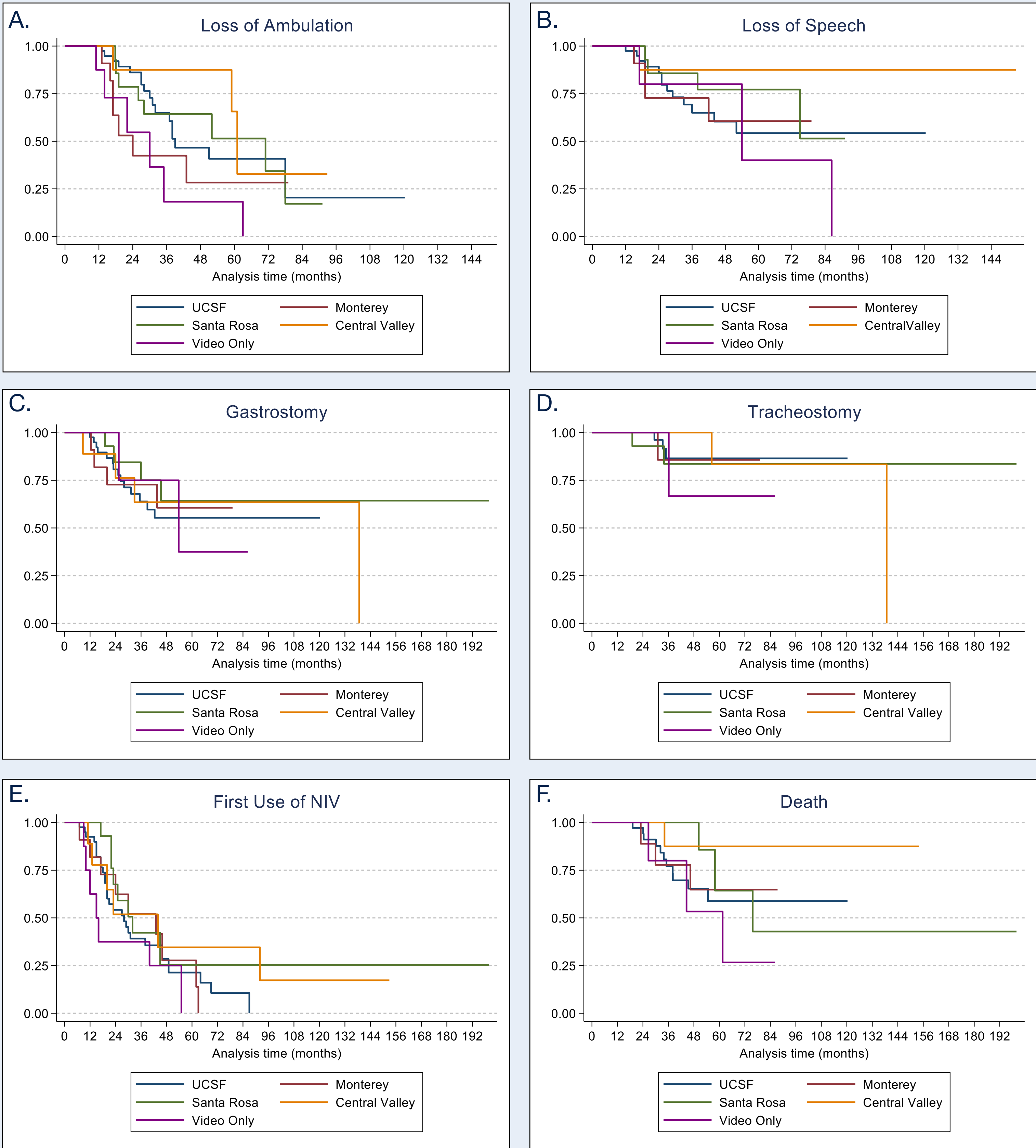
It remains unknown whether there are geographical and SES effects on the natural history of disease progression of ALS. Time to major clinical milestones was reported by a large Australian cohort study, but in the United States, this data has traditionally been reported in cohorts from relatively short duration clinical trials or single tertiary care centers. These cohorts may be skewed towards more advanced disease, higher SES or level of education, and patient residence within close proximity to a large city. We anticipate that there will be geographic or SES effects on the progression of ALS in our cohorts, which may inform future resource allocation and improve access to care and patient representation within future clinical trials for this uniformly fatal neurodegenerative disease.

Methods, continued

All research participants provided informed consent for enrollment into the Muscular Dystrophy Association (MDA) neuromuscular ObserVational Research (MOVR) Data Hub, a multi-center standardized national data hub of patients with neuromuscular disease. Enrollment is actively ongoing with 82 patients enrolled by November 19, 2023. All patients seen at the satellite clinics between July and November 2023 were offered enrollment.

Area Deprivation Index:
Using the Area Deprivation Index mapping tool by the University of Wisconsin School of Medicine and Public Health, patients’ neighborhoods (defined by US Census block group) were ranked by socioeconomic disadvantage, stratified by deciles within the state of California. The Area Deprivation Index tool factors various domains including education, income, employment, and quality of housing at the neighborhood level. Although SES is on average higher in San Francisco, there is sufficient range of SES represented in all 3 clinics to allow for an examination of independent effects of geography and SES in the full data set.

Time-to-event analysis was performed with Kaplan-Meier plots from symptom onset to event date or censor date (last date of clinical evaluation at which point the event had not occurred for that patient) for each primary outcome.



Future Directions

As we continue the project, and in planning future studies, we will continue to grow the cohort to strengthen our power to draw conclusions. Additionally, we intend to investigate the differential effects of geography and socioeconomic status, by comparing progression through disease milestones in the highest and lowest SES levels. Our satellite ALS clinics help improve patient access to healthcare and specialty neurological care. This project, by highlighting healthcare disparities in under-resourced areas of California, may lead to better allocation of resources to communities in need. In addition, our video-only cohort could influence the healthcare team’s decision to prioritize in-person vs. telehealth exams.

References

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