Racial differences in intervention rates in individuals with ALS

A case-control study

Saman Qadri, MS, Carl D. Langefeld, PhD, Carol Milligan, PhD, James B. Caress, MD, and Michael S. Cartwright, MD, MS

Neurology® 2019;92:e1969-e1974. doi:10.1212/WNL.0000000000007366

Correspondence

Dr. Cartwright
mcartwri@wakehealth.edu

Abstract

Objective

This study was conducted to determine whether longer lifespans in African Americans with amyotrophic lateral sclerosis (ALS), compared to white non-Hispanics, are secondary to higher rates of tracheostomy and invasive ventilation (TIV) in African Americans.

Methods

A retrospective case-control study was conducted with 49 African Americans with ALS matched by age, gender, and site of onset to 137 white persons with ALS.

Results

African Americans had longer survival than whites when the outcome was death ($p = 0.016$), but this was no longer significant when the outcome was death or TIV ($p = 0.100$). African Americans also had a lower rate of noninvasive ventilation use compared to whites (27 [55%] vs 96 [70%], $p = 0.015$) and a higher rate of TIV (8 [16%] vs 7 [5%], $p = 0.016$), but after controlling for baseline severity, only the noninvasive ventilation difference ($p = 0.036$), and not the TIV difference ($p = 0.115$), remained significant.

Conclusion

African Americans with ALS live longer than white persons with ALS, and this may be secondary to higher rates of TIV use among African Americans.

RELATED ARTICLE

Editorial

Intrinsic race differences in ALS survival in a US clinic population independent of ventilation

Page 781

MORE ONLINE

CME Course

[NPub.org/cmelist](https://www.npub.org/cmelist)

From the Department of Neurosciences, Health Disparities in Neuroscience-related Disorders Program (S.Q., C.M.), and Departments of Biostatistics and Data Science (C.D.L.) and Neurology (J.B.C., M.S.C.), Wake Forest School of Medicine, Winston-Salem, NC.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ALS = amyotrophic lateral sclerosis; **ALSFRS-R** = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; **FVC** = forced vital capacity; **NIV** = noninvasive ventilation; **PEG** = percutaneous enteral gastrostomy; **TIV** = tracheostomy and invasive ventilation.

NPub.org/929901

doi: 10.1212/WNL.0000000000007366

Copyright © 2019 American Academy of Neurology

Neurology®

Amyotrophic lateral sclerosis (ALS) can affect individuals of any race or ethnicity, but in the United States, it is more common in white non-Hispanics than in African Americans and other races/ethnicities.^{1,2} Previous studies suggest that African Americans with ALS live longer than white persons with ALS, but the reason for this difference is unknown.^{1,3} We hypothesized that African Americans with ALS may have a higher rate of tracheostomy and invasive ventilation (TIV) than whites, which may contribute to their longer survival time. To explore this hypothesis, we completed a retrospective case-control study to examine differences in rates of several interventions based on self-identified race.

Methods

Approval was obtained from the Wake Forest School of Medicine institutional review board prior to initiation of this study.

Patient sample and data collection

Individuals newly diagnosed with “possible,” “probable (including laboratory supported),” and “definite” ALS

based on El Escorial criteria and enrolled in the Wake Forest ALS Center from 2012 to 2016 were assessed through review of the electronic medical record.⁴ Those with primary muscular atrophy and primary lateral sclerosis were excluded. Forty-nine African Americans were identified over this time period and matched in a 1:3 manner with white non-Hispanics based on gender, age at diagnosis (± 4 years), and site of onset (bulbar, upper limb, or lower limb). For 10 African Americans, only a 1:2 match was possible based on the matching criteria, which resulted in a total of 137 matched whites. Age at diagnosis, body mass index, site of onset, and time to diagnosis (time from symptom onset to diagnosis in the ALS Clinic) were recorded for each individual. Baseline severity variables, including the revised ALS Functional Rating Scale (ALSFRS-R) and forced vital capacity (FVC) percent-predicted, were also collected from the first ALS Clinic visit. Individuals whose FVC was too low to be detected were assigned an FVC of 10%, as this was the lowest measured FVC in patients in this dataset. The rate of disease progression prior to entering the ALS Clinic was calculated by subtracting 48 (the maximum ALSFRS-R score) from the ALSFRS-R at the time of diagnosis, and

Table 1 Patient demographics

	White (n = 137)	African American (n = 49)	p Value
Gender, female, n (%)	66 (48)	24 (49)	0.923
Age at diagnosis, y	63.44 (29–83) [11.27]	62.24 (27–81) [13.08]	0.540
BMI, kg/m²	27.30 (16.82–41.72) [5.44]	27.16 (15.82–40.92) [6.34]	0.938
Site of onset, n (%)			0.970
Upper limb	56 (41)	21 (43)	
Lower limb	43 (31)	15 (31)	
Bulbar	38 (28)	13 (27)	
Time to diagnosis, mo	12.41 (0–50) [8.58]	15.24 (4–82) [13.57]	0.177
ALSFRS-R score	38.89 (19–48) [5.49]	36.57 (9–46) [8.39]	0.112; 0.282 ^a
FVC, %	71.37 (12–141) [25.23]	65.27 (10–129) [32.37]	0.237; 0.111 ^a

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI = body mass index; FVC = forced vital capacity. The data represent mean (range) [SD] or n (%).

^a The *p* values are based on linear regression adjusting for gender, site of onset, and age at diagnosis.

dividing this by the time to diagnosis, to obtain a disease “preslope.” Each chart was reviewed from enrollment in the clinic until either death or January 2018 to determine whether each individual started riluzole, underwent percutaneous enteral gastrostomy (PEG) placement, tried noninvasive ventilation (NIV), or had a tracheostomy and invasive ventilation (TIV). Finally, each individual was assigned to 1 of 8 possible intervention “sequences,” defined by the specific combination of NIV use, TIV use, and death (yes/no to each of these 3 categories).

Statistical analyses

All variables were examined and transformed as necessary to meet the respective statistical assumptions of the tests. Baseline demographics were compared between the groups with either *t* tests or χ^2 tests, and the ALSFRS-R and FVC were tested using linear regression after controlling for gender, site of onset, and age at diagnosis.

Survival was assessed from the time of disease onset to “death” or “death or TIV” using Kaplan-Meier survival curves and Cox proportional hazards models and controlling for gender, site of onset, age at diagnosis, ALSFRS-R, and FVC. To evaluate intervention rates, percentages were calculated for use of riluzole, PEG, NIV, and TIV. Conditional logistic regression models were fit, explicitly accounting for the matching, where stratum was the matched set for intervention rates. Further analyses also controlled for baseline severity using ALSFRS-R and FVC at

diagnosis. Ad hoc analyses explored the contribution of disease “preslope” in the analyses described above.

Conditional logistic regression analyses under a proportional hazards model, where the matched sets were stratum, were used to assess the frequency of the 8 different event sequences to determine whether they varied from the expected values.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

Baseline variables are listed in table 1, and there were no significant differences between the groups. African Americans had slightly longer time to diagnosis, lower ALSFRS-R scores, and lower FVC, but none of these differences reached statistical significance, even after controlling for gender, site of onset, and age at diagnosis.

Cox proportional hazards models showed the African American cohort lived longer than the white cohort (hazard ratio = 1.82, *p* = 0.016) when the outcome was “death” (figure). When the preslope variable was included in this model, the hazard ratio for the African American cohort living longer did not reach statistical significance (hazard ratio 1.64, *p* = 0.056). This difference appears to be driven by the African American quartile that lived the longest. The 75th percentile for survival was 53 months in African Americans and 40 months in whites, and an ad hoc analysis using only individuals with >30 months of survival was significant (*p* = 0.022), even when the preslope variable was included. When this same modeling was computed using “death or TIV” as the outcome, there was no significant difference in survival between the groups (*p* = 0.100).

Rates of the interventions are reported in table 2. Riluzole use did not differ between the 2 groups. PEG placement was not significantly different, though 51 (37%) white persons had a PEG placed compared to 13 (27%) African Americans, which approached statistical significance after controlling for gender, site of onset, age at diagnosis, ALSFRS-R, and FVC (*p* = 0.058). NIV use was higher in whites (96 [70%]) than in African Americans (27 [55%]) in both models (*p* = 0.025 and 0.036). TIV was lower in whites (7 [5%]) than in African Americans (8 [16%]) and this was significant in the first model (*p* = 0.026) but lost significance once ALSFRS-R and FVC were included in the model (*p* = 0.139). Inclusion of the preslope variable did not alter the significance of any of these results.

Matched analyses found an association between sequence and race (*p* = 0.005) (table 3). The greatest magnitude of difference is for sequences 7 (no NIV, had TIV, did not die) and 6 (had NIV, had TIV, and then died). The greatest absolute difference is for sequence 4 (had NIV, did not have TIV, and then died).

Figure Kaplan-Meier survival curve and quartile survival estimates from Cox proportional hazards model by self-identified race

Survival percentile	White (n = 137) Survival (months, 95% CI)	African American (n = 49) Survival (months, 95% CI)
75th (longest-surviving quartile)	40.0 (34-47)	53.0 (29-84)
50th (median survival)	27.5 (25-30)	25.0 (21-45)
25th (shortest-surviving quartile)	18.5 (15-22)	21 (14-22)

CI = confidence interval.

Discussion

This study tested whether there were racial differences in the rates of specific interventions for ALS through a matched case-control study. Similar to previous studies, the African American cohort lived longer than the white cohort when “death” was the outcome, but this survival difference was not present when “death or TIV” was the outcome.^{1,3} This is the first indication from our data that TIV may be driving longer survival in African Americans with ALS. The second indication is that African Americans had a TIV rate that was more than 3 times the rate in whites (8 [16%] vs 7 [5%]). Although no longer significant when controlling for baseline ALSFRS-R and FVC, these findings raise the possibility that African Americans have higher TIV rates than whites and this difference is, at least in part, responsible for the longer survival in African Americans. Previous studies of survival in African Americans with ALS did not investigate TIV use and only used death as the outcome.¹⁻³ Finally, the sequence of interventions and events was statistically different between African Americans and whites, with the greatest magnitude of difference

demonstrating that African Americans were 6 times more likely (6% vs 1%) to have a sequence of events that involved “not using NIV, using TIV, and not dying” by the end of the study.

Table 2 Rates of intervention

	White (n = 137)	African American (n = 49)	p Value ^a	p Value ^b
Riluzole	104 (76)	33 (67)	0.152	0.639
PEG	51 (37)	13 (27)	0.121	0.058
NIV	96 (70)	27 (55)	0.025	0.036
TIV	7 (5)	8 (16)	0.026	0.139

Abbreviations: NIV = noninvasive ventilation; PEG = percutaneous endoscopic gastrostomy; TIV = tracheostomy with invasive ventilation. Data represent n (%).

^a The p values are based on 1:M matched analyses using Cox proportional hazards model with stratum being the matched sets.

^b The p values are based on 1:M matched analysis using Cox proportional hazards model with stratum being the matched sets and adjusting for gender, site of onset, age at diagnosis, and baseline severity via Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised and forced vital capacity at time of diagnosis.

Table 3 Sequences of interventions

Sequence no.	NIV	TIV	Death	White (n = 137)	African American (n = 49)	Total (n = 186)
1	No	No	No	11 (8)	8 (16)	19 (10)
2	No	No	Yes	27 (20)	11 (22)	38 (20)
3	Yes	No	No	11 (8)	8 (16)	19 (10)
4	Yes	No	Yes	81 (59)	14 (29)	95 (51)
5	Yes	Yes	No	1 (1)	0 (0)	1 (1)
6	Yes	Yes	Yes	3 (2)	4 (8)	7 (4)
7	No	Yes	No	2 (1)	3 (6)	5 (3)
8	No	Yes	Yes	1 (1)	1 (2)	2 (1)

Abbreviations: NIV = noninvasive ventilation; TIV = tracheostomy with invasive ventilation.

Data represent n (%). Conditional logistic regression analyses, under a proportional hazards model where the matched sets were stratum, found a significant association between disease sequence and race ($p = 0.005$). The greatest absolute value difference is for sequence 4 (30% difference), and the greatest magnitude of difference is for sequence 7 (6 times) and sequence 6 (4 times).

The rate of NIV use was higher in whites than African Americans, and this remained significant when controlling for all other variables. It is therefore possible that African Americans could encounter respiratory crisis more often than whites (because they less often have NIV available), which could ultimately result in higher rates of TIV as an emergent intervention for respiratory crisis.

The reason for the different rates of interventions for ALS between these 2 groups is unknown. It is unlikely this difference is related to differing disease pathophysiology or symptoms, as the onset site and other baseline variables were well-balanced between the 2 groups. One possible driver of different intervention rates may be medical mistrust in the African American cohort. This has been demonstrated in other conditions, and could lead to a lower use of earlier interventions (PEG and NIV), which then results in a higher need for later interventions (TIV).^{5,6} Of note, the Wake Forest ALS Center is multidisciplinary, with 10 different medical professionals, but none of the current care team members are African American. One intervention that could be considered to address the differences detected in this study is to incorporate care team members of similar race/ethnicity to the patient population.⁷

This study does have limitations. Perhaps the largest limitation is that all patients received care at a single site, so the results may not be generalizable to other clinics and regions. Another limitation is that the sample size is only moderate, with 186 total participants.

Formal, well-designed efforts to replicate these results and further explore these questions are needed. In addition to multicenter studies and larger sample sizes, investigations into other potential drivers of the difference in intervention rates, such as socioeconomic status and caregiver presence, are critical. Focus groups and ethicists can contribute to this discussion. In addition, investigation into the rates of other interventions, such as edaravone use, would be informative.

Author contributions

Ms. Qadri participated in study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Langefeld participated in analysis and interpretation of data and critical revision of the manuscript for important intellectual content. Dr. Milligan participated in analysis and interpretation of data and critical revision of the manuscript for important intellectual content. Dr. Caress participated in analysis and interpretation of data and critical revision of the manuscript for important intellectual content. Dr. Cartwright participated in study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.

Study funding

No targeted funding reported.

Disclosure

S. Qadri was a student supported by NIH grant 5R25NS089458. C. Langefeld reports no disclosures relevant to the manuscript. C. Milligan was the co-principal investigator of the grant. J. Caress and M. Cartwright report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* August 23, 2018. Accepted in final form January 2, 2019.

References

1. Roberts AL, Johnson NJ, Chen JT, Cudkowicz ME, Weisskopf MG. Race/ethnicity, socioeconomic status, and ALS mortality in the United States. *Neurology* 2016;87:2300–2308.
2. Zaldivar T, Gutierrez J, Lara G, Carbonara M, Logroscino G, Hardiman O. Reduced frequency of ALS in an ethnically mixed population: a population-based mortality study. *Neurology* 2009;72:1640–1645.

3. Jordan H, Fagliano J, Rechtman L, Lefkowitz D, Kaye W. Effects of demographic factors on survival time after a diagnosis of amyotrophic lateral sclerosis. *Neuroepidemiology* 2015;44:114–120.
4. Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Motor Neuron Disord* 2000;1:293–299.
5. Smirnoff M, Wilets I, Ragin DF, et al. A paradigm for understanding trust and mistrust in medical research: the Community VOICES study. *AJOB Empir Bioeth* 2018;9:39–47.
6. Glover LM, Sims M, Winters K. Perceived discrimination and reported trust and satisfaction with providers in African Americans: the Jackson Heart Study. *Ethn Dis* 2017;27:209–216.
7. Traylor AH, Schmittiel JA, Uratsu CS, Mangione CM, Subramanian U. The predictors of patient-physician race and ethnic concordance: a medical facility fixed-effects approach. *Health Serv Res* 2010;45:792–805.