ALS is a multistep process in South Korean, Japanese, and Australian patients

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Study objective and summary result
This study tested the hypothesis that the development of amyotrophic lateral sclerosis (ALS) involves more steps in patients of East Asian ancestry than it does in patients of European ancestry, but the results suggested that processes with similar step numbers were at work in both patients of East Asian ancestry and those of European ancestry.

What is known and what this paper adds
The incidence of ALS is highest in ethnically European populations and lowest in ethnically Southeast Asian populations, and some scholars have suggested that the development of ALS may require more steps in Asian populations. This investigation’s results provide evidence against that explanation.

Participants and setting
The investigators analyzed data from 3 groups of patients with ALS: 6,524 Australian patients, 2,264 Japanese patients, and 3,049 South Korean patients. The investigators obtained these data through the Pan-Asian Consortium for Treatment and Research in ALS. Data collection occurred between 2007 and 2016 for the Australian patients, between 2009 and 2010 for the Japanese patients, and between 2011 and 2015 for the South Korean patients.

Design, size, and duration
The investigators quantified the steps for ALS development in each population by using the Armitage and Doll method, which involves a least-squares regression of logarithmic age-specific incidence data against logarithmic age data. The slope estimates derived from this method represent the number of steps minus 1.

Primary outcome measures
The primary outcomes were the population-specific slope estimates obtained from the Armitage and Doll analyses.

Main results and the role of chance
The slope estimates were 5.4 (95% confidence interval, 4.8–5.5) in the Japanese patients, 5.4 (95% confidence interval, 5.2–5.7) in the Australian patients, and 4.4 (95% confidence interval, 4.2–4.8) in the South Korean patients.

Bias, confounding, and other reasons for caution
The definitions of ALS used in Japan, South Korea, and Australia may differ in subtle ways.

Generalizability to other populations
The present study’s focus on patients of European or East Asian racial backgrounds may limit the generalizability of the results to other racial groups.

Study funding/potential competing interests
This study was funded by the Motor Neuron Disease Research Institute of Australia and the Australian and Korean governments. Professor Vucic and Professor Kiernan serve as editors for the Journal of Neurology, Neurosurgery, and Psychiatry. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.
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Editors’ Note: Cause of Death in Spontaneous Intracerebral Hemorrhage Survivors: Multistate Longitudinal Study

Using administrative claims data from 3 US states, Dr. Kuohn et al. report the long-term mortality rate of survivors with spontaneous intracerebral hemorrhage (ICH). Using an original population of 104,000 patients who were screened for eligibility, 72,432 survivors of the index hospitalization were followed for a median of 4 years. The 1-year risk of death or discharge to hospice was 9.5% (95% CI 9.2%–9.7%), with the most common proximate causes of death being infection (34%) or subsequent intracranial hemorrhage (13%). The median time from ICH to death was 10 months (IQR 2–31 months). Dr. Llamas-Nieves and colleagues highlight the importance of confounders such as diabetes, which was independently associated with death as shown in the multivariable regression model (HR 1.22, 95% CI 1.17–1.27), as this may be an important mediator of death because of infectious causes. The investigators acknowledge that diabetes contributes to death in the overall population; however, it was not independently associated with death due to infection (OR 1.16, 95% CI 0.86–1.55). The authors posit that diabetes (as well as age, post-ICH disability, and other comorbidities) are important contributors to the development of later infection, but it remains unclear why diabetes is not an independent modifier of death risk among patients who develop infection.

James E. Siegler, MD, and Steven Galetta, MD
Neurology® 2021;97:148. doi:10.1212/WNL.0000000000012281

Reader Response: Cause of Death in Spontaneous Intracerebral Hemorrhage Survivors: Multistate Longitudinal Study

Andrés E. Llamas-Nieves (Cartagena, Colombia), Ivan D. Lozada-Martinez (Cartagena, Colombia), Daniela M. Torres-Llinás (Cartagena, Colombia), and Luis R. Moscote-Salazar (Cartagena, Colombia)
Neurology® 2021;97:148–149. doi:10.1212/WNL.000000000012282

We read with great interest the recent article by Kuohn et al.¹ The authors conducted a comprehensive review on the factors associated with mortality in patients who survived spontaneous intracerebral hemorrhage, where they showed that the infection was the main cause of death in such a group with a value of 34%. However, they do not emphasize other comorbidities that could have influenced the morbidity and mortality of patients in the infection group, such as diabetes. Diabetes is a disease that increases susceptibility to infections such as those involving the skin, urinary tract, or lungs.² Lau et al. performed a systematic review and meta-analysis, where they found that isolated diabetes is strongly associated with poor prognosis after stroke, including increased morbidity, mortality, and disability.³ For this reason, it is very important to know the factors that underlie and really impact on the subject of study, to obtain certainty in the
results of the research, and to avoid underestimations as what likely happened in the study of Kuohn et al. We suggest separate future study groups to avoid this type of bias during data analysis.

1. Kuohn LR, Leasure AC, Acosta JN, et al. Cause of death in spontaneous intracerebral hemorrhage survivors: multistate longitudinal study. Neurology. 2020;95(20):e2736-e2745.
2. Pannu AK, Saroch A, Singla V, et al. Clinical spectrum, etiology and outcome of infectious disease emergencies in adult diabetic patients in northern India. Diabetes Metab Syndr. 2020;14(5):921-925.
3. Lau L-H, Lew J, Borschmann K, Thiù V, Ellinci E. Prevalence of diabetes and its effects on stroke outcomes: a meta-analysis and literature review. J Diabetes Invest. 2019;10(3):780-792.

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Author Response: Cause of Death in Spontaneous Intracerebral Hemorrhage Survivors: Multistate Longitudinal Study

Lindsey Kuohn (New York) and Kevin Sheth (New Haven, CT)

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We thank Dr. Llamas-Nieves et al. for their interest in our article1 and recognize that coexisting diabetes, among other comorbidities, may influence infection-related mortality in ICH survivors. We hypothesized that the high proportion of deaths caused by infections may be due to the burden of disability in this population. Intracerebral hemorrhage (ICH) survivors often require chronic hospitalization and are prone to infections such as Clostridium difficile, urinary tract infections, and aspiration pneumonia. Our finding that older age was an independent risk factor for death caused by infection supports this hypothesis. However, we agree that increased susceptibility to infection in patients with diabetes should be considered as a potential driver of infection-related deaths in patients with ICH.2 Diabetes was included as a covariate in the adjusted multinomial logistic regression model of causes of death during follow-up in our study (table 3). Diabetes was not associated with increased odds of death caused by infection (odds ratio 1.16, 95% confidence interval 0.86–1.55), although diabetes did correlate with increased risk for death overall (hazard ratio 1.22, 95% confidence interval 1.17–1.27). The cause of elevated mortality after ICH in patients with diabetes is not clear, and our results are not conclusive regarding the potential association with infection. As Dr. Llama-Nieves et al. point out, future studies of the specific causes of infection-related morbidity and mortality are warranted and necessary to improve long-term outcomes after ICH.

1. Kuohn LR, Leasure AC, Acosta JN, et al. Cause of death in spontaneous intracerebral hemorrhage survivors: multistate longitudinal study. Neurology. 2020;95(20):e2736-e2745.
2. Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. Diabetes Metab. 1992;18(3):187-201.

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Author disclosures are available upon request (journal@neurology.org).
Reader Response: Sex, Race, and Risk of Dementia Diagnosis After Traumatic Brain Injury Among Older Veterans

Jomar S. Roberts I (Matthews, NC)

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I read the article by Kornblith et al. with interest. It seems this “trend” in diagnostic bias is not exclusive to veterans alone. As this article is being published, Black NFL and former NFL athletes are involved in litigation regarding the discrepancy in qualifying postconcussion dementia diagnoses applied to White athletes vs Black. White athletes are diagnosed with postconcussion “dementia” and receive greater compensation for this disability. More importantly, Dr. Roberts emphasizes that this racial discrepancy in dementia diagnoses is not likely an indicator of differential disease burden between races but is more reflective of racial care inequality. Dr. Kornblith agrees that racial disparities in health care are ubiquitous and demand more than just our attention. They demand action.

In my experience as a veteran TBI neurologist, observing this bias is commonplace and not limited to concussion or any particular disease. The health care system is riddled with bias from the provider level on down. It manifests openly in less care being given to Black patients, less concern being given to their disease, and less resources allocated to deep diving into their illnesses. This is not a secret to Black neurologists or providers in any field and is openly discussed and hard fought against, daily.

To be perfectly honest, these authors are speaking softly about an issue that needs to be addressed much more openly. Racial bias in health care provision starts at the individual provider level. We need to further examine how providers’ backgrounds affect their patterns of diagnosis, test ordering, and prescribing patterns. This should be prominently displayed in some metric for all patients to use when choosing a provider, a “bias report card” so to speak. Only with full transparency will patients be given the assurance their doctor/provider is giving full, ethically unbiased care to all.

1. Kornblith E, Peltz CB, Xia F, et al. Sex, race, and risk of dementia diagnosis after traumatic brain injury among older veterans. Neurology. 2020;95(13):e1768-e1775.

2. Raslovsky I, Beaton A. Lawsuit alleges NFL’s concussion settlement discriminates against black players. In: The Wall Street Journal. Available at: wsj.com/articles/lawsuit-alleges-nfls-concussion-settlement-discriminates-against-black-players-11598371843.

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Author Response: Sex, Race, and Risk of Dementia Diagnosis After Traumatic Brain Injury Among Older Veterans

Erica S. Kornblith (San Francisco)

Thank you for the thoughtful comment on our article, Dr. Roberts. We agree that racial bias in health care is pervasive and must be addressed. We hope that our work draws attention to this issue and highlights the need for research aimed at identifying and mitigating disparities.

1. Kornblith E, Peltz CB, Xia F, et al. Sex, race, and risk of dementia diagnosis after traumatic brain injury among older veterans. Neurology. 2020;95(13):e1768-e1775.

CORRECTIONS

Thrombolysis in Acute Ischemic Stroke in Patients With Dementia
A Swedish Registry Study

In the article “Thrombolysis in Acute Ischemic Stroke in Patients With Dementia: A Swedish Registry Study” by Zupanic et al., the affiliations for Drs. Zupanic and Kramberger should include “Faculty of Medicine, University of Ljubljana, Slovenia.” The authors regret the error.

Reference
1. Zupanic E, von Euler M, Kåreholt I, et al. Thrombolysis in acute ischemic stroke in patients with dementia: a Swedish registry study. Neurology. 2017;89(18):1860-1868.

ALS is a Multistep Process in South Korean, Japanese, and Australian Patients

In the infographic corresponding with the article “ALS is a Multistep Process in South Korean, Japanese, and Australian Patients” by Vucic et al., the labels for the pictures of South Korea and Japan should be switched so that South Korea reads as a 5-step process and Japan reads as a 6-step process. The editorial team regrets the error.

Reference
1. Vucic S, Higashihara M, Sobue G, et al. ALS is a multistep process in South Korean, Japanese, and Australian patients. Neurology. 2020;94(15):e1657-e1663.