

Assessment of the interaction of age and sex on 90-day outcome after intracerebral hemorrhage

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ABSTRACT

Objective: Because age affects hormonal production differently in women compared with men, we sought to define sex and age interactions across a multiracial/ethnic population after intracerebral hemorrhage (ICH) to uncover evidence that loss of gonadal hormone production would result in loss of the known neuroprotective effects of gonadal hormones.

Methods: Clinical and radiographic data from participants in the Ethnic/Racial Variations of Intracerebral Hemorrhage study and the Genetic and Environmental Risk Factors for Hemorrhagic Stroke study prior to December 2013 were used. Relationships among sex, age, and outcome after ICH in 616 non-Hispanic black, 590 Hispanic, and 868 non-Hispanic white participants were evaluated using multivariable logistic regression analysis. Poor outcome was defined as modified Rankin Scale score ≥ 3 at 90 days after ICH.

Results: Sex differences were found in multiple variables among the racial/ethnic groups, including age at onset, premorbid neurologic status, and neurologic outcome after ICH. Overall, no sex-age interaction effect was found for mortality ($p = 0.183$) or modified Rankin Scale score ($p = 0.378$) at 90 days after ICH. In racial/ethnic subgroups, only the non-Hispanic black cohort provided possible evidence of a sex-age interaction on 90-day modified Rankin Scale score ($p = 0.003$).

Conclusion: Unlike in ischemic stroke, there was no evidence that patient sex modified the effect of age on 90-day outcomes after ICH in a large multiracial/ethnic population. Future studies should evaluate biological reasons for these differences between stroke subtypes.

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GLOSSARY

BMI = body mass index; **ERICH** = Ethnic/Racial Variations of Intracerebral Hemorrhage; **GCS** = Glasgow Coma Scale; **GERFHS** = Genetic and Environmental Risk Factors for Hemorrhagic Stroke; **ICH** = intracerebral hemorrhage; **IVH** = intraventricular hemorrhage; **mRS** = modified Rankin Scale.

Intracerebral hemorrhage (ICH) results in a greater degree of morbidity, mortality, and loss of quality of life than other forms of stroke.¹ ICH remains without any proven therapeutic intervention, as evidenced by several multicenter clinical trials. Successful development of therapeutic interventions may result from our evolving understanding of the role of sex in neurologic recovery.

Although a number of acute brain injuries have demonstrated sex differences in outcome,²⁻⁴ sex differences in ICH need to be more fully characterized. No studies have directly addressed sex differences in long-term outcome after ICH while controlling for covariates.⁵ However,

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female gonadal steroids demonstrate neuroprotective effects in ongoing preclinical work.⁶ In addition, age affects sexual dimorphism in the brain,^{7,8} and lack of gonadal hormones, such as that brought on by aging, significantly worsens recovery in preclinical models of ICH.^{9,10} Given these results, we sought to determine whether sex and age interact to affect outcome after ICH.

In the present study, sex differences in the effect of age on outcome after ICH were assessed in a multiethnic population with data from 2 multicenter studies: Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH)¹¹ and Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS).¹² Due to the loss of gonadal hormone effects in women after menopause, the specific hypothesis for the present study was that the risk of unfavorable outcome in women increases with age to a greater degree than in men, as occurs in ischemic stroke. Further, because the ERICH study allows evaluation in multiethnic populations, the influence of race/ethnicity on the potential age and sex interactions on outcome after ICH was examined as a secondary endpoint.

METHODS Standard protocol approvals, registrations, and patient consents. Institutional review boards at each participating institution approved both studies prior to initiation of study enrollment. Informed consent was obtained from each enrolled participant or legally authorized representative. A Spanish-language consent form was available for Spanish only-speaking participants or for those who preferred the Spanish consent. Prior to an interview, the patient's capacity to give consent was screened using a consent comprehension questionnaire. If the patient failed this screen, a legally authorized representative was contacted for enrollment with priority to guardian/power of attorney, spouse, adult children, parents, and siblings, in that order.

Study population. Methods for the ERICH¹¹ and GERFHS¹² studies have been described previously. Briefly, the ERICH study is a multicenter, prospective study of ICH designed to recruit 1,000 non-Hispanic white, 1,000 non-Hispanic black, and 1,000 Hispanic patients with spontaneous ICH. The GERFHS study is a prospective study of non-Hispanic white patients with ICH from 16 hospitals in the Greater Cincinnati/Northern Kentucky region. GERFHS and ERICH utilize similar clinical data and neuroimaging collection methods and ICH case ascertainment.

Patients diagnosed with first-ever, spontaneous ICH, who were over 18 years of age, resided within 50 miles of the recruiting center (within 100 miles for population centers fewer than 1 million) for at least 6 months prior to onset of ICH, and provided informed consent (by the patient or legally authorized representative) were eligible for the present study. Cases of ICH due to malignancies that led to coagulopathy, dural venous sinus

thrombosis-associated hemorrhage, vascular malformations, aneurysms, tumors, or hemorrhagic conversion of recent ischemic stroke were not eligible for the studies. To determine a patient's eligibility as a study case, study neurologists reviewed the patient's clinical presentation and neuroimaging.

Participant characteristics. As previously described,^{11,12} researchers interviewed enrolled participants or their proxies using a standardized form and used standardized chart abstraction for each case to provide additional clinical data, including discharge status and outcome. Each surviving participant was scheduled to be contacted at 90 days for evaluation of modified Rankin Scale (mRS).

From the data collected, items of interest for the present analysis were age, sex, race/ethnicity, body mass index (BMI), Glasgow Coma Scale (GCS) score on admission, mRS prior to stroke, history of alcohol, smoking, and illicit drug use, presence of coagulopathy, and history of hypertension, diabetes, and heart disease. Alcohol abuse was defined as self-report of more than 2 alcoholic drinks per day (on average), binge drinking (>5 drinks in a single setting) in the last 90 days, or history of alcohol abuse. Smoking history was classified as current, former, or never. Illicit drug use was defined as positive urine toxicology screen on admission or self-reported use. Presence of coagulopathy was defined as international normalized ratio greater than 1.5, partial thromboplastin time greater than 40 seconds, or platelet count less than 80,000/ μ L values on admission. History of heart disease was defined as history of any cardiac disease, including coronary artery disease, valvular disease, aberrant rhythms, or cardiomyopathy.

Imaging. All neuroimaging obtained from participants is stored on DICOM software, deidentified on site, and uploaded electronically to a dedicated workstation at the neuroimaging repository (Massachusetts General Hospital and University of Arizona-Tucson) using Alice software (Parexel Corporation, Waltham, MA) for centralized analyses by image reviewers blinded to all clinical information. The initial diagnostic CT images were used to measure hematoma volume, hematoma location, and presence of intraventricular hemorrhage (IVH). Hematoma volumes were measured by planimetric analysis as previously published.¹³⁻¹⁵ This method has high interrater reliability (0.99 test-retest intraclass and interobserver correlation coefficients in 2 independent readers evaluating 20 CT scans).¹³ Hematoma location was defined as deep (i.e., basal ganglia or thalamus), lobar, brainstem, cerebellum, or primary IVH.

Outcomes. The primary outcome was defined as unfavorable outcome, based on mRS ≥ 3 at 90 days after ICH onset. Secondary outcome was death within 90 days.

Statistical analysis. Descriptive statistics are presented as means, SD, and medians for continuous variables and as percentages for categorical variables. Patient characteristics are compared between men and women with Wilcoxon rank sum test for continuous (age, hematoma volume, BMI) and ordinal variables (GCS), and with χ^2 tests for categorical variables (alcohol abuse, smoking, illicit drug use, heart disease, hypertension, and diabetes).

To test for associations with outcome, univariate and multivariable logistic regression models were computed. Covariates were selected a priori based on known associations with outcome. For continuous predictors, the functional form (e.g., linear, quadratic) was tested. Initial analyses demonstrated a nonlinear distribution of hematoma volume and age; thus, all hematoma volumes were fit as the natural logarithm of volume plus 1, and age was modeled with both a linear and quadratic term; the

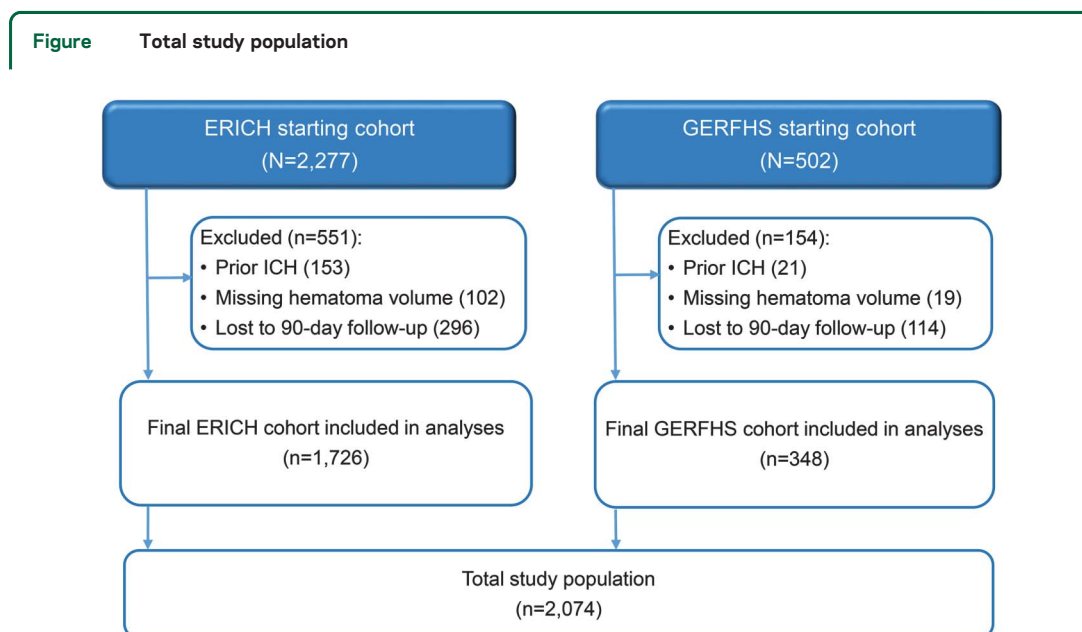
quadratic term was centered by the mean age of the sample. To test for a potential modifying effect of sex on age at ICH onset, the multivariable model adjusted for a priori covariates and modeled the age–sex interaction terms as centered cross products. Odds ratios for the effect of female sex were calculated at selected ages as examples to demonstrate the change in effect with increasing age. In addition, men and women from each racial/ethnic group were modeled in separate multivariable analyses, and the effect of age on outcome was assessed within each subgroup. Collinearity and influence diagnostics were examined.

RESULTS From July 2008 through January 2013, 502 participants from the GERFHS study, and from September 2010 through December 2013, 2,277 participants from the ERICH study were available for analysis. Due to participants with incomplete data (figure), final analyses were based on 2,074 participants (1,187 men and 887 women), which included 616 non-Hispanic black, 590 Hispanic, and 868 non-Hispanic white participants.

There were significant differences in study characteristics between men and women in the overall study population (table 1). On average, women were 5 years older than men, had higher premorbid mRS, and were less likely to smoke, abuse alcohol, or use illicit drugs. A higher proportion of women had lobar hemorrhages compared with men. Also, a higher proportion of women died within 90 days of onset, and surviving women had higher mRS than men, on average, at both discharge and 90 days. Finally, multiple differences were found across racial/ethnic groups, including age, pre-ICH mRS, history of alcohol abuse, smoking, and illicit drug use, and history of diabetes and heart disease.

Table 2 contains associations with 90-day outcome. Age, hematoma volume, premorbid and discharge mRS, coagulopathy, history of heart disease, and IVH were directly associated with mRS ≥ 3 at and mortality through 90 days after ICH. Male sex, admission GCS, and history of alcohol abuse or illicit drug use were inversely associated with mRS ≥ 3 at and mortality through 90 days after ICH. Stratifying by ethnic/racial background, associations were retained for age, hematoma volume, premorbid and discharge mRS, and presence of IVH in all 3 racial/ethnic groups.

Table 3 presents results of the multivariable logistic regression model for mRS ≥ 3 at and mortality through 90 days after ICH, including a test for sex-by-age interaction. In this model, age, admission GCS, initial hematoma volume, premorbid mRS, and presence of IVH retain significant independent associations in the overall study population. Similar logistic regression models were constructed for each racial/ethnic group. Interestingly, in these models, lobar location of ICH was significantly associated with mortality in Hispanic participants and unfavorable mRS (≥ 3) in the overall population, Hispanic participants, and white participants. However, there was no association between lobar location and outcomes in black participants. There was no evidence of a sex-by-age interaction effect in the individual ethnic-specific analyses or the joint analyses (table 3). While associations between multiple variables and outcome at 90 days were found in different race/ethnicities, admission GCS and hematoma volume were independently associated with higher



Total study population derived from Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) and Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) studies of patients with intracerebral hemorrhage (ICH) from July 2008 to December 2013.

Table 1 Study cohort demographic and descriptive statistics

	Overall			Non-Hispanic black			Hispanic			Non-Hispanic white			Meta, p value
	Men (n = 1,187)	Women (n = 887)	p Value	Men (n = 351)	Women (n = 265)	p Value	Men (n = 362)	Women (n = 228)	p Value	Men (n = 474)	(Women n = 394)	p Value	
Age, y, median	60.9 ± 14.0 (60.0)	66.1 ± 15.5 (66.0)	<0.001	55.3 ± 11.5 (55.0)	61.0 ± 14.0 (59.0)	<0.001	57.1 ± 13.7 (56.0)	61.2 ± 15.6 (59.5)	0.001	67.9 ± 12.9 (69.0)	72.4 ± 14.2 (74.0)	<0.001	<0.001
BMI, median	28.6 ± 6.7 (27.6)	29.2 ± 9.3 (27.4)	0.74	28.7 ± 6.6 (27.9)	31.2 ± 9.2 (29.6)	0.004	28.6 ± 6.3 (27.6)	29.0 ± 7.1 (27.9)	0.8	28.7 ± 7.0 (27.2)	28.0 ± 10.3 (25.8)	0.002	0.703
Admission GCS (IQR)	15 (11-15)	14 (10-15)	0.001	14 (10-15)	14 (9-15)	0.484	15 (11-15)	14 (8.5-15)	0.009	15 (13-15)	14 (11-15)	0.012	0.045
Initial ICH volume, mL, median	22.5 ± 28.7 (12.4)	21.9 ± 27.4 (11.3)	0.475	17.2 ± 22.1 (9.7)	20.1 ± 27.5 (10.3)	0.876	22.9 ± 27.9 (12.5)	21.5 ± 23.2 (13.1)	0.907	26.2 ± 32.7 (13.5)	23.3 ± 29.6 (11.8)	0.158	0.609
Pre-ICH mRS ≤2, %	1,119 (94.5)	761 (86.2)	<0.001	332 (94.6)	237 (89.4)	0.017	352 (97.2)	207 (90.8)	0.001	435 (92.4)	317 (81.3)	<0.001	<0.001
Alcohol abuse, %	362 (30.6)	103 (11.6)	<0.001	112 (32.3)	44 (16.7)	<0.001	134 (37.0)	21 (9.2)	<0.001	116 (24.5)	38 (9.6)	<0.001	<0.001
Smoking, %			<0.001			0.01			<0.001			<0.001	<0.001
Current	310 (27.6)	149 (17.9)		132 (40.1)	69 (28.1)		89 (26.0)	34 (15.7)		89 (19.6)	46 (12.4)		
Former	400 (35.6)	243 (29.2)		74 (22.5)	62 (25.2)		109 (31.9)	49 (22.7)		217 (47.9)	132 (35.6)		
Never	414 (36.8)	441 (52.9)		123 (37.4)	115 (46.7)		144 (42.1)	133 (61.6)		147 (32.5)	193 (52.0)		
Illicit drug use, %	224 (19.1)	102 (11.5)	<0.001	121 (35.0)	50 (19.0)	<0.001	66 (18.4)	30 (13.2)	0.092	37 (7.9)	22 (5.6)	0.187	0.007
Coagulopathy, %	302 (28.2)	224 (28.6)	0.841	61 (18.8)	68 (28.2)	0.009	89 (27.1)	55 (27.8)	0.873	152 (36.1)	101 (29.3)	0.046	0.053
Hypertension, %	1,009 (85.4)	737 (83.5)	0.238	316 (90.5)	244 (93.1)	0.253	297 (82.7)	181 (79.4)	0.31	396 (83.5)	312 (79.4)	0.116	0.190
Diabetes, %	374 (31.5)	242 (27.3)	0.036	97 (27.7)	79 (29.8)	0.569	119 (32.9)	76 (33.3)	0.908	158 (33.3)	87 (22.1)	<0.001	0.016
Heart disease, %	425 (35.8)	285 (32.2)	0.084	104 (29.6)	76 (28.7)	0.797	85 (23.5)	55 (24.2)	0.836	236 (49.8)	154 (39.1)	0.002	0.040
Location, %			0.001			0.560			0.066			0.106	0.157
Deep	690 (58.1)	451 (50.9)		222 (63.2)	157 (59.3)		230 (63.5)	130 (57.0)		238 (50.2)	164 (41.6)		
Lobar	303 (25.5)	298 (33.6)		71 (20.2)	66 (24.9)		70 (19.3)	64 (28.1)		162 (34.2)	168 (42.6)		
Brainstem	77 (6.5)	45 (5.1)		28 (8.0)	18 (6.8)		23 (6.4)	7 (3.1)		26 (5.5)	20 (5.1)		
Cerebellum	88 (7.4)	71 (8.0)		22 (6.3)	20 (7.6)		31 (8.6)	21 (9.2)		35 (7.4)	30 (7.6)		
Primary IVH	29 (2.4)	22 (2.5)		8 (2.3)	4 (1.5)		8 (2.2)	6 (2.6)		13 (2.7)	12 (3.1)		
Presence of IVH, %	519 (43.7)	393 (44.3)	0.791	177 (50.4)	122 (46.0)	0.281	151 (41.7)	104 (45.6)	0.352	191 (40.3)	167 (42.4)	0.533	0.385
Outcomes													
Discharge mRS ≤2, %	272 (23.0)	180 (20.3)	0.147	79 (22.6)	55 (20.8)	0.589	84 (23.2)	43 (18.9)	0.211	109 (23.0)	82 (20.8)	0.43	0.371
90-d mRS (IQR)	3 (2-5)	4 (2-6)	<0.001	3 (2-5)	4 (2-6)	0.029	3 (2-4)	4 (2-5)	0.003	3 (1-5)	4 (2-6)	0.042	0.018
90-d mRS ≤2, %	487 (41.0)	296 (33.4)	<0.001	148 (42.2)	91 (34.3)	0.048	155 (42.8)	68 (29.8)	0.002	184 (38.8)	137 (34.8)	0.219	0.030

Continued

Table 1 Continued

	Overall		Non-Hispanic black		Hispanic		Non-Hispanic white		Meta, p value
	Men (n = 1,187)	Women (n = 887)	Men (n = 351)	Women (n = 265)	Men (n = 362)	Women (n = 228)	Men (n = 474)	Women (n = 394)	
Discharge mortality, %	151 (12.7)	141 (15.9)	33 (9.4)	39 (14.7)	46 (12.7)	37 (16.2)	72 (15.2)	65 (16.5)	0.608
90-d mortality, %	236 (19.9)	239 (26.9)	61 (17.4)	69 (26.0)	68 (18.8)	53 (23.3)	107 (22.6)	117 (29.7)	0.017
									0.191
									0.028

Abbreviations: BMI = body mass index; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale. Values are reported as number of participants (%) or mean \pm SD. Meta p value represents the statistical significance of the transthenic weighted inverse normal meta-analysis, where cohorts are weighted by their respective sample size.

mortality and poorer mRS at 90 days after ICH in each racial/ethnic group. There is suggestive evidence of a sex-by-age interaction effect in the non-Hispanic black cohort for mortality ($p = 0.003$), but not for $mRS \geq 3$ at ($p = 0.402$), at 90 days after ICH. This pattern was not observed in other analyses: Hispanic participants ($p = 0.842$ and 0.471 ; mortality and $mRS \geq 3$, respectively), non-Hispanic white participants ($p = 0.756$ and 0.342 ; mortality and $mRS \geq 3$, respectively), or transthenicity ($p = 0.183$ and 0.378 ; mortality and $mRS \geq 3$, respectively). In addition, significance of the interaction term in the non-Hispanic black cohort disappears after adjustment for multiple comparisons. Finally, sensitivity analyses were performed for regression modeling with and without patients lost to follow up at 90 days (table e-1 at Neurology.org), and model results did not differ (data not shown).

DISCUSSION As the largest study from a multiracial/ethnic population of patients with ICH, the present study found multiple sex differences in clinically relevant variables and outcomes; however, in multivariable models, neither sex nor sex-by-age interaction was associated with mortality or mRS at 90 days after ICH. While epidemiologic studies have often treated patients with ICH as a subset of total stroke patients rather than as a distinct category, confirmation of sex differences in ICH has been difficult to achieve.^{1,16-18} Regardless, sexual dimorphism in recovery from brain injury is biologically plausible given that female gonadal steroids have a neuroprotective effect in a variety of preclinical models,^{19,20} including ICH.²¹⁻²³ In fact, sex differences in other stroke subtypes are readily apparent in humans.^{24,25} While gonadal hormones do not completely explain known sex differences in cellular responses, loss of gonadal hormones during menopause in women may mean that age differentially affects women compared with men. Prior publications on sex differences after ICH have reported conflicting results regarding correlations with both mortality²⁶⁻²⁹ and neurologic recovery.³⁰⁻³³

The effects of aging in ICH have received substantial attention. In the present study, baseline age differed for men and women in each racial/ethnic group and, in fact, was a modifier of 90-day outcome in multivariate models. Incidence, mechanisms, and outcomes of ICH are known to vary by age, and results presented here are not significantly different from prior publications.³⁴ For instance, amyloid angiopathy increases as a cause of ICH in older populations.³⁵ Further, increasing age is strongly associated with poorer outcome after ICH.³⁶ This association may be related to aging effects on hematoma volume³⁷ and neuroinflammation.^{38,39} However, the

Table 2 Ethnic-specific and combined univariate associations with outcome

	Overall		Non-Hispanic black		Hispanic		Non-Hispanic white	
	mRS ≥ 3	Mortality	mRS ≥ 3	Mortality	mRS ≥ 3	Mortality	mRS ≥ 3	Mortality
Age/y	1.03 (1.02-1.04)	1.04 (1.03-1.05)	1.04 (1.02-1.05)	1.05 (1.03-1.07)	1.04 (1.03-1.05)	1.04 (1.03-1.06)	1.03 (1.02-1.04)	1.04 (1.02-1.05)
BMI	1.00 (0.98-1.01)	0.98 (0.97-0.99)	1.00 (0.98-1.02)	0.97 (0.94-1.00)	0.98 (0.96-1.01)	0.96 (0.93-0.99)	1.00 (0.99-1.02)	1.00 (0.97-1.01)
Male	0.72 (0.60-0.86)	0.67 (0.55-0.83)	0.72 (0.51-1.00)	0.60 (0.40-0.88)	0.57 (0.40-0.80)	0.76 (0.51-1.15)	0.84 (0.64-1.11)	0.69 (0.51-0.94)
Admission GCS per point	0.76 (0.73-0.79)	0.78 (0.76-0.80)	0.78 (0.73-0.83)	0.80 (0.76-0.84)	0.77 (0.72-0.82)	0.79 (0.75-0.83)	0.70 (0.64-0.75)	0.73 (0.69-0.77)
ICH volume	1.90 (1.75-2.07)	2.16 (1.95-2.40)	1.88 (1.61-2.21)	2.28 (1.87-2.81)	2.27 (1.91-2.72)	2.38 (1.92-2.99)	1.76 (1.56-1.99)	1.99 (1.73-2.32)
Pre-ICH mRS	1.83 (1.63-2.06)	1.45 (1.33-1.58)	1.88 (1.50-2.42)	1.53 (1.30-1.80)	1.44 (1.17-1.82)	1.39 (1.15-1.68)	2.06 (1.75-2.46)	1.42 (1.26-1.60)
Discharge mRS	3.62 (3.25-4.07)	9.92 (8.07-12.38)	2.89 (2.44-3.47)	7.58 (5.42-11.05)	3.55 (2.92-4.43)	24.22 (13.65-48.77)	4.59 (3.77-5.69)	8.96 (6.71-12.34)
Alcohol abuse	0.73 (0.59-0.90)	0.75 (0.58-0.97)	0.87 (0.60-1.26)	0.70 (0.43-1.11)	0.55 (0.38-0.80)	0.96 (0.60-1.50)	0.82 (0.57-1.17)	0.71 (0.46-1.08)
Smoking								
Current	0.96 (0.76-1.21)	0.95 (0.72-1.26)	1.04 (0.71-1.53)	1.06 (0.66-1.71)	0.92 (0.60-1.43)	0.87 (0.49-1.50)	0.95 (0.63-1.42)	1.00 (0.62-1.58)
Former	1.14 (0.92-1.40)	1.07 (0.84-1.37)	1.57 (1.01-2.45)	1.36 (0.81-2.26)	0.87 (0.59-1.30)	0.99 (0.60-1.62)	1.12 (0.83-1.53)	0.94 (0.66-1.33)
Illicit drug use	0.72 (0.57-0.92)	0.74 (0.54-0.99)	0.72 (0.50-1.03)	0.73 (0.46-1.13)	0.67 (0.43-1.04)	0.68 (0.36-1.20)	0.85 (0.50-1.47)	1.07 (0.57-1.90)
Coagulopathy	1.44 (1.16-1.79)	2.04 (1.62-2.56)	1.55 (1.02-2.38)	2.29 (1.46-3.55)	1.21 (0.81-1.80)	2.01 (1.28-3.14)	1.54 (1.12-2.13)	1.86 (1.33-2.59)
Hypertension	1.54 (1.21-1.96)	1.20 (0.89-1.62)	1.32 (0.73-2.34)	1.23 (0.61-2.77)	1.49 (0.98-2.27)	1.15 (0.68-2.00)	1.73 (1.22-2.45)	1.28 (0.86-1.95)
Diabetes	1.30 (1.07-1.59)	1.18 (0.94-1.47)	1.07 (0.75-1.54)	0.99 (0.64-1.51)	1.38 (0.96-1.98)	1.51 (0.99-2.27)	1.44 (1.06-1.98)	1.15 (0.82-1.60)
Heart disease	1.51 (1.25-1.83)	1.76 (1.43-2.17)	1.30 (0.91-1.87)	1.44 (0.95-2.16)	1.45 (0.97-2.18)	1.64 (1.05-2.54)	1.70 (1.29-2.26)	1.90 (1.40-2.58)
Lobar vs nonlobar location	0.73 (0.60-0.89)	1.21 (0.96-1.50)	0.80 (0.54-1.17)	1.46 (0.93-2.26)	0.71 (0.48-1.06)	0.81 (0.48-1.31)	0.67 (0.51-0.89)	1.19 (0.87-1.62)
Presence of IVH	2.90 (2.40-3.51)	3.11 (2.51-3.86)	2.00 (1.44-2.79)	2.73 (1.82-4.14)	3.79 (2.63-5.51)	4.82 (3.13-7.59)	3.35 (2.47-4.57)	2.79 (2.05-3.82)

Abbreviations: BMI = body mass index; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale.

Values are reported as odds ratios (95% confidence interval). ICH volume was fit as the natural logarithm of volume plus 1, due to a highly skewed distribution leading to overly influential observations in the extreme of the distribution. Significant difference in univariate analysis set at $p < 0.05$.

Table 3 Combined samples and ethnic-specific multiple logistic regression models for outcome

	Overall		Non-Hispanic black		Hispanic		Non-Hispanic white	
	mRS ≥ 3	Mortality	mRS ≥ 3	Mortality	mRS ≥ 3	Mortality	mRS ≥ 3	Mortality
Age linear	1.05 (1.03-1.06)	1.05 (1.03-1.06)	1.04 (1.01-1.07)	1.06 (1.03-1.09)	1.06 (1.04-1.09)	1.06 (1.03-1.09)	1.04 (1.02-1.07)	1.03 (1.01-1.06)
Quadratic	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.99-1.01)	1.01 (1.01-1.01)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.99-1.00)
Male	0.78 (0.61-1.00)	0.92 (0.68-1.23)	0.68 (0.43-1.07)	0.73 (0.43-1.24)	0.63 (0.38-1.05)	1.34 (0.70-2.59)	0.91 (0.60-1.37)	0.99 (0.62-1.58)
GCS	0.82 (0.79-0.86)	0.79 (0.76-0.82)	0.84 (0.78-0.90)	0.83 (0.78-0.89)	0.82 (0.76-0.90)	0.79 (0.74-0.85)	0.79 (0.72-0.86)	0.73 (0.69-0.78)
ICH volume	2.28 (2.00-2.58)	1.84 (1.60-2.11)	1.92 (1.54-2.39)	1.73 (1.33-2.24)	2.66 (2.07-3.43)	2.14 (1.56-2.93)	2.38 (1.93-2.94)	1.79 (1.45-2.21)
Pre-ICH mRS	1.84 (1.58-2.13)	1.39 (1.23-1.57)	1.75 (1.30-2.36)	1.21 (0.95-1.55)	1.28 (0.93-1.75)	1.46 (1.11-1.93)	2.19 (1.76-2.72)	1.49 (1.25-1.78)
Illicit drug use	0.80 (0.58-1.12)	0.98 (0.64-1.50)	0.78 (0.49-1.24)	1.00 (0.54-1.84)	0.77 (0.41-1.45)	0.64 (0.28-1.48)	1.04 (0.47-2.29)	1.63 (0.67-3.97)
Coagulopathy	1.06 (0.80-1.41)	1.87 (1.38-2.53)	1.06 (0.63-1.79)	1.87 (1.06-3.28)	1.15 (0.65-2.03)	2.24 (1.19-4.22)	1.08 (0.69-1.69)	1.81 (1.14-2.88)
Hypertension	1.36 (0.96-1.93)	1.02 (0.67-1.57)	1.17 (0.53-2.57)	1.20 (0.44-3.27)	1.38 (0.75-2.54)	0.61 (0.27-1.40)	1.40 (0.82-2.40)	1.09 (0.58-2.03)
Diabetes	1.09 (0.83-1.43)	1.01 (0.74-1.39)	0.88 (0.54-1.42)	0.73 (0.40-1.34)	1.14 (0.66-1.97)	1.78 (0.95-3.33)	1.34 (0.85-2.11)	0.90 (0.55-1.47)
Heart disease	1.18 (0.89-1.56)	1.29 (0.94-1.76)	1.20 (0.75-1.93)	1.22 (0.69-2.16)	0.96 (0.52-1.76)	0.99 (0.50-1.94)	1.22 (0.79-1.89)	1.61 (0.99-2.62)
Lobar location	0.28 (0.21-0.38)	0.77 (0.56-1.07)	0.31 (0.18-0.54)	1.21 (0.64-2.30)	0.26 (0.14-0.48)	0.44 (0.21-0.91)	0.25 (0.16-0.40)	0.82 (0.51-1.34)
Presence of IVH	1.80 (1.40-2.32)	1.72 (1.29-2.30)	1.32 (0.85-2.03)	2.01 (1.17-3.45)	2.57 (1.57-4.20)	2.64 (1.43-4.89)	1.97 (1.31-2.98)	1.27 (0.82-1.98)
Age*sex	0.38	0.18	0.40	<0.01	0.47	0.84	0.34	0.76

Abbreviations: GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale.

Values are reported as odds ratios (95% confidence interval) except for the interaction term (age*sex), for which the p value is given. Due to a highly skewed distribution leading to inappropriate influence of values in the extreme of the volume distribution, ICH volume was modeled using the natural logarithm of volume plus 1. To model the nonlinear effect of age, a linear term for age and a quadratic term (i.e., [age - mean age]²) were modeled (i.e., centered quadratic term). Modeling of the interaction term of age and sex includes a linear term for age and centered cross-product with sex (i.e., [age - mean age]*[indicator variable for male - proportion males in sample]) and a quadratic term (i.e., [age - mean age]²*[indicator variable for male - proportion males in sample]). Main effects (i.e., sex and age) of variables included in an interaction term (i.e., sex-by-age interaction) are not directly interpretable without considering the interaction term estimates and their covariance. Although not significant, the interaction terms are included in the models reported as they represent the primary hypothesis. Significant difference in each multivariate model set at $p < 0.05$.

present study controlled for differences and effects of age and sex as covariates in multivariable models. Hematoma volume, admission GCS, and (to a slightly lesser degree) pre-morbid mRS were consistently found to have associations with both 90-day mortality and neurologic recovery across all race/ethnicities.

Although the NIH Stroke Scale was not collected and thus could not be included as a measure of stroke severity in these analyses, the present results are consistent with associations between 90-day outcome and age, admission GCS, hematoma volume, and pre-ICH mRS in all groups. Furthermore, covariates in the analytical model included the individual components of the ICH Score,³⁶ which has been demonstrated to correlate well with long-term outcome after ICH.⁴⁰ Thus, although we were unable to control directly for stroke severity, accepted predictors of outcome appear to behave as expected in the present study population. In fact, fewer than 10% of data were missing in all variables except presence of coagulopathy, suggesting little potential for bias in measured effects.

Despite using prospectively collected data, the retrospective nature of the analyses limits the current study. The present study was unable to address questions regarding sex differences in quality of life or adequately represent certain patient populations (e.g., patients at the extremes of the age distribution or patients with brainstem hemorrhage or IVH). The present findings do not include other racial/ethnic groups such as Asians or Native Americans, whose outcomes after ICH may behave differently after ICH. Some factors that may influence outcome after ICH were not included in the models. Menopausal status and gonadal hormones concentration (serum and brain) were not measured as the underlying biology for the hypothesis for an age–sex interaction. Although the accepted standard for clinical trials, mRS is not the only metric for assessing recovery after ICH, and 90-day outcome may not accurately reflect outcome at 1 year after ICH. Thus, future work should include these patient populations. Despite these limitations, the present study utilized a large cohort of 3 racial/ethnic groups prominent in the United States, collected prospectively with strict definitions for ICH ascertainment, comorbidities, imaging, and outcomes to assess for a biologically plausible interaction between age and sex. While this sample represents the largest and most statistically powerful test of a sex-by-age interaction to date, existence of sex-by-age interaction effect in each of ethnic/racial cohorts cannot be absolutely excluded. However, given the size of the present sample, any interaction is unlikely to have significant clinical implications. Failure to find an outcome effect from sex or sex–age interaction may be due to study limits; however, the overall worse

prognosis after ICH compared to ischemic stroke may limit the potential hormonal effects associated with sex.

In the largest cohort of patients with ICH to date, sex differences were found in multiple study characteristics and racial/ethnic backgrounds; however, there is little evidence that sex interacts with age to affect 90-day mRS and mortality.

AUTHOR CONTRIBUTIONS

Dr. James designed and conceptualized the study, interpreted the data, and drafted the manuscript. Dr. Langefeld designed the study, analyzed and interpreted the data, and revised the manuscript. P. Sekar designed the study, analyzed and interpreted the data, and revised the manuscript. Dr. Moomaw designed the study, interpreted the data, and revised the manuscript. Dr. Elkind designed the study, interpreted the data, and revised the manuscript. Dr. Worrall designed the study, interpreted the data, and revised the manuscript. Dr. Sheth designed the study, interpreted the data, and revised the manuscript. Dr. Martini designed the study, interpreted the data, and revised the manuscript. J. Osborne designed the study, interpreted the data, and revised the manuscript. Dr. Woo conceptualized and designed the study, interpreted the data, and revised the manuscript.

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DISCLOSURE

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