Aggressiveness of care following intracerebral hemorrhage in women and men

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ABSTRACT

Objective: To compare comorbidities and use of surgery and palliative care between men and women with intracerebral hemorrhage (ICH).

Methods: The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study is a prospective, multicenter, case-control study of ICH risk factors and outcomes. We compared comorbidities, treatments, and use of do-not-resuscitate (DNR) orders in men vs women. Multivariate analysis was used to assess the likelihood of ICH surgery and palliative care after adjustment for variables that were $p < 0.1$ in univariate analyses and backward elimination to retain those that were significant ($p < 0.05$).

Results: Women were older on average (65.0 vs 59.9, $p < 0.0001$), and higher proportions of women had previous stroke (24.1% vs 19.3%, $p = 0.002$), had dementia (6.1% vs 3.4%, $p = 0.0007$), lived alone (23.1% vs 18.0%, $p = 0.0005$), and took anticoagulants (12.8% vs 10.1%, $p = 0.02$), compared with men. Men had higher rates of alcohol and cocaine use. After adjusting for age, hematoma volume, and ICH location, there was no difference in rates of surgical treatment by sex (odds ratio [OR] 0.93 for men vs women, 95% confidence interval [CI] 0.68–1.28, $p = 0.67$), and there was no difference in DNR/comfort care decisions after adjustment for ICH score, prior stroke, and dementia (OR 0.96, CI 0.77–1.22, $p = 0.76$).

Conclusions: After ICH, women do not receive less aggressive care than men after controlling for the substantial comorbidity differences. Future studies on sex bias should include the presence of comorbidities, prestroke disability, and other factors that may influence management. *Neurology*® 2017;89:349–354

GLOSSARY

CAA = cerebral amyloid angiopathy; CI = confidence interval; DNR = do not resuscitate; ERICH = Ethnic and Racial Variations of Intracerebral Hemorrhage; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; OR = odds ratio; SBP = systolic blood pressure.

Patient sex and race may influence physician perception of vascular disease severity. Prior studies have demonstrated that nonwhite women are less likely to be referred for cardiovascular procedures, such as cardiac catheterizations, than white men.^{1,2} In addition, studies have shown that women with ischemic stroke are less likely to have a complete etiologic workup, and they receive fewer proven therapies for secondary prevention. A retrospective chart review of 501 ischemic stroke patients found that two-thirds of women left the hospital with an incomplete workup, compared with half of men.³ The reason for this disparity was unclear but was echoed in similar research in Europe.⁴ Further, women with TIA less frequently undergo carotid endarterectomy, and those who do must meet a higher threshold ABCD2 score and frequently have longer delays before surgery.⁵ These differences persist despite growing evidence that women endure greater risk of disability or death after stroke or myocardial infarction.^{6–8} However, women may present later in life than men and thus have accrued greater rates of comorbidities such as dementia, which may influence aggressiveness of workup and care.

Supplemental data
at Neurology.org

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Identification of sex bias is important in reducing the global burden of stroke, which has increased from 1990 to 2010.⁹ Though more people in the world have ischemic stroke, hemorrhagic stroke results in greater death and disability.¹⁰ Despite this, sex differences in intracerebral hemorrhage (ICH) have received less attention.¹¹ The Ethnic and

Racial Variations of Intracerebral Hemorrhage (ERICH) database contains information about risk factors and outcomes for nearly 3,000 individuals drawn from a triethnic population. We sought to compare comorbidities and use of surgical treatments and palliative care between men and women to assess the hypothesis that women receive less aggressive care after ICH.

Table 1 Characteristics of men and women with intracerebral hemorrhage (ICH)

	Men (n = 1,744)	Women (n = 1,220)	p Value
Age, y, mean (SD)	59.9 (13.6)	65.0 (15.3)	<0.0001
Race			
Black	573 (32.9)	422 (34.6)	
Hispanic	617 (35.4)	365 (29.9)	
White	554 (31.8)	433 (35.5)	0.006
Hypertension	1,475 (84.9)	1,021 (84.0)	0.50
Diabetes	515 (29.6)	339 (27.8)	0.29
Hyperlipidemia	773 (45.2)	562 (46.6)	0.43
Smoking			
Current	363 (21.0)	186 (15.4)	
Former	554 (32.0)	325 (26.8)	
Never	815 (47.1)	701 (57.8)	<0.0001
Alcohol use (total n = 2,897)			
Never/rare	870 (51.4)	882 (73.3)	
Moderate	487 (28.8)	249 (20.7)	
Intermediate	93 (5.5)	27 (2.2)	
Heavy	244 (14.4)	45 (3.7)	<0.0001
Cocaine use	160 (10.1)	53 (4.7)	<0.0001
Atrial fibrillation	198 (11.4)	137 (11.3)	0.91
Dementia	60 (3.4)	74 (6.1)	0.001
Previous stroke	337 (19.3)	293 (24.1)	0.002
Anticoagulant	176 (10.1)	156 (12.8)	0.02
Initial SBP (n = 2,690), median (IQR)	186 (159–215)	181 (155–213)	0.01
Initial GCS, median (IQR)	15 (11–15)	14 (10–15)	0.001
ICH score (n = 2,815), median (IQR)	1 (0–2)	1 (0–2)	<0.0001
Any medical insurance	1,174 (67.3)	962 (78.9)	<0.0001
Private	687 (39.4)	531 (43.5)	0.02
Medicare	591 (33.9)	555 (45.5)	<0.0001
Medicaid	259 (14.9)	259 (21.2)	<0.0001
VA	44 (2.5)	4 (0.3)	<0.0001
Marital status/lives with			
Lives alone	313 (18.0)	282 (23.1)	0.001
Married/lives with partner	970 (55.6)	452 (37.1)	<0.0001
Prestroke mRS, median (IQR)	0 (0–1)	0 (0–1)	<0.0001

Abbreviations: GCS = Glasgow Coma Scale; IQR = interquartile range; mRS = modified Rankin Scale; SBP = systolic blood pressure.
Values are n (%) unless noted otherwise.

METHODS Detailed methods of the ERICH study are published elsewhere.¹² Briefly, ERICH is a prospective, multicenter, observational study of ICH risk factors and outcomes that aims to identify clinical, radiographic, and genetic factors that influence risk of and outcome in non-Hispanic white, non-Hispanic black, and Hispanic patients with ICH. We compared use of aggressive treatments such as hematoma evacuation, palliative care, and use of do-not-resuscitate (DNR) between men and women in ERICH. Individuals were identified and approached for enrollment using a prospective hot pursuit method to limit survival bias.

Participants included any person with a spontaneous ICH who met the following eligibility criteria: age ≥ 18 years; residency for at least 6 months within a 50- to 100-mile radius of the recruiting center, depending on the population density; self-identified white, black, or Hispanic race/ethnicity; and ability of the patient or legal representative to provide informed consent.¹² A member of the research team interviewed patients or their proxy to capture demographics (age, sex, and race) and clinical variables such as comorbidities, and pre-ICH functional status recorded as a modified Rankin Scale (mRS) score. In addition, clinical and imaging data were used to ascertain presenting injury severity using the ICH score, which incorporates age, Glasgow Coma Scale (GCS) on presentation, hematoma location and volume, and presence of intraventricular hemorrhage (IVH).^{13,14} We used the first available CT scan for standardized, central review. Hematoma location was categorized as supratentorial (deep, lobar) or infratentorial (brainstem, cerebellar). We defined deep ICH as originating from the thalamus, basal ganglia, internal capsule, or deep periventricular white matter and lobar ICH as originating at the cortex or cortical-subcortical junction. We measured hematoma volume using a previously published method for the Analyze version 9.0 (Mayo Clinic, Rochester, MN) software.¹⁵ Presence or absence of IVH was recorded separately.

Clinical coordinators reviewed details of hospitalization from available hospital records for each ICH case and captured use of surgical intervention, palliative care, or active DNR orders. Use of these interventions was compared between men and women. Neurosurgical procedures included craniotomy, craniectomy for clot evacuation, external ventricular drain, ventriculoperitoneal shunt placement, and any other neurosurgeries. Surgical treatments included placement of a percutaneous endoscopy tube, gastrostomy, and tracheostomy. Other outcomes of interest included discharge disposition, in-hospital death, use of palliative/comfort care/hospice services, and use of a new DNR order. Through a planning committee that included neurologists and neurointensivists, we defined aggressive care as receiving ≥ 2 of 3 aggressive measures (craniotomy, feeding tube placement, or tracheostomy).

Statistical analysis. Descriptive statistics are presented as means with SD, frequencies with percentages, or median with interquartile range (IQR), depending on the type and distribution of the variable. Men and women were compared for race, preexisting and

Table 2 Intracerebral hemorrhage location

	Men (n = 1,744)	Women (n = 1,220)	p Value
Brainstem	92 (5.5)	63 (5.3)	<0.0001
Cerebellum	125 (7.4)	101 (8.5)	
Deep	980 (58.0)	567 (47.8)	
Lobar	460 (27.2)	436 (36.8)	
Primary intraventricular hemorrhage	32 (1.9)	19 (1.6)	

Values are n (%).

presenting medical conditions, substance use, anticoagulant use before stroke, poststroke interventions such as ventriculostomy and surgical evacuation, medical insurance status, and discharge disposition using χ^2 or Fisher exact tests. Hematoma volume was divided into 3 categories: <30, 30–60, and >60 mL. A 2-sample *t* test was used to compare age. The Wilcoxon rank-sum test was used to compare men and women on presenting systolic blood pressure (SBP), presenting GCS, ICH score, prestroke mRS, and length of hospital stay. Univariate logistic regressions modeling the probability of surgical hematoma evacuation against each of the preexisting and presenting conditions were constructed. No individuals with brainstem hematoma underwent surgical evacuation; therefore, brainstem hemorrhages were excluded from logistic regressions modeling surgical evacuation to avoid convergence bias. Multivariable analysis was used to assess the likelihood of surgical hematoma evacuation. All conditions that were $p < 0.1$ in the univariate analysis were included in the multivariate model; backward elimination was used to retain only those with $p < 0.05$. A similar multivariate model was constructed to assess the likelihood of palliative care.

Standard protocol approvals, registrations, and patient consents. The institutional review boards of each enrolling site approved the study. Informed consent was obtained from all individuals or their legal representatives.

RESULTS The total study population consisted of 2,964 patients, of whom 1,220 were women. Table 1

presents baseline characteristics by sex. With regard to risk factors, similar proportions of men and women had hypertension and atrial fibrillation. Higher proportions of men had a history of cocaine use (10.1% vs 4.7%, $p < 0.0001$) or were heavy drinkers (14.4% vs 3.7%, $p < 0.0001$), and men had higher initial average SBP. Women were older, on average, at the time of presentation (65.0 vs 59.9 years, $p < 0.0001$). Higher proportions of women had a history of stroke or dementia, were on anticoagulation, were living alone at time of presentation (23.1% vs 18.0%, $p = 0.0005$), and had dementia (6.1% vs 3.4%, $p = 0.0007$).

Table 2 outlines the anatomic differences between men and women. Lobar ICH was more prevalent in the women (36.8% vs 27.2%, $p < 0.0001$). Deep ICH (58.0% vs 47.8%, $p < 0.0001$) and primary IVH were more prevalent in men.

Table 3 details poststroke interventions and outcomes by sex. A higher proportion of men underwent a ventriculostomy (21% vs 17.5%, $p = 0.0187$), but there were no statistical differences in the proportion of men and women who underwent surgical evacuation of hemorrhage (8.8% vs 8.2%, $p = 0.5820$), percutaneous endoscopic gastrostomy (18.2% vs 17.8%, $p = 0.76$), tracheostomy (3.1% vs 3.8%, $p = 0.32$), or endotracheal intubation (36.7% vs 37.1%, $p = 0.81$). After adjustment for age, hematoma volume, and hematoma location, there was no difference in surgical treatment between sexes (odds ratio [OR] 0.93 for men vs women, 95% confidence interval [CI] 0.68–1.28, $p = 0.67$). In both men and women, increasing age was associated with a lower likelihood of surgical evacuation of the ICH (tables e-1 and e-2 at Neurology.org).

ORs were calculated for different variables related to surgical evacuation (table 4 and tables e-3 and e-4). Increasing age (OR 0.97, CI 0.96–0.98), history of prior stroke (OR 0.53, CI 0.36–0.77), and presence of dementia (OR 0.37, CI 0.18–0.76) were associated with decreased likelihood of undergoing surgery. Presence of anticoagulation, evidence of IVH, and diminished premorbid functional status as defined by mRS >3 were not significantly associated with surgery. When patients with early withdrawal of care were excluded from the analysis, there was no difference in the rate of surgical evacuation between men and women (OR 0.93, CI 0.66–1.30). Time to surgical interventions did not differ between men and women (log-rank test, p value 0.62).

The median length of stay was slightly longer for men (8.5 vs 7.0 days, $p = 0.0017$). Although there was no significant difference in the proportions of in-hospital death for women vs men (11.9% vs 10.6%, $p = 0.28$), higher proportions of women were discharged to hospice/nursing facilities (25.2% vs

Table 3 Poststroke interventions and outcomes

	Men (n = 1,744)	Women (n = 1,220)	p Value
Ventriculostomy	365 (21.0)	213 (17.5)	0.02
Surgical evacuation of hemorrhage	153 (8.8)	100 (8.2)	0.58
Other surgical treatment	12 (0.7)	8 (0.7)	0.92
PEG/NG tube	318 (18.2)	217 (17.8)	0.76
ET intubation	640 (36.7)	453 (37.1)	0.81
Tracheostomy	54 (3.1)	46 (3.8)	0.32
≥ 2 of 3 Aggressive care	101 (5.8)	76 (6.2)	0.62
Discharge to hospice/nursing home	345 (19.8)	307 (25.2)	0.001
Death during hospitalization	185 (10.6)	145 (11.9)	0.28
Made DNR/comfort care	266 (15.3)	237 (19.4)	0.003
Length of stay for index hospitalization, median (IQR)	8.5 (5–17)	7.0 (4–15)	0.002

Abbreviations: DNR = do not resuscitate; ET = endotracheal; IQR = interquartile range; NG = nasogastric; PEG = percutaneous endoscopic gastrostomy. Values are n (%) unless noted otherwise.

Table 4 Univariate analysis of variables associated with surgical evacuation

	OR (CI)	p Value
Male vs female	1.08 (0.83-1.41)	0.5726
Location		<0.0001
Deep	0.36 (0.27-0.48)	<0.0001
Lobar	Reference	
Cerebellum	2.40 (1.68-3.42)	<0.0001
Age	0.97 (0.96-0.98)	<0.0001
Prior stroke	0.53 (0.36-0.77)	0.001
Alzheimer/dementia	0.37 (0.18-0.76)	0.007
Anticoagulant	1.40 (0.96-2.02)	0.078
Presence of IVH	1.23 (0.93-1.62)	0.14
Prestroke mRS >3	0.55 (0.22-1.37)	0.20
Volume category		<0.0001
<30 mL	Reference	
30-60 mL	6.44 (4.63-8.96)	<0.0001
>60 mL	10.11 (6.98-14.66)	<0.0001

Abbreviations: CI = confidence interval; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; OR = odds ratio.

19.4%, $p < 0.0005$) and utilized palliative care measures (19.4% vs 15.3%, $p = 0.003$). Palliative care measures were no longer significantly different after adjustment for ICH score, prior stroke, and dementia (OR 0.96 for men vs women, CI 0.77–1.22, $p = 0.76$).

DISCUSSION We hypothesized that women with ICH would receive less aggressive care than men, as has been observed in other cardiovascular conditions. However, we found that there were no differences after adjusting for severity of ICH and comorbidities such as prior stroke and dementia. Three important baseline characteristics stood out in the ERICH cohort. First, anticoagulation was more prevalent in women. This may reflect the increasing prevalence of warfarin-associated ICH in the United States.¹⁶ In addition, more women had a history of stroke. This could represent the accumulated burden of modifiable risk factors (hypertension, diabetes, hyperlipidemia, and smoking history) in older women. It could also reflect the fact that the women in our study were older than the men, and may reflect underutilization of secondary stroke prevention measures in women. Finally, dementia was more prevalent in women, which is consistent with higher age and lobar hematoma location in women. Lobar hemorrhage is a common location for ICH in patients with cerebral amyloid angiopathy (CAA).¹⁷ The prevalence of CAA increases with age and has a female predominance.^{18,19} ICH secondary to CAA is associated with larger hematoma volume at onset but lower

likelihood of expansion compared with other etiologies of ICH.²⁰ This possible clinical course may influence presentation of risks and benefits for surgical procedures and bias towards less aggressive measures. However, these baseline comorbidities do not appear to limit the aggressiveness of treatment in women with ICH.

Overall, women were more likely to receive new DNR orders. However, after correcting for severity of ICH score, dementia, and history of prior stroke, there was no difference in the proportion of women who had a new DNR order placed during hospitalization. This was in contrast to a prior study that demonstrated that women were more likely to initiate DNR orders within 24 hours of admission regardless of their ICH severity or age.²¹ This difference may reflect the experience at a single center vs that of multiple sites. The ERICH database also included nearly 2,500 more patients.

Women in our study population were potentially more vulnerable to bias in clinical decision-making because they were more likely to have dementia and hence at baseline may be at higher risk for having impaired decision-making capacity after ICH. Prior to presentation, more women lived alone, which may have resulted in the higher proportion of women discharged to nursing homes and hospice facilities. Further, variability in physician decision-making in ICH patients is well-documented, along with the limitations of existing ICH scales.^{22,23} A recent single-center study found that women with ICH were older and had worse functional status prior to the stroke.²⁴ This study, similar to our results, found that men were more likely to have excess alcohol use. After adjustment for baseline functional status and ICH severity, there were no differences in 3-month mortality or rate of poor outcome between the sexes.

The findings in this study have implications for patient counseling and management. Young men with excess alcohol use or drug abuse should be counseled that hemorrhagic stroke is a major health risk. For women, the increased frequency of lobar hemorrhages makes it imperative to monitor anticoagulation and blood pressure closely in older women.

Our study has limitations. Most of the recruitment centers for the ERICH study specialize in the treatment of ICH, which may bias towards aggressive treatment because of the ability to provide comprehensive postsurgical care and rehabilitation. However, some sites in ERICH included data from community hospitals. All recruiting sites are from the United States. Worldwide differences have been demonstrated in the incidence, fatality, and outcome of ICH.^{10,11} This may limit the global applicability of results in our study. In addition, studies focused on sex differences in the treatment of specific types of

ICH, such as anticoagulant-related brain hemorrhage, would be of interest in the future. In addition, practice variation in settings with reduced access to neurology or neurosurgery expertise would also be worthy of future study. Multiple factors may influence aggressive care, including age of the patient, anticoagulant use, and patient socioeconomic status. The reason why aggressive care is not chosen may not be explicitly stated in the medical chart.

In this analysis, we identified key differences in women presenting with ICH compared to men, including older age and increased baseline prevalence of prior dementia and stroke. We also identified a greater prevalence of lobar hemorrhage in women, which may be secondary to a higher rate of CAA in this older population. After adjustment for these variables, we did not find any difference in aggressiveness of care in women following ICH.

AUTHOR CONTRIBUTIONS

Rahul Guha: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Amelia Boehme: drafting/revising

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Comment:

Does patient sex affect decision-making after hemorrhagic stroke?

Women do worse than men after both ischemic and hemorrhagic stroke, with evidence that sex bias in physician decision-making may contribute to this increased morbidity and mortality.¹ Intracerebral hemorrhage (ICH) poses additional challenges, as the etiologies—amyloid angiopathy associated with prior cognitive decline, illicit drug use—carry their own assumptions. Guha et al.² report findings from the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study, a prospective, multicenter, triethnic, case-control study of ICH risk factors and outcomes. In almost 3,000 people, they examined comorbidities, treatments, and use of do not resuscitate (DNR) orders, comparing men vs women (n = 1,220). The outcome measure was aggressiveness of care, measured via use of surgical therapies for hematoma treatment and avoidance of DNR orders.

They found that women with brain hemorrhage were older, and more likely to have had previous stroke or dementia, whereas men were more likely to be abusers of cocaine and alcohol. There were additional differences in prior living status, discharge location, and oral anticoagulant use. However, the authors found no significant difference in rates of surgical treatment or DNR/comfort care decisions after adjustment for ICH score, prior stroke, and dementia. They conclude that women with ICH receive comparable care to men, after controlling for the substantial comorbidity differences.

This is a good and useful study, which will likely reassure US clinicians treating patients with ICH. Some readers will have reservations about the use of logistic regression for time-to-event data, as perhaps a time-to-event analysis (e.g., Cox model) may have been more appropriate. So much is down to the art, not science, of how we intervene after ICH.³ It is important that we continue to interrogate potential implicit bias underlying our clinical decision-making.

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DISCLOSURE

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