

Gender Disparities among Intracerebral Hemorrhage Patients from a Multi-ethnic Population

Alexandra Galati BA; Sage L. King MPH; and Kazuma Nakagawa MD

Abstract

Background: Intracerebral hemorrhage (ICH) is a hemorrhagic stroke with high morbidity and mortality. Recent studies have shown that minorities such as Native Hawaiians and other Pacific Islanders (NHOPI) with ICH are significantly younger compared to whites. However, the interaction of race and gender, and its impact on observed disparities among a multi-ethnic population in Hawai'i, have not been studied.

Methods: Consecutive ICH patients (whites, Asians or NHOPI), who were hospitalized at a single tertiary center on O'ahu between 2006 and 2013 were retrospectively studied. Clinical characteristics were compared between men and women among the entire cohort, and within the major racial groups.

Results: A total of 791 patients (NHOPI 19%, Asians 65%, whites 16%) were studied. Overall, men were younger than women (62 ± 16 years vs 67 ± 18 years respectively, $P < .0001$). Among whites, ages of men and women were similar (men: 67 ± 14 years vs women: 67 ± 17 years, $P = .86$). However, among Asians, men were significantly younger than women (men: 63 ± 16 years vs women: 70 ± 17 years, $P < .0001$). Among NHOPI, ages of men and women were similar (men: 53 ± 15 years vs women: 56 ± 17 years, $P = .34$), although NHOPI group overall had significantly younger age compared to whites and Asians (NHOPI: 54 ± 16 years vs whites: 67 ± 15 years, $P < .0001$; vs Asians: 66 ± 17 , $P < .0001$).

Conclusions: Overall, men have younger age of ICH presentation than women. However, this observed gender difference was most significant among Asians, but not among whites or NHOPI.

Introduction

Spontaneous intracerebral hemorrhage (ICH) is a hemorrhagic stroke with high morbidity and mortality, and accounts for 10-15% of the approximately 700,000 annual strokes in the United States.¹⁻³ Recent studies have shown that minorities such as African Americans, Native Hawaiian/other Pacific Islanders (NHOPI), and some Asians with ICH are younger and have higher cardiovascular risk factors compared to whites with ICH.⁴ Furthermore, younger minorities with ICH have been reported to have worse outcomes compared to whites.⁵⁻⁷ In addition to racial disparities, studies have shown gender disparities—men having higher incidence of ICH compared to women.^{8,9} However, the variation of gender differences for each racial group with ICH have not been adequately studied. This study sought to assess the gender differences in the clinical characteristics for the entire ICH population and for each major racial group that were hospitalized at a tertiary stroke center on O'ahu.

Methods

The Queen's Medical Center (QMC) Research and Institutional Review Committee approved to conduct this retrospective study of all spontaneous ICH patients hospitalized at QMC between January 1, 2006 and December 31, 2013. QMC is a 505-bed medical center located in Honolulu, O'ahu, and the largest hospital in Hawai'i. During the study period, QMC was the

only Joint Commission-certified Primary Stroke Center, the only American College of Surgeons-verified trauma center with full neurosurgical coverage, and the only dedicated NSICU in the state of Hawai'i.

Patients

All patients hospitalized at QMC between January 1, 2006 and December 31, 2013 with a diagnosis of spontaneous ICH were retrospectively identified using the institution's stroke database. Case ascertainment of admissions for ICH was conducted by prospective clinical identification and retrospective verification by a review of electronic medical record (Epic). Patients with ICH related to trauma, ruptured cerebral aneurysm or ischemic stroke with hemorrhagic conversion were excluded since these conditions are managed differently from spontaneous ICH.

Data Collection

Patient demographics and medical history, including history of hypertension, diabetes mellitus, atrial fibrillation/atrial flutter, coronary artery disease (CAD) or prior myocardial infarction (MI), and smoking, were obtained from the database. Initial Glasgow Coma Scale score and coagulopathy were obtained from the electronic medical record. Coagulopathy was defined as the initial international normalized ratio > 1.4 . All initial head computed tomography scans were retrospectively reviewed by a board-certified neurologist/neurointensivist using a standardized protocol, blinded to race, gender and clinical data. Hematoma volume was measured using the ABC/2 method.¹⁰ Presence of intraventricular hemorrhage (IVH) was recorded, and ICH location was coded as basal ganglia, lobar, thalamus, brainstem, cerebellar or primary IVH.

Race and ethnicity information were collected by administrative personnel during the registration process or by the nurses during the intake process on admission. Race was categorized as NHOPI, Asian, or white, black or "other" race. Due to the low number of black patients in Hawai'i, this racial group was combined with the "other" group in subsequent analyses. Since mixed racial background is relatively common in Hawai'i, race was defined as the racial/cultural background that the patient most closely associated with, and was based on patient self-identification or family's identification if the patient was incapacitated.

Statistical Analysis

Data were analyzed using SPSS (SPSS 22.0, IBM SPSS Inc., New York, USA). Patient characteristics were summarized using descriptive statistics appropriate to variable type. The NHOPI

and Asian racial groups were compared to white subjects (used as the reference group) using chi-squared test for categorical data and 2-tailed t-test for normally distributed, continuous variables. Age of presentation of intracerebral hemorrhage was compared between men and women among the entire cohort, and within each of the major racial groups. Data are presented as means \pm SD, and levels of $P < .05$ were considered statistically significant.

Results

A total of 825 spontaneous ICH patients hospitalized at QMC between 2006 and 2013 were initially identified. Among them, 34 patients with “other” race were excluded for the analysis. As a result, a total of 791 patients (NHOPI 19%, Asians 65%, whites 16%) were included in the final analyses. The clinical characteristics of ICH patients by gender are shown in Table 1. Overall, men were younger compared to women (62 ± 16 years vs 67 ± 18 years respectively, $P < .0001$). Men had a higher incidence of smoking as compared to women (36% vs 22% respectively, $P < .0001$). There were no other significant differences in risk factors between men and women overall.

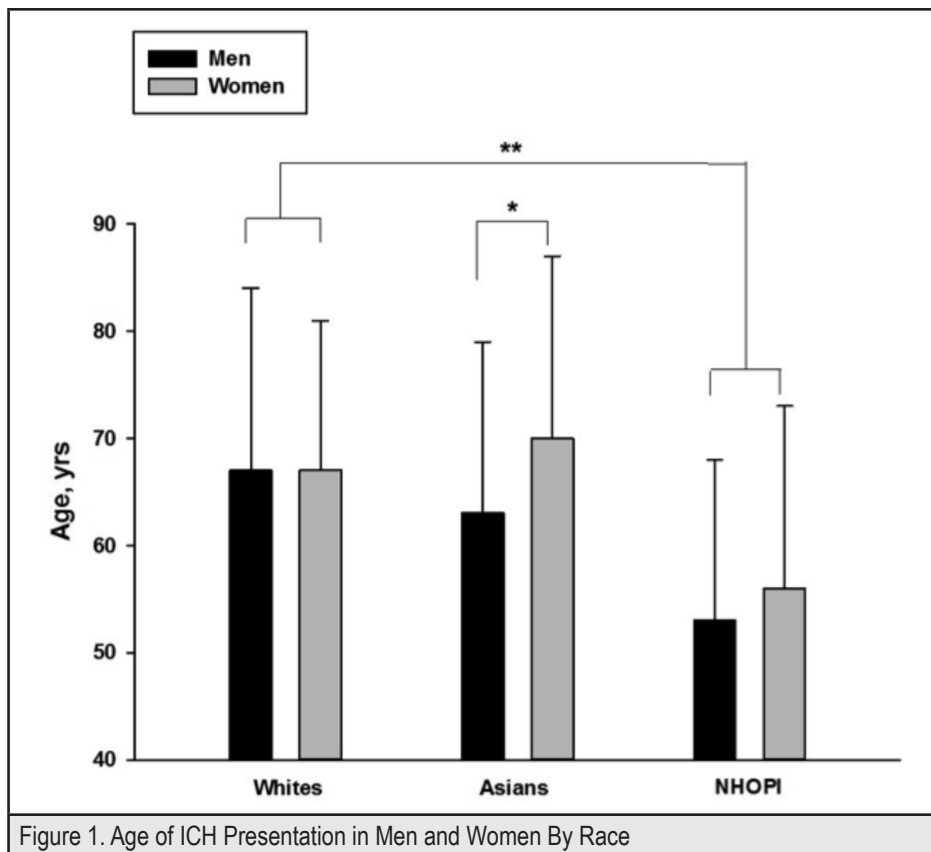
	Men (N = 447)	Women (N = 344)	P
Age, years	62 \pm 16	67 \pm 18	<.0001
Race			.41
Whites	79 (18)	49 (14)	
Asians	282 (63)	229 (67)	
NHOPI	86 (19)	66 (19)	
Risk factors			
Hypertension	360 (81)	258 (75)	.06
Diabetes mellitus	122 (27)	77 (22)	.12
Hypercholesterolemia	171 (38)	123 (36)	.47
Coronary artery disease or prior MI	63 (14)	36 (11)	.13
Atrial fibrillation	63 (14)	44 (13)	.60
Coagulopathy	53 (12)	42 (12)	.88
Smoking	162 (36)	76 (22)	<.0001
Hematoma location			.02
Basal ganglia	148 (33)	107 (31)	
Thalamus	94 (21)	45 (13)	
Lobar	122 (27)	122 (36)	
Brainstem	24 (6)	17 (5)	
Cerebellum	45 (10)	36 (10)	
Primary IVH	14 (3)	17 (5)	
Any IVH	209 (47)	147 (43)	.26
Hematoma volume (cm ³)	34 \pm 45	36 \pm 47	.57
Hospital length of stay, days	11 \pm 17	9 \pm 11	.008
Mortality	107 (24)	92 (27)	.37

NHOPI, Native Hawaiians and other Pacific Islanders; MI, myocardial infarction; IVH, intraventricular hemorrhage. Data are presented as mean \pm SD or n (%).

The gender comparison for each racial group is shown in Table 2. Among whites, the mean age of men and women were not significantly different (men: 67 ± 14 years vs women: 67 ± 17 years, $P = .86$). Among Asians, men were significantly younger than women (men: 63 ± 16 years vs women: 70 ± 17 years, $P < .0001$) (Figure 1). Among NHOPI, mean age of men and women was similar (male: 53 ± 15 years vs female: 56 ± 17 years, $P = .34$), although the NHOPI group overall was significantly younger at age of spontaneous ICH as compared to whites and Asians (NHOPI: 54 ± 16 years vs whites: 67 ± 15 years, $P < .0001$; vs Asians: 66 ± 17 , $P < .0001$) (Figure 1).

	Men	Women	P
Whites (N = 128)			
N	79	49	
Age, years	67 \pm 17	67 \pm 14	.86
Hypertension	57 (72)	30 (61)	.20
Diabetes mellitus	15 (19)	8 (16)	.70
Hypercholesterolemia	34 (43)	17 (35)	.35
Coronary artery disease or prior MI	22 (28)	3 (6)	.003
Atrial fibrillation	17 (22)	11 (22)	.90
Coagulopathy	13 (17)	7 (14)	.74
Smoking	30 (38)	9 (18)	.02
Asians (N = 511)			
N	282	229	
Age, years	63 \pm 16	70 \pm 17	<.0001
Hypertension	234 (83)	177 (77)	.11
Diabetes mellitus	75 (27)	45 (20)	.07
Hypercholesterolemia	110 (39)	87 (38)	.81
Coronary artery disease or prior MI	31 (11)	23 (10)	.73
Atrial fibrillation	35 (12)	25 (11)	.60
Coagulopathy	29 (10)	24 (11)	.94
Smoking	98 (35)	43 (19)	<.0001
NHOPI (N = 152)			
N	86	66	
Age, years	53 \pm 15	56 \pm 17	.34
Hypertension	69 (80)	51 (77)	.66
Diabetes mellitus	32 (37)	24 (36)	.92
Hypercholesterolemia	27 (31)	19 (29)	.73
Coronary artery disease or prior MI	10 (12)	10 (15)	.52
Atrial fibrillation	11 (13)	8 (12)	.90
Coagulopathy	11 (13)	11 (17)	.50
Smoking	34 (40)	24 (36)	.69

NHOPI, Native Hawaiians and other Pacific Islanders; MI, myocardial infarction. Data are presented as mean \pm SD or n (%).



Discussion

This multi-ethnic ICH study demonstrated that men with ICH are younger than women with ICH, which is consistent with prior studies.^{8,9} However, this gender difference in age was mainly driven by the Asian group and not by whites or NHOPI.

Gender differences in age of presentation have been reported in other cardiovascular diseases. For example, women have been shown to develop coronary heart disease 10-15 years later than men.¹¹ Similarly, women have been shown to develop atrial fibrillation at an older age compared to men who develop atrial fibrillation.¹²

Reasons for gender disparities in cardiovascular diseases are complex, and likely involve both biological and social determinants of the disease. Hormonal differences in men and women have been shown to account for some of the gender disparities. Estrogen is known to be cardioprotective in a number of ways.¹³ In animal studies, estrogen inhibits formation of atherosclerotic plaque via suppressing proliferation of smooth muscle cells, decreasing lipoprotein(a) sequestration and oxidation as well as preventing platelet thrombi formation.^{14,15} Androgens, on the other hand, increase proliferation of smooth muscle cells,¹⁶ which may hasten the progression of atherosclerosis. Sex hormones affect cerebrovascular pathways as well. Estrogen influences cerebral vascular reactivity by increasing the production of and the sensitivity to vasodilatory factors,¹⁷⁻¹⁹ thus decreasing vascular tone. In comparison, androgens increase vascular tone.²⁰⁻²² Estrogen shifts the balance

of prostanoid production toward vasodilatory factors such as prostacyclin (PGI₂); testosterone, on the other hand, shifts the balance toward vasoconstrictors such as thromboxane.¹² Estrogen has also been shown to be neuroprotective by improving blood flow during and after ischemic cerebrovascular events.²³⁻²⁵

Although these biological differences may have contributed to the disparities seen in this study, differences in social and behavioral factors such as diet, lifestyle, and medication compliance may have also affected the gender differences. Since the gender difference was more significant among one ethnic group compared to other groups, more non-biological factors such as cultural factors may have accounted for our observation. Longitudinal studies demonstrate that gender is an important predictor of healthcare utilization; women utilize health services more frequently than men do.²⁶ For example, women in the United Kingdom are twice as likely to have visited their primary care physician within the last year compared to men.²⁷ Similarly, men may be more reluctant than women to consult a physician,^{28,29} putting them at risk of delayed diagnosis and treatment. Men tend to use emergency services more often than women, whereas women make use of preventive services more often than men.³⁰ Along with utilizing more primary care services as compared to men, it has been shown that women implement lifestyle changes according to dietary recommendations more so than their male counterparts.³¹ Research demonstrates that women with heart failure were more adherent to a salt-restricted diet compared to men.³²

Unfortunately, there is paucity of data on gender disparities in healthcare access and outcome among Asian Americans. One study showed that Chinese immigrant men were less likely to be adherent to their hypertensive medications compared to Chinese immigrant women.³³ Further research is needed to thoroughly assess the underlying causes of the gender disparities found within the Asian American population.

This study has several limitations. First, the data is derived from a single-center study and thus may lack generalizability. Second, because our institution is a tertiary referral center, there may have been a referral bias toward more severe ICH patients as ICH patients with small hematomas and minor neurologic symptoms may not be transferred to our facility. It is also possible that some of the older ICH patients with preexisting do-not-resuscitate orders or those with terminal illness may not have been transferred to our facility, creating a possible selection bias toward younger ICH patients. Lastly, Asian race was not further specified (ie, Japanese, Filipino, Chinese, Korean) and thus it is unclear if similar age and gender disparities exist within each specific Asian race.

This study demonstrates not only racial disparities in stroke risk factors, but also gender disparities in stroke risk factors in the state of Hawai'i, which have not been previously studied. Further studies are needed to determine factors contributing to the gender disparity in this multi-ethnic population.

Conflict of Interest

None of the authors identify any conflict of interest. Funding: This study was supported in part by the National Institute on Minority Health and Health Disparities of the National Institutes of Health (P20MD000173). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health.

Authors' Affiliations:

- John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (AG, KN)
 - Neuroscience Institute, The Queen's Medical Center, Honolulu, HI (SLK, KN)

Correspondence to:

Kazuma Nakagawa MD; The Queen's Medical Center, Neuroscience Institute, 1301 Punchbowl St., Honolulu, HI 96813;
 Email: kazuma.nakagawa@hawaii.edu

References

- van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol.* 2010;9:167-76.
- Elijovich L, Patel PV, Hemphill JC 3rd. Intracerebral hemorrhage. *Semin Neurol.* 2008;28:657-67.
- Qureshi AI, Mendelow AD, Hanley DF. Intracerebral hemorrhage. *Lancet.* 2009;373:1632-44.
- Nakagawa K, Koenig MA, Seto TB, Asai SM, Chang CW. Racial disparities among Native Hawaiians and Pacific Islanders with intracerebral hemorrhage. *Neurology.* 2012;79:675-80.
- Stansbury JP, Jia H, Williams LS, Vogel WB, Duncan PW. Ethnic disparities in stroke: epidemiology, acute care, and postacute outcomes. *Stroke.* 2005;36:374-86.
- Sacco RL, Boden-Albala B, Gan R, et al. Stroke incidence among white, black and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidemiol.* 1998;147:259-68.
- Sacco RL, Boden-Albala B, Gan R, et al. Race-ethnic disparities in the impact of stroke risk factors: the Northern Manhattan Stroke Study. *Stroke.* 2001;32:1725-31.
- Rincon F, Mayer SA. The epidemiology of intracerebral hemorrhage in the United States from 1979 to 2008. *Neurocrit Care.* 2013;19:95-102.
- Sankalp G, Caplan LR, James ML. Sex differences in incidence, pathophysiology, and outcome of primary intracerebral hemorrhage. *Stroke.* 2015;46:886-92.
- Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke.* 1996;27:1304-5.
- Rossouw, Jacques E. Hormones, genetic factors, and gender differences in cardiovascular disease. *Cardiovascular Research.* 2002;53:3:550-557.
- Humphries, Karin H., et al. New-onset atrial fibrillation sex differences in presentation, treatment, and outcome. *Circulation.* 2001;103:19:2365-2370.
- Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *New Engl J Med.* 1999;340:1801-1811.
- Nathan L, Chaudhuri G. Estrogens and atherosclerosis. *Annu Rev Pharmacol Toxicol.* 1997;37:477-515.
- Haast, Roy AM, Deborah R. Gustafson, and Amanda J. Kiliaan. Sex differences in stroke. *Journal of Cerebral Blood Flow & Metabolism.* 2012;32:12:2100-2107.
- Chrissobolis S, Budzyn K, Marley PD, and Sobey CG. Evidence that estrogen suppresses rho-kinase function in the cerebral circulation in vivo. *Stroke.* 2004;35:2200-2205.
- Chrissobolis S, Sobey CG. Influence of gender on K-induced cerebral vasodilatation. *Stroke.* 2004;35:747-752.
- Geary GG, Krause DN, Duckles SP. Estrogen reduces mouse cerebral artery tone through endothelial NOS- and cyclooxygenase- dependent mechanisms. *Am J Physiol Heart Circ Physiol.* 2000;279:H511-H519.
- Geary GG, Krause DN, Duckles SP. Estrogen reduces myogenic tone through a nitric oxide-dependent mechanism in rat cerebral arteries. *Am J Physiol Heart Circ Physiol.* 1998;275:H292-H300.
- Geary GG, Krause DN, Duckles SP. Gonadal hormones affect diameter of male rat cerebral arteries through endothelium-dependent mechanisms. *Am J Physiol Heart Circ Physiol.* 2000;279:H610-H618.
- Gonzales RJ, Ghaffari AA, Duckles SP, and Krause DN. Testosterone treatment increases thromboxane function in rat cerebral arteries. *Am J Physiol Heart Circ Physiol.* 2005;289:H578-H585.
- Gonzales RJ, Krause DN, and Duckles SP. Testosterone suppresses endothelium-dependent dilation of rat middle cerebral arteries. *Am J Physiol Heart Circ Physiol.* 2004;286: H552-H560.
- Carswell HV, Anderson NH, Morton JJ, McCulloch J, Dominiczak AF, and Macrae IM. Investigation of estrogen status and increased stroke sensitivity on cerebral blood flow after a focal ischemic insult. *J Cereb Blood Flow Metab.* 2000;20:931-936.
- He Z, He YJ, Day AL, and Simpkins JW. Proestrus levels of estradiol during transient global cerebral ischemia improves the histological outcome of the hippocampal CA1 region: perfusion-dependent and independent mechanisms. *J Neuro Sci.* 2002;193:79-87.
- Hurn PD, Littleton-Kearney MT, Kirsch JR, Dharmarajan AM, and Traystman RJ. Postischemic cerebral blood flow recovery in the female: effect of 17 beta-estradiol. *J Cereb Blood Flow Metab.* 1995;15: 666-672.
- Green CA, Clyde RP. Gender, psychosocial factors and the use of medical services: a longitudinal analysis. *Social Science & Medicine.* 1999;48.10:1363-1372.
- Office for National Statistics. General Lifestyle Survey: a report on the 2009 General Lifestyle Survey. In: Dunstan S. ed. London: Office for National Statistics 2011.
- Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. *J Adv Nurs.* 2005;49:616-23.
- Townsend A, Wyke S, Hunt K. Frequent consulting and multiple morbidity: a qualitative comparison of 'high' and 'low' consulters of GPs. *Fam Pract.* 2008;25:168-75.
- Redondo-Sendino, Áurea, et al. Gender differences in the utilization of health-care services among the older adult population of Spain. *BMC Public Health.* 2006;6.1:155.
- Fagerli RA, Wandel M. Gender Differences in Opinions and Practices with Regard to "a Healthy Diet". *Appetite.* 1999;32.2:171-190.
- Chung ML, et al. Gender differences in adherence to the sodium-restricted diet in patients with heart failure. *Journal of Cardiac Failure.* 2006;12.8:628-634.
- Li W, Wallhagen MI, Froelicher ES. Hypertension control, predictors for medication adherence and gender differences in older Chinese immigrants. *Journal of Advanced Nursing.* 2008;61.3:326-335.