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Demographic Risk Factors for Vascular Lesions as Etiology of Intraventricular Hemorrhage in Prospectively Screened Cases

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Abstract

Background—Spontaneous intraventricular hemorrhage (IVH) is associated with high rates of morbidity and mortality despite critical care and other advances. An important step in clinical management is to confirm/rule out an underlying vascular lesion, which influences further treatment, potential for further bleeding and prognosis. Our aim is to compare demographic and clinical characteristics between IVH patients with and without an underlying vascular lesion, and among cohorts with different vascular lesions.

Methods—We analyzed prospectively collected data of IVH patients screened for eligibility as part of the Clot Lysis: Evaluation Accelerated Resolution of Intraventricular Hemorrhage-CLEAR Phase III clinical trial. The trial adopted a structured screening process to systematically exclude patients with an underlying vascular lesion as etiology of IVH. We collected age, sex, ethnicity and primary diagnosis on these cases and vascular lesions were categorized prospectively as aneurysm, vascular malformation (arteriovenous malformation, dural arteriovenous fistula, cavernoma), Moyamoya disease or other vascular lesion. We excluded cases < 18 or > 80 years of age. Baseline characteristics were compared between the CLEAR group (IVH screened without vascular lesion) and the group of IVH patients screened and excluded from CLEAR because of an identified vascular lesion. We further analyzed the differential demographic and clinical characteristics among subcohorts with different vascular lesions.

Results—10,538 consecutive IVH cases were prospectively screened for the trial between 2011 and 2015. 496 cases (4.7%) screened negative for underlying vascular lesion, met the inclusion criteria and were enrolled in the trial (no vascular etiology group), and 1,205 cases (11.4%) were concurrently screened and excluded from the trial because of a demonstrated underlying vascular

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lesion (vascular etiology group). Cases with vascular lesion were less likely to be older than 45 years of age (OR 0.28 CI 0.20–0.40), African-American (OR 0.23 CI 0.18–0.31) or male (OR 0.48 CI 0.38–0.60), and more likely to present with primary IVH (OR 1.85 CI 1.37–2.51) compared to those with no vascular etiology ($p<0.001$). Other demographic factors were associated with specific vascular lesion etiologies. A combination of demographic features increases the association with the absence of vascular lesion, but not with absolute reliability (OR 0.1, CI 0.06–0.17, $p<0.001$).

Conclusion—An underlying vascular lesion as etiology of intraventricular hemorrhage cannot be excluded solely by demographic parameters in any patient. Some form of vascular imaging is necessary in screening patients before contemplating interventions like intraventricular fibrinolysis, where safety may be impacted by the presence of vascular lesion.

Keywords

Intraventricular hemorrhage; Risk Factors; Etiology; Screening; Cerebral angiography

INTRODUCTION

Intraventricular hemorrhage (IVH) is a distinct subtype of intracerebral hemorrhage that results from blood gaining access to (or, less commonly, arising within) the brain ventricles [1]. The condition is invariably associated with high risk of mortality and poor functional outcome despite advances in clinical practice [2–8].

The presence of an underlying vascular lesion is important for prognosis, estimating risk of re-bleeding which consequently dictates further management in ICH/IVH such as the decision and timing for surgical and/or endovascular interventions. Other aspects of patient management are also influenced by the presence or absence of an unsecured vascular lesion, including blood pressure control, and prophylactic or therapeutic anticoagulation for venous or cardiogenic thromboembolism[9–14].

Guidelines for the selection of patients with ICH/IVH for vascular etiology screening are lacking. Recommendations by the American Heart Association and European Stroke Organization are based on low levels of evidence [15–17]. The decision about whether and how to deploy vascular imaging varies greatly in current practice [18–20]. The relative contribution of demographic factors to the likelihood of an underlying vascular lesion has not been carefully assessed. We hypothesize that patients with IVH secondary to a vascular lesion have distinctive demographic characteristics which differ according to the pathological nature of the underlying vascular etiology.

METHODS

CLEAR III Trial

The “Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage Phase III” (CLEAR III) clinical trial is an international multicenter double-blinded phase III clinical trial investigating the effect of an intraventricular recombinant tissue plasminogen activator (alteplase) on outcomes in patients with IVH. The methodology and results of the

trial have been published [21,22]. Approximately 75 study centers throughout the U.S., Canada and Europe participated in enrolling 500 subjects for the trial between April 2009 and January 2015. Patients presenting with supratentorial IVH who met the inclusion criteria were recruited through sites' emergency departments, neurological ICUs and clinical stroke services and underwent a detailed screening process to confirm the absence of other exclusion criteria, including a structural vascular lesion as etiology of hemorrhage. This utilized computed tomographic angiography (CTA) as the default modality, or magnetic resonance angiography (MRA)/magnetic resonance imaging (MRI) in cases unable to receive iodinated contrast agent, as per CLEAR III protocol. A catheter cerebral angiogram was used in young patients, atypical bleeds, or with suspect findings on CTA, MRA or MRI with two step decision making by the site and then under advisement from the CLEAR III Surgical Center. Each participating site recorded inclusion/exclusion information about all screened patients into the VISION web-based electronic case report form (eCRF) system, which was then confirmed centrally by the trial's Surgical and Reading centers [21].

Patients and Methods

This is a retrospective case-controlled analysis of prospectively collected data of IVH patients screened for eligibility as part of the CLEAR III clinical trial. The study was approved by the institutional review board of respective participating sites and conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA). We considered all patients who tested negative on vascular imaging and subsequently enrolled in the trial as the group with no vascular etiology. We identified cases where reason(s) of exclusion was documented as "Aneurysm, mycotic aneurysm, Moyamoya, vascular malformation, etc." or "Other" (Reason for exclusion is recorded as "Other" when a patient failed to satisfy one or more inclusion criteria and/or had one or more exclusion criteria). Other than harboring a structural vascular lesion, exclusionary criteria from CLEAR included infra-tentorial hemorrhage, systemic coagulopathy, ongoing internal bleeding, pregnancy, participation in another medical investigation or clinical trial and lack of subject or legal representative to give written informed consent. All cases were then manually screened to exclude patients with no documentation of an identified vascular lesion confirmed on further imaging studies through the screening process (Figure 1). The group with vascular etiology was ultimately defined as IVH patients who were excluded from the trial after confirmation of a distinct structural etiology on vascular imaging studies. We included one case enrolled into the trial and later found on subsequent imaging to harbor Moyamoya disease. In both groups, subjects outside the age range 18–80 years (n=24) were excluded for consistency, resulting in 496 cases in the group with no vascular etiology group and 1,205 cases in the group with vascular etiology (4.7% and 11.4% of 10, 538 patients screened for the trial, respectively).

For all patients in our analysis we collected age, sex, ethnicity and primary diagnosis (i.e. primary IVH or IVH with ICH). Age was used as a continuous variable in comparing baseline demographic characteristics and as a binary variable for logistic regression with a cut-off age of less than or equal to 45 years in accordance with relevant literature [19]. Vascular lesions were categorized as aneurysm, vascular malformations (arteriovenous malformation, dural arteriovenous fistula, cavernoma or non-specified vascular

malformation), or Moyamoya disease. Baseline characteristics of the two groups were directly compared to identify any associated demographic patterns. In the vascular etiology group, we further analyzed the baseline characteristics between subgroups with different vascular lesions.

Statistical Analyses

All statistical analyses were performed using STATA12 (StataCorp LP, College Station, Texas). To compare baseline demographic characteristics, Student's t test was used for continuous variables and Chi square test was used for categorical variables. Logistic regression was used to investigate the association between vascular etiology and variables of interest. Multinomial logistic regression was applied to test the association between vascular lesions as etiology and variables of interest. Forward stepwise method was performed to assess combined effects with a significance level of 0.05 for both variable entry and retention.

RESULTS

Study and Patient Characteristics

Our final analysis was therefore based on 1,701 IVH patients comprising a group with no structural vascular etiology (*No Vascular Etiology*, n=496) and those harboring a culprit vascular lesion (*Vascular etiology*, n=1,205). Demographic characteristics of the two groups are summarized in Table 1. The most common lesions diagnosed throughout the screening process were cerebral aneurysms (n=835) followed by vascular malformations (n=320) and Moyamoya disease (n=35). In three cases the vascular etiology could not be classified further. Imaging modalities used for vascular etiology screening of enrolled subjects comprised CTA (n=404, 81%), MRI (n=45, 9%), MRA/V (n=37, 7%) and formal catheter angiography (n=65, 13%).

The vascular etiology group was significantly younger and more likely to be female. While an ICH was very common in both groups, IVH secondary to vascular etiology was less likely to be associated with intracerebral hemorrhage (primary IVH was more prevalent in cases with vascular etiology). Racial distribution revealed a marked prevalence of African-American patients in the IVH group lacking a structural etiology (Table 1).

Differential demographic characteristics were compared within the vascular etiology group among different vascular lesions (Table 2). Patients with cerebral aneurysm were older compared to vascular malformation and Moyamoya disease (mean age 57.9 vs 46.9 vs 44.2, $p<0.001$); they also exhibited the strongest female predominance (66.2% vs 45.4% vs 60.0%, $p<0.001$). Racial distribution among patients with cerebral aneurysm and vascular malformation were very similar. In both groups there was a predominance of Whites, constituting a little over two thirds of cases, followed by a very close prevalence of patients of African-American and Hispanic ethnicity. Excluding other minor ethnicities, Asian patients were the least prevalent, comprising roughly one-thirtieth of patients. Moyamoya patients in contrast had a distinctively different racial distribution. Compared to other vascular etiologies, Moyamoya had a significantly higher prevalence of Asians (OR 8.4

p<0.0001) and, to a lesser extent, African-Americans (OR 2.3 p=0.03). Conversely the Moyamoya showed the least prevalence of Hispanic (OR 0.4 p=0.22) and White patients (OR 0.4, p=0.003). Finally, patients with Moyamoya disease were significantly more likely to present with primary IVH compared to other vascular lesions (45.5% vs 21.0% and 23.4%, p=0.01). (Table 2)

Logistic regression analysis for the presence of structural vascular etiology revealed a strong association with some of the demographic characteristics, p=0.001 (Table 3). Such association was strongest with age < 45, female gender, and non-AA ethnicities. Whites, on the other hand, exhibited a subtle predilection to harboring a vascular lesion. Likewise, subjects presenting with primary IVH were more likely to have an underlying lesion compared to those with associated overt ICH. These variables retained their significance after multivariate modeling. Baseline characteristics having the weakest correlation with vascular etiology were combined to identify a cohort of IVH patients with the least likelihood of harboring an underlying structural etiology. The combined cohort consisted of African-American, male patients, aged > 45 years and presenting with overt ICH associated IVH. This group was found to have the least likelihood of harboring a structural vascular etiology. Nevertheless, even within this group of combined demographics, there were still non-negligible odds of harboring a vascular etiology (Figure 2).

DISCUSSION

A systematic review of published literature recently compiled by Cordonnier, et al. in 2010 included 20 studies (n=1,933) and addressed the utilization of vascular imaging in the investigation of ICH [23]. The review highlighted the paucity of data, preponderance of selection bias, and small sample sizes, limiting the generalizability of most studies. Yet roughly one third of cases in that review had an AVM or aneurysm. Decisions about whether and how to deploy vascular imaging after diagnostic plain CT to determine ICH cause were generally based on patient's age, ICH location and pre-stroke hypertension, hence introducing significant biases regarding true rates of vascular etiologies and their demographic associations. Other studies have advocated that harboring a vascular etiology is exceptionally rare in the elderly, especially in the context of a deep ICH and history of hypertension [24,25]. Our study aimed primarily at addressing the relative prevalence of demographic features (age, sex and ethnicity) in cases with and without vascular etiology in association with IVH, subjected to systematic screening for vascular etiology (Figure 3).

Pattern of bleeding on initial non-contract CT scan is pivotal in triaging patients for angiography but remains far from being conclusive. In a study by Delgado Almandoz et al, 179 Plain CT scans were categorized as "low-probability" for vascular etiology by 2 blinded neuroradiologists, 4 of which (2.2%) were later found to harbor a lesion. More than two thirds of plain CT scans in the study were deemed indeterminate (n=421), 17.1% of these cases were later found to have an underlying vascular etiology [19]. In our study, diagnostic and stability CT images of all cases enrolled in the CLEAR III trial were reviewed through the trial Surgical Center led by the senior author (IAA) to recommend cases for more rigorous vascular etiology screening if there was a suspicious pattern of bleeding. But we could not assess the relative roles of individual screening modalities (CTA versus MRA, nor

the role of MRI and catheter DSA) as a range of options were allowed in the study protocol, deployed per clinician judgment, with guidance by the trial's Surgical Center, and we did not have access to all imaging features of cases excluded from the trial.

Previous reports on the prevalence of vascular malformation in ICH range from 5% to as high as 23% depending on the study design and target population [26,27]. In our study almost 11% of screened patient were excluded from CLEAR III for harboring a vascular malformation (7.9% Aneurysms, 3% AVM and 0.3% Moyamoya disease). Though in keeping with previous studies, these figures should be interpreted with caution since vascular imaging was not systemically applied to all screened cases, and some cases were excluded for other reasons (e.g. death, poor functional scores, withdrawal of consent, etc.) before undergoing etiology screening. Our study recruited subjects from multiple centers around the world, hence the threshold of vascular screening and the choice of modalities were undoubtedly influenced by different local practices.

We also did not have access to systematic past medical histories of excluded cases so we could not address other potential factors such as history of hypertension (and its treatment), smoking, and drug or anticoagulant use, in the excluded cohort. Other cases excluded during the screening process, for causes other than vascular etiology, were not included in our analysis, hence our demographic associations only apply to cases who met all criteria for CLEAR III (with definite exclusion of vascular etiology) versus those excluded for definite vascular etiology. And as with all such studies, screening may not have identified angiographically occult vascular etiologies such as cavernous malformations.

Despite these limitations, the strength of this study lies primarily in the number of cases of IVH with and without etiology, identified concurrently at 73 sites worldwide, based on a common strategy of screening all potential trial cases for vascular etiology. The differences in demographic features between groups with and without vascular etiology, and among cohorts with vascular etiology, could not otherwise be gleaned in smaller or single site series.

We demonstrated that being younger, female sex, white race and primary IVH are significantly more prevalent among patients with vascular etiology than without. Our findings also suggest that, in IVH with a structural vascular etiology, patient demographics can help predict the pathological nature of the underlying lesion, particularly Asian ethnicity in association with Moyamoya disease. In this large multinational cohort of IVH patients, there was no combination of demographic features which would predict the presence or absence of vascular etiology with better than 90% reliability. Structural vascular lesions were still encountered in hypertensive elderly patients presenting with deep ICH. An underlying vascular etiology for IVH therefore, cannot be ruled out solely on demographic features in any patient.

The relatively rare primary IVH (without an overt ICH on CT scan), believed to represent 3% of ICH cases [28,29], presents an additional challenge due to a rather similar CT picture regardless of bleeding etiology. Hence clinical suspicion of vascular etiology in primary IVH is more dependent on baseline demographic features than the distribution of blood. Our

findings suggest that primary IVH cases have higher odds of harboring an underlying structural etiology compared to IVH with an intraparenchymal ICH component. Results are in keeping with previous series in literature reporting higher etiologic diagnostic yield in primary IVH ranging between 29–65% [24,30–32].

We have also illustrated that when vascular etiology screening is judiciously utilized, structural vascular lesions can be found in groups of patients formerly believed to be at low-risk of harboring a vascular etiology. No demographic risk factor(s) can be deemed fully exclusionary for vascular etiology. Our findings advocate that alongside sound clinical judgment, some form of routine vascular imaging is likely needed when screening IVH patients before contemplating interventions like intraventricular fibrinolysis.

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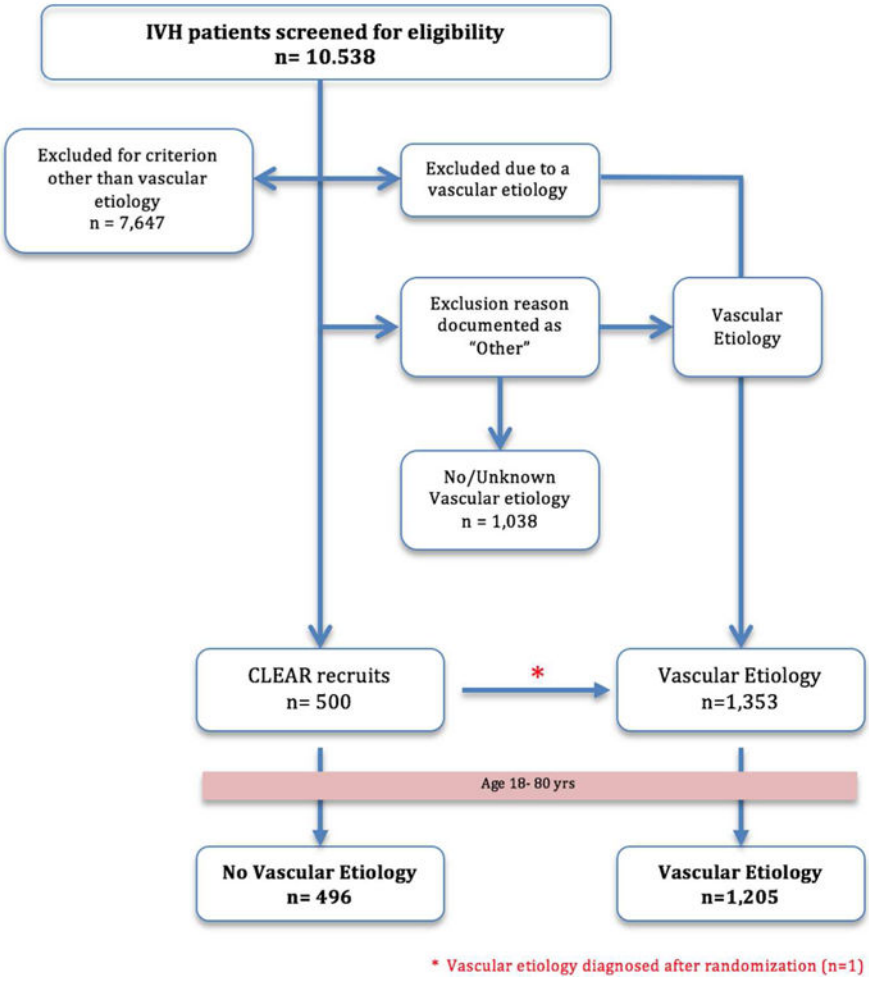

Figure 1.
Breakdown of groups involved in the analysis

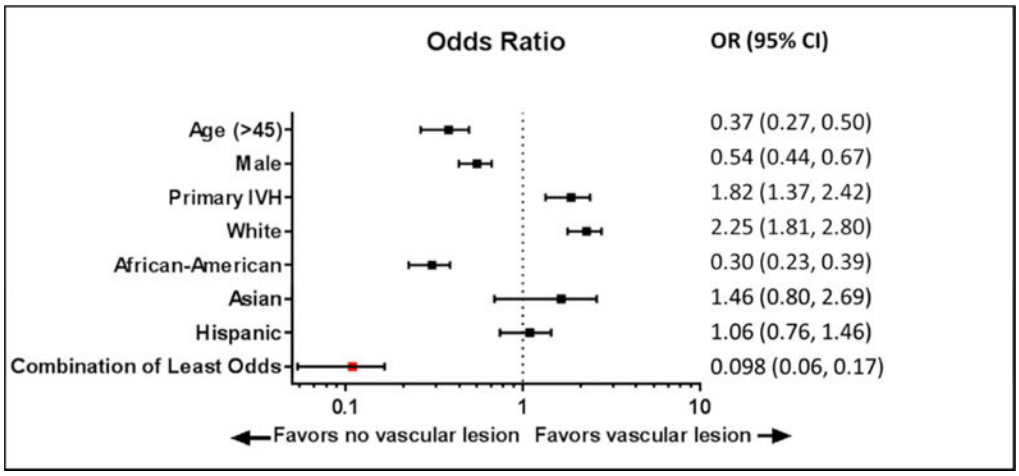

Figure 2.

Forest plot illustration of the impact of different demographic features among cohorts with and without underlying vascular lesion as etiology of IVH

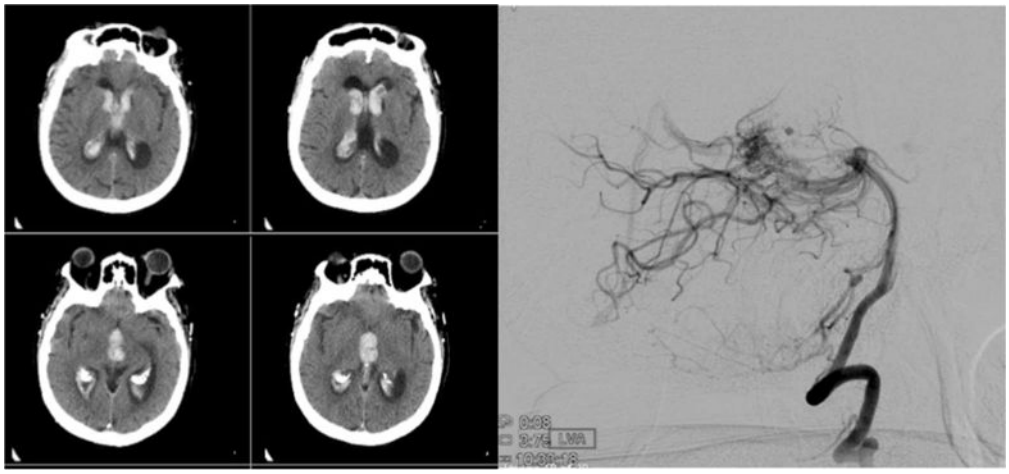

Figure 3. Arteriovenous malformation diagnosed on catheter angiogram during screening in a 78 year old female patient

Angiography was performed in view of suspicious finding on less invasive computed tomographic angiogram (CTA). The appearance of IVH on diagnostic CT scan alone would not have raised suspicion of underlying vascular etiology

Table 1

Demographic features of cases with and without vascular lesion as etiology.

	No Vascular Lesion n=496	Vascular Lesion n=1,205	P
Age (mean)	58.4	53.9	0.001
Male (n, %)	275 (55.4)	483 (40.0)	<0.001
Ethnicity (n, %)			
• **AA**	168 (33.6)	145 (13.1)	<0.001
• **Asian**	14 (2.8)	44 (4.0)	0.38
• **Hispanic**	60 (12.0)	141 (12.8)	0.69
• **White**	252 (50.4)	765 (69.40)	<0.001
• **Other**	6 (1.2)	8 (0.7)	0.34
Primary IVH (n, %)	72 (14.4)	260 (23.7)	<0.001
Etiology screening:			
Imaging technique (n, %)			
• **CTA**	404 (81)		
• **MRI**	45 (9)		
• **MRA**	37 (7)		
• **Catheter Angiography**	65 (13)		
Etiology (n, %)			
• **Aneurysm**		835 (68.0)	
• **Vascular Malformation**			
○ **AVM**		320 (26.1)	
○ **dAVF**		13 (1.0)	
○ **CCM**		11 (0.9)	
○ **VM/Galen**		3 (0.2)	
○ **VM:NOS**		3 (0.2)	
• **Moyamoya**		35 (2.9)	
• **Other**			
○ **Vasculitis**		1 (0.08)	
○ **Mycotic Aneurysm**		4 (0.3)	

AA: African-American, Other: American Indian/Alaskan Native, Native Hawaiian/other Pacific Islander, mixed or unknown ethnicity, AVM = arteriovenous malformation, dAVF= dural arteriovenous fistula, CCM = cerebral cavernous malformation, VM = venous malformation, Galen = vein of Galen malformation, VM: NOS = unspecified vascular malformations.

Table 2

Demographic features in cases with different vascular lesions as etiology of IVH

	Cerebral Aneurysm n=835	Vascular Malformation n=350	Moyamoya disease n=35	p
Age (mean)	57.96	46.85	44.14	<0.001
Male (n, %)	282 (33.8)	191 (54.6)	14 (40.0)	<0.001
Ethnicity (n, %)				
• **AA**	90 (11.9)	46 (15.2)	9 (25.7)	0.06
• **Asian**	27 (3.6)	9 (3.0)	8 (22.8)	<0.001
• **Hispanic**	91 (12.0)	45 (14.9)	2 (5.7)	0.01
• **White**	542 (71.6)	204 (67.6)	16 (45.7)	0.002
• **Other**	7 (0.9)	1 (0.3)	0	0.23

AA: African-American, Other: American Indian/Alaskan Native, Native Hawaiian/other Pacific Islander, mixed or unknown ethnicity

Table 3

Logistic regression analysis of demographic features with likelihood of vascular lesion as etiology of IVH.

	Univariate logistic regression		Multivariable logistic regression	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Age (>45)	0.37 (0.27, 0.50)	0.001	0.28 (0.20, 0.40)	<0.001
Gender (Male)	0.54 (0.44, 0.67)	<0.001	0.48 (0.38, 0.60)	<0.001
Primary IVH	1.82 (1.37, 2.42)	<0.001	1.85 (1.37, 2.51)	<0.001
AA	0.27 (0.21, 0.34)	<0.001	0.23 (0.18, 0.31)	<0.001
White	1.65 (1.34, 2.04)	<0.001		
Asian	1.32 (0.71, 2.41)	0.38		
Hispanic	0.94 (0.68, 1.29)	0.69		
Combination	0.10 (0.06, 0.17)	<0.001		

AA: African-American, Combination: Represents the Group with least likelihood (Age >45, Male, African American, IVH associated with ICH),