How Does Preexisting Hypertension Affect Patients with Intracerebral Hemorrhage?

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Background and Purpose: Patients with intracerebral hemorrhage (ICH) frequently present with hypertension, but it is unclear if this is due to pre-existing hypertension (prHTN) or to the bleed itself or associated pain. We sought to assess the relationship between prHTN and admission systolic blood pressure (aBP) and bleed severity. *Methods:* We retrospectively assessed the relationship between prHTN and aBP and NIHSS in patients with ICH at 3 institutions. *Results:* Of 251 patients, 170 (68%) had prHTN based on history of hypertension/antihypertensive use. Median aBP was significantly higher in those with prHTN (155 mm Hg (IQR 135-181) versus 139 mm Hg (IQR 124-158), $P < .001$). Patients with left ventricular hypertrophy (LVH) on electrocardiogram (ECG) or transthoracic echocardiogram (TTE) had significantly higher aBP than those without LVH (median aBP 195 mm Hg (IQR 155-216) for patients with LVH on ECG versus 147 mm Hg (IQR 129-163) for patients with no LVH on ECG, $P < .001$; median aBP 181 mm Hg (IQR 153-214) for patients with LVH on TTE versus 152 mm Hg (IQR 137-169) for patients with no LVH on TTE, $P = .01$). prHTN was associated with a higher median NIHSS (11 (IQR 3-20) for patients with history of hypertension/antihypertensive use versus 6 (IQR 1-14) for patients without this history ($P = .02$); 9 (IQR 3-19) versus 5 (IQR 2-13) for patients with/without LVH on ECG ($P = .085$); and 10 (IQR 5-18) versus 5 (IQR 1-13) for patients with/without LVH on TTE ($P = .046$). *Conclusions:* Patients with ICH who have prHTN have higher aBP and NIHSS, suggesting that prHTN may worsen reactive hypertension in the setting of ICH.

Key Words: Intracerebral hemorrhage—hypertension

Introduction

One clinical sign that helps to distinguish intracerebral hemorrhage (ICH) from ischemic stroke is hypertension.[1,2] While 75% of patients with ischemic and hemorrhagic stroke are hypertensive at the time of presentation, patients with ICH tend to present with significantly higher admission systolic blood pressure (aBP).[3-5] In fact, Fischer et al found that among 653 patients with stroke, those with ICH had a mean aBP of 189 mm Hg, while those with ischemic stroke had a mean aBP of 158 mm Hg ($P < .0001$).[5] In acute ischemic stroke, hypertension can be explained by the body's attempt to optimize perfusion to the stroke bed via the cerebral ischemic response, through mechanisms that remain somewhat unclear.[6-8] In ICH, however, the etiology of hypertension is not always clear. Hypertension can be the cause for ICH, a contributing

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Received September 10, 2018; revision received November 14, 2018; accepted November 21, 2018.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.11.023

factor, or a result of the ICH.[3,5] Pre-existing hypertension (prHTN) is a major risk factor for spontaneous and secondary ICH[4,9-11] and is considered to be the proximal cause in 70%-90% of cases.[12,13] However, it is not fully clear whether hypertension at the time of presentation is the cause or the result of bleeding in many ICH patients, as some studies suggest that hypertension at the time of presentation may be the result of pain, anxiety, or a sympathetic response to the acute rise in intracranial pressure or cerebral ischemia from the bleed itself.[6,8,14-16]

Chronic hypertension can be broken down into stages based on blood pressure at rest, spikes in blood pressure with activity, and the presence or absence of end organ damage; historically, a sustained blood pressure greater than 140/90 (individual systolic, diastolic, or both) was the accepted cutoff for chronic hypertension, although recent data suggested that threshold should be lowered.[17-19] Markers for prHTN include a diagnosis of hypertension, documented elevated blood pressure at 1 or more outpatient appointments, prescriptions for antihypertensives, and presence of left ventricular hypertrophy (LVH) on an electrocardiogram (ECG) or echocardiogram. The relationship between LVH and hypertension has been evaluated in a number of studies.[20-26] Pearson et al found that in comparison with normotensive subjects who had a mean systolic blood pressure (sBP) of 131 mm Hg, significantly more subjects with hypertension (mean sBP of 171 mm Hg) met criteria for LVH on a transthoracic echocardiogram (TTE).[20] Sagie et al found that in comparison with normotensive subjects (defined as sBP <140 mm Hg), subjects with borderline hypertension (defined as sBP 140-159 mm Hg) had significantly thicker left ventricular walls on TTE.[21] Regarding LVH on ECG, a recent meta-analysis of 26 publications found that, while detection of LVH on ECG varied based on methodology, LVH was found in up to 40% of patients with hypertension (sBP >140) and only 18% of normotensive patients.[24] Interestingly, left ventricular changes may begin prior to the onset of clinical hypertension. In a prospective study of 2680 patients from the Framingham Heart Study, Post et al found that left ventricular mass was significantly associated with risk of developing hypertension ($P = .01$); after adjusting for sex, age, systolic and diastolic blood pressures, sBP 8 years earlier, body mass index and alcohol use, the odds ratio for developing hypertension over a 4-year follow-up period was 1.20 for standard deviation increment in left ventricular mass index and 1.16 for 1 standard deviation increment in left ventricular wall thickness.[22]

The relationship between prHTN and hypertension at the time of ICH presentation is poorly understood. Because of this, we sought to establish the relationship between markers of prHTN in patients with ICH and blood pressure on admission. As secondary objectives, we sought to evaluate the relationship between prHTN and (1) imaging characteristics, (2) clinical presentation, and (3) acute antihypertensive requirements.

Methods

Data Collection

We collected data on prHTN for patients over age 18 with nontraumatic ICH who were admitted to Mount Sinai Hospital between April 2008 and December 2011, Cleveland Clinic between February 2013 and June 2016 and NYU Langone Medical Center (NYULMC) between January 2013 and February 2017. The data for patients at Mount Sinai Hospital and Cleveland Clinic were extracted from IRB-approved prospective databases and the data from NYULMC were extracted from an IRB-approved combined retrospective (2013 and 2014) and prospective (2015+) database. Patients were excluded if data on history of hypertension/use of antihypertensive medications or aBP was not available or if they initially presented to another hospital, as they may have received treatment for hypertension before the aBP was recorded. All patients were stratified based on whether or not they had any evidence of prHTN, defined as history of hypertension or use of antihypertensive medications. Because additional data were available in the NYULMC database, these patients were also stratified based on prHTN as defined by (1) presence of LVH on the automated reading of the admission ECG and (2) presence of LVH on a TTE reviewed by a board-certified cardiologist within 6 months of admission.

Extracted data for all patients included age, sex, race, aBP, ICH volume and location, ICH score, ICH mechanism, NIHSS, and presence of prHTN. Additionally, we were able to extract data for patients admitted to NYULMC on nicardipine requirements during the admission. Imaging data, admission NIHSS, and ICH mechanism were recorded for all patients by board-certified neurologists prior to conceptualization of this study.

Data Analysis

Analysis was completed using SPSS Statistics 21. Fisher's exact tests, chi-square tests, likelihood ratios and Mann−Whitney U tests were used as appropriate for data analysis. A P value $< .05$ was considered to be statistically significant.

Results

See Table 1 for demographic data and Figure 1 for data on bleed etiology for the 251 patients included in this study.

prHTN As Defined by History of Hypertension/Use of Antihypertensive Medications

A total of 170 patients (68%) had prHTN based on a history of hypertension or use of antihypertensive medications. Patients with a history of hypertension/use of home antihypertensives had a significantly higher median

Table 1. *Demographics There was a roughly equal distribution of (1) male:female patients, (2) white:nonwhite patients, and (3) lobar:nonlobar bleeds. Nearly two thirds of patients had a known history of HTN/took antihypertensives, but less than a quarter of patients had evidence of LVH on ECG or TTE*

	N = 251
Sex	
Male	129 (51%)
Female	122 (49%)
Age (median)	65 (IQR 53-77)
Race and ethnicity	
White	128 (51%)
Black	43 (17%)
Asian	26 (10%)
Mixed	8 (3%)
Hispanic	37 (15%)
Unknown	9 (4%)
Clinical features	
Home antihypertensive use or history of hypertension	170 (68%)
LVH on ECG	18 (16%)*
LVH on TTE	17 (24%)†
aSBP (median)	151 (IQR 130-173)‡
ICH Volume (median)	17 (IQR 6-50)§
NIHSS (mean)	11.5 (SD 10)
ICH Score (median)	2 (IQR 1-3)‖
Location of bleed	
Brainstem	11 (5%)
Cerebellum	27 (11%)
Lobar	121 (51%)
Deep	69 (29%)
Intraventricular	7 (3%)
Unknown	16 (6%)

Abbreviations: ECG, electrocardiogram; HTN, hypertension; ICH, intracerebral hemorrhage; LVH, left ventricular hypertrophy; TTE, transthoracic echocardiogram.
*ECG results were only available for 110 patients.
†TTE results were only available for 72 patients.
‡sBP was only available for 249 patients.
§Volume was only available for 226 patients.
‖ICH score was only available for 237 patients.

aBP (155 mm Hg (IQR 135-181) versus 139 mm Hg (IQR 124-158), $P < .001$). While there was no significant difference in bleed location based on prHTN using this definition (see Fig 2), of the patients with supratentorial bleeds (lobar or deep), there were significantly more deep bleeds in patients with prHTN using this definition (43% of patients with history of hypertension/use of home antihypertensives who had supratentorial bleeds versus 22% of patients without history of hypertension/use of home antihypertensives, $P = .004$). There was no difference in bleed volume for patients with history of hypertension/home antihypertensive use (17 cm^3 (IQR 5-53) for patients with history of hypertension/home antihypertensive use versus 17 cm^3 (IQR 7-48) for patients without with history of hypertension/home antihypertensive use, $P = .94$). NIHSS on presentation was significantly higher for patients with prHTN using this definition as compared with patients without prHTN, (median NIHSS 11 (IQR 3-20) for patients with history of hypertension/use of home antihypertensives and 6 (IQR 1-14) for patients without history of hypertension/use of home antihypertensives, $P = .02$).

prHTN As Defined by Presence of LVH on ECG

There was ECG data for 110 patients in the NYULMC database, 18 (16%) of whom had LVH on their ECG. There was a significant relationship between the use of home antihypertensives/history of hypertension and LVH on ECG (of the 67 patients with a history of hypertension/antihypertensive use with ECG data, 16 had LVH on ECG (24%, $P = .008$). Patients with LVH on ECG had significantly higher aBP ($P < .001$) and were significantly more likely to have deep bleeds ($P = .017$) and require nicardipine to manage their blood pressure ($P = .018$) than patients who did not have LVH on ECG. See Table 2.

prHTN As Defined by Presence of LVH on a TTE

There were 72 patients in the NYULMC database who had a TTE within 6 months of admission for their ICH; of these, 17 (24%) had LVH on their TTE. There was no correlation between the use of home antihypertensives/history of hypertension and LVH on TTE (of the 53 patients with a history of hypertension/antihypertensive use with TTE data, 15 had LVH (28%, $P = .21$)). There was a significant correlation between the presence of LVH on TTE and LVH on ECG; for those with LVH on TTE, 12 of 17 (71%) also had LVH on ECG whereas only 3 of 54 (6%) without LVH on TTE had LVH on ECG ($P < .001$; 1 patient who had a TTE did not have an ECG). Patients with LVH on TTE had significantly higher aBP ($P = .01$) and NIHSS ($P = .046$) and were more likely to require nicardipine to manage their blood pressure ($P = .016$) than patients who did not have LVH on TTE. See Table 2.

Discussion

prHTN is a major risk factor for ICH,[4] but because hypertension can be the cause, a contributing factor, or a result of ICH, the etiology of presenting HTN in patients with ICH is often unclear.[3,5] We assessed the relationship of prHTN and blood pressure on admission, imaging characteristics, clinical presentation, and acute antihypertensive requirements in patients with ICH. We found that prHTN was associated with higher aBP, more deep bleeds, higher NIHSS, and greater likelihood to require nicardipine.

Markers of prHTN

We used self-reported history of hypertension/use of antihypertensive medications and presence of LVH on ECG and/or TTE as markers of prHTN. Each of these methods is imperfect, however; up to 36% of patients

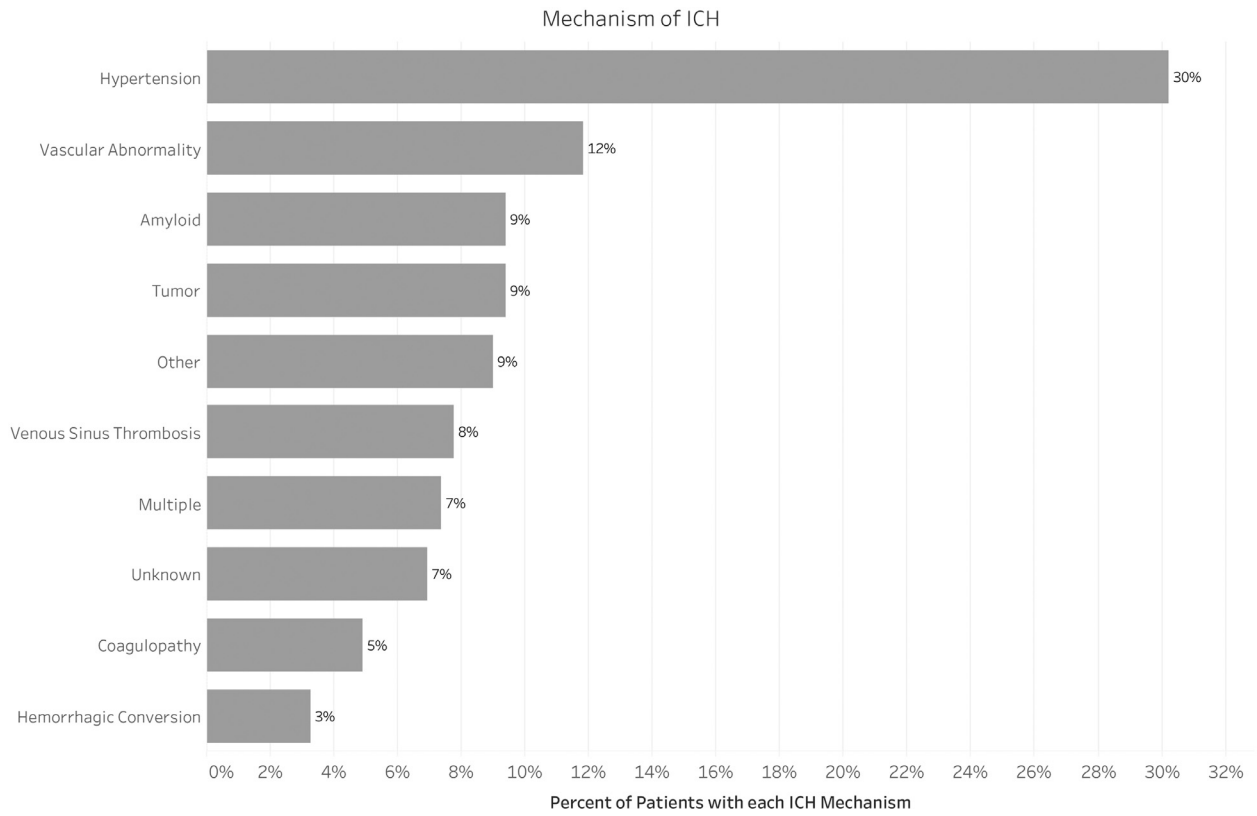

Figure 1. *Mechanisms of ICH.*
This bar graph illustrates the etiology for ICH among all 251 patients. Hypertension was the most common etiology. Abbreviations: ICH, intracerebral hemorrhage.

with hypertension are unaware of their condition, and 25% who are aware of it do not take home antihypertensives.[27,28] Detection of LVH may also vary, as postmortem studies of LVH suggest ECG has a sensitivity of 50% and specificity of 95% while TTE has a sensitivity of 93% and specificity of 95%.[29]

For those patients with ECG and TTE data, we found a significant relationship between the presence of LVH on ECG and LVH on TTE, but not between either of these markers and use of one or more home antihypertensives. History of hypertension/antihypertensive use may not be an accurate surrogate for LVH due to several factors, as LVH has been shown to precede hypertension[22]; even when patients develop elevated blood pressure, it can remain "silent" characterized by under diagnosis, minimal follow-up, and poor medication compliance due to limited symptoms and/or access to medical care.[27,30,31]

While the presence of any of these markers can identify patients with prHTN, it does not credibly establish the severity or degree of control of prHTN; clarifying these differences is critical, as well-controlled prHTN would not be expected to cause or contribute to a bleed. Assessing prHTN severity and control is also complicated by recent guidelines prompting more aggressive use of antihypertensives by lowering the threshold for stage 1 hypertension from a systolic pressure of 140 or above to 130 or above and a diastolic pressure from 90 or above to 80 or above; with this change, nearly half of adults in the United States are now considered hypertensive, meriting pharmacologic intervention.[32,33]

Home antihypertensive use as a marker of prHTN severity is also confounded by noncompliance, or refractory hypertension despite compliance. Multiple studies suggest the rate of noncompliance for antihypertensives—defined as missing more than 1 in 5 doses—can be as high as 45%, for reasons ranging from price to side effects to excessive pill burden. Patients on complex regimens are, unfortunately, the most likely to be both noncompliant and to have severe or difficult to control hypertension.[34-37] Even with compliance, hypertension may be suboptimally controlled, due to either physician therapeutic inertia or, for nearly 20% of patients with prHTN, refractory hypertension despite optimal medical management.[38-40]

prHTN and In-Hospital Blood Pressure

Admission sBP was significantly higher for patients with prHTN using all definitions. For patients with data on in-hospital antihypertensive requirements, those with LVH on ECG or TTE were significantly more likely to require nicardipine and trended toward requiring it for a longer duration. This suggests that patients with ICH

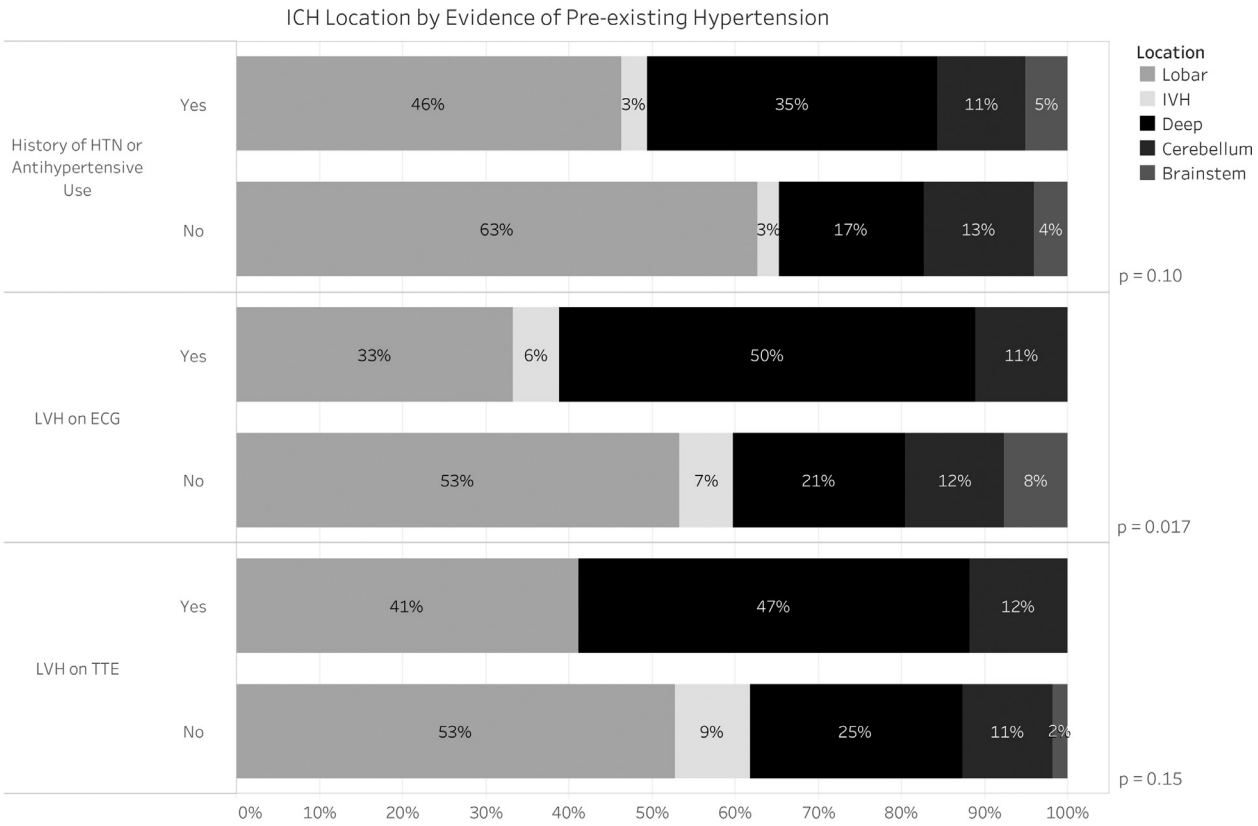

Figure 2. *ICH location by evidence of pre-existing hypertension*

This bar graph illustrates bleed location based on presence of pre-existing hypertension. There was no significant relationship between prHTN, by any definition, and ICH location. However, of the supratentorial bleeds, there were more deep bleeds than lobar bleeds in patients with pre-existing hypertension, by all definitions. This was significant for patients with history of hypertension/antihypertensive use ($P = .004$) and patients with LVH on ECG ($P = .017$). Abbreviations: ECG, electrocardiogram; ICH, intracerebral hemorrhage; LVH, left ventricular hypertrophy; prHTN, pre-existing hypertension.

who are hypertensive on and throughout their admission are likely to have prHTN.

However, prHTN may be a contributor, rather than cause, for elevated aBP and increased acute antihypertensive requirements. The pain resulting from ICH may itself increase aBP given that painful stimulation, such as nailbed or supraorbital ridge pressure, can raise mean arterial pressure by 20 mm Hg.[14] Anxiety in the setting of ICH may also lead to increased aBP, as a meta-analysis of over 150,000 subjects found an odds ratio of 1.18 for developing hypertension with anxiety.[16] Even if a patient with ICH is not experiencing significant pain, the neuronal hypoxia that results from ICH can lead to enhanced sympathetic tone prompting an acute rise in blood pressure.[6-8]

Table 2. *Bleed characteristics with and without LVH on ECG and TTE LVH was associated with higher presenting sBP and NIHSS, more deep bleeds, and greater nicardipine requirements*

	ECG (n = 110)			TTE* (n = 72)		
	LVH (n = 18)	No LVH (n = 92)	*P* value	LVH (n = 17)	No LVH (n = 55)	*P* value
Admission BP (mm Hg)	195 (IQR 155-216)	147 (IQR 129-163)	<.001	181 (IQR 153-214)	152 (IQR 137-169)	.01
NIHSS	9 (IQR 3-19)	5 (IQR 2-13	.085	10 (IQR 5-18)	5 (IQR 1-13)	.046
Deep bleeds	60%	28%	.017	53%	33%	.15
ICH volume (mL)	12 (IQR 6-32)	12 (IQR 5-29)	.5	12 (IQR 6-32)	13 (IQR 5-29)	.8
Required nicardipine	83%	52%	.018	94%	64%	.016
Duration of nicardipine requirement (hours)	18 (IQR 3-29)	1 (IQR 0-25)	.09	23 (IQR 11-49)	10 (IQR 0-48)	.09

Abbreviations: ECG, electrocardiogram; ICH, intracerebral hemorrhage; LVH, left ventricular hypertrophy; TTE, transthoracic echocardiogram.

*Within 6 months of ICH presentation.

prHTN and Bleed Characteristics

As expected, deep bleeds were more common in patients with prHTN given that hypertension is a risk factor for bleeds in the basal ganglia, internal capsule, and thalamus.[41] However, it was somewhat surprising that bleed volume was not related to any measure of prHTN.

prHTN and Clinical Status

Median NIHSS was higher for patients with a history of hypertension/antihypertensive use and patients with LVH on ECG or TTE. Concordant with this, Khawaja et al recently noted that compared with patients who were discharged on <3 antihypertensives after ICH, those discharged on >3 antihypertensives were more likely to have a history of hypertension, higher admission sBP, worse NIHSS and worse functional outcome. The authors hypothesized that patients with resistant hypertension have a worse clinical ICH presentation,[42] possibly due bleed location given that, as discussed, more patients with prHTN had deep bleeds, and INTERACT2 data demonstrates that deep bleeds are associated with worse clinical outcomes.[43]

Limitations

Limitations to this study include the fact that (1) the sample size was relatively small; (2) ECG and TTE data were not available for everyone; and (3) some of the data were collected retrospectively.

Conclusion

The relationship between prHTN and blood pressure on admission, imaging characteristics, clinical presentation, and acute antihypertensive requirements in patients with ICH varies somewhat depending on the criteria used to define prHTN. Despite this, it appears that ICH patients with prHTN are more likely to have higher sBP on admission, deep bleeds, higher NIHSS, and require nicardipine than those without prHTN. This suggests that hypertension in ICH is both a cause and effect of the bleed.

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