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ORIGINAL RESEARCH

Blood Pressure and Outcomes in Patients With Different Etiologies of Intracerebral Hemorrhage: A Multicenter Cohort Study

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BACKGROUND: We aimed to investigate the association between blood pressure (BP) and outcomes in intracerebral hemorrhage (ICH) subtypes with different etiologies.

METHODS AND RESULTS: A total of 5656 in-hospital patients with spontaneous ICH were included between January 2012 and December 2016 in a prospective multicenter cohort study. Etiological subtypes of ICH were assigned using SMASH-U (structural lesion, medication, amyloid angiopathy, systemic/other disease, hypertension, undetermined) classification. Elevated systolic BP was defined as ≥140 mm Hg. Hypertension was defined as elevated BP for >1 month before the onset of ICH. The primary outcomes were measured as 1-month survival rate and 3-month mortality. A total of 5380 patients with ICH were analyzed, of whom 4052 (75.3%) had elevated systolic BP on admission and 3015 (56.0%) had hypertension. In multinomial analysis of patients who passed away by 3 months, systolic BP on admission was significantly different in cerebral amyloid angiopathy (P<0.001), structural lesion (P<0.001), and undetermined subtypes (P=0.003), compared with the hypertensive angiopathy subtype. Elevated systolic BP was dose-responsively associated with higher 3-month mortality in hypertensive angiopathy (P_{trend}=0.013) and undetermined (P_{trend}=0.005) subtypes. In cerebral amyloid angiopathy, hypertension history had significant inverse association with 3-month mortality (adjusted odds ratio, 0.37, 95% CI, 0.20–0.65; P<0.001). Similarly, adjusted Cox regression indicated decreased risk of 1-month survival rate in the presence of hypertension in patients with cerebral amyloid angiopathy (adjusted hazard ratio, 0.47; 95% CI, 0.24–0.92; P=0.027).

CONCLUSIONS: This study suggests that the association between BP and ICH outcomes might specifically depend on its subtypes, and cerebral amyloid angiopathy might be pathologically distinctive from the others. Future studies of individualized BP-lowering strategy are needed to validate our findings.

Key Words: 1-month survival rate ■ 3-month death ■ blood pressure ■ etiologies ■ intracerebral hemorrhage

Intracerebral hemorrhage (ICH), a heterogeneous group of cerebrovascular diseases of different etiologies, is the least treatable form of stroke, and no specific proven therapy is available.[1] Based on a national community-based study in China, ICH accounts for ≈25% of all cases of stroke, which is significantly higher than the 8% to 15% in Western populations.[2,3] One reason may be that hypertension in China is highly prevalent (28%) but poorly controlled (<20%).[4] Blood pressure (BP) control is a priority for clinicians treating cases of ICH. Elevated BP occurs in many patients with acute ICH, which likely reflects the contributions of stress, pain, increased intracranial pressure, and premorbid acute or persistent elevation of BP.[5] Elevated BP is associated with greater hematoma expansion, neurological deterioration, and death or dependence of activities of daily living after ICH.[6,7] Although most clinicians try to lower BP in the acute phase of ICH, whether

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CLINICAL PERSPECTIVE

What Is New?

- The association between blood pressure and intracerebral hemorrhage outcomes might specifically depend on its subtypes and cerebral amyloid angiopathy might be pathologically distinctive from the others.
- Our results suggest differential contribution of blood pressure to the pathological mechanism underlying different intracerebral hemorrhage subtypes.

What Are the Clinical Implications?

- These findings will be of significance for future research to individualize the blood pressure–lowering strategy.

Nonstandard Abbreviations and Acronyms

CAA	cerebral amyloid angiopathy
DBP	diastolic blood pressure
HA	hypertensive angiopathy
H-ATOMIC	hypertension, cerebral amyloid angiopathy, tumor, oral anticoagulants, vascular malformation, infrequent causes, and cryptogenic
ICH	intracerebral hemorrhage
INTERACT2	Intensive BP Reduction in the Acute Cerebral Hemorrhage clinical trial
SBP	systolic blood pressure
SMASH-U	structural lesion, medication, amyloid angiopathy, systemic/other disease, hypertension, and undetermined

such lowering improves primary outcomes is controversial.[8,9] The INTERACT2 (Intensive BP Reduction in the Acute Cerebral Hemorrhage) clinical trial has shown that rapid and intensive BP lowering (systolic blood pressure [SBP] <140 mm Hg in 6 hours) is safe and that surviving patients show better functional recovery.[8] According to the American Heart Association/American Stroke Association Guideline for ICH, acutely elevated SBP between 150 and 200 mm Hg should be lowered to 140 mm Hg in patients without contraindication to acute BP-lowering treatment.[10]

BP during the acute phase of ischemic stroke varies with its etiology.[11–14] It is possible that BP varies with ICH etiology and the BP-lowering therapies may have different efficacies depending on ICH etiology. The SMASH-U (structural lesion, medication, amyloid angiopathy, systemic/other disease, hypertension, undetermined) classification is an easy-to-use and computed tomography–based approach that rapidly categorizes ICH into 6 subtypes according to conventional risk factors, medical history, and computed tomography.[15] Here, we report the first analysis of the association of BP on clinical outcomes among different ICH subtypes. This large in-patient study was performed at 21 medical centers across China.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

We used a cohort study design based on a prospective, multicenter, hospital-based registry that collected data on patients with acute first-ever ICH admitted between January 2012 and December 2016 to 21 tertiary hospitals across a wide range of cities in China. The study was approved by the Biomedical Research Ethics Committee and the Committee on Human Research of West China Hospital, Sichuan University (2013 [124]).[16] Informed consent was obtained from participants or their guardians.

Procedures

Patients with first-ever ICH were recruited. The inclusion criteria were (1) at least 18 years old, (2) a diagnosis of ICH that was detected by noncontrast computed tomography performed within 72 hours from the presumed symptom onset. The patients with aneurysmal subarachnoid hemorrhages and lobar bleeding were included. Patients were excluded as nonstrokes if they were diagnosed with (1) traumatic ICH, primary subdural/epidural hematoma, intracranial venous thrombosis, or hemorrhage caused by a tumor or recurrent ICH; or (2) hemorrhagic transformation of a cerebral infarction. All centers follow the same minimum diagnostic flow diagram to manage patients with ICH (Figure S1).

Patients' demographics was obtained predominantly by in-person interviews. In-hospital details including clinical features and diagnosis were obtained through medical records and interviews with patients or their families. Follow-up details were obtained through telephone interviews at 1 and 3 months after ICH. Medical history details included the following diseases: hypertension, diabetes

mellitus, hyperlipidemia, stroke, heart disease (includes any history of atrial fibrillation/heart attack/myocardial infarction, angina, coronary heart disease, or valvular heart disease) either self-reported or diagnosed in-hospital before this ICH onset. Drinking was confirmed if the patients drank alcohol at least once per week during the past 12 months. Clinical features included routine blood tests result, severity on admission (assessed by Glasgow Coma Scale [from 3 to 15, with a lower score indicating a worse conscious state] and National Institutes of Health Stroke Scale [from 0 to 42, with higher scores indicating more severe neurological deficits]). Brain computed tomography scans were done in all patients on admission with the same protocol. Hematoma volume was determined by the formula of ellipsoids (A×B×C/2). Surgical interventions were indicated according to Guidelines for the management of spontaneous ICH.[17] SBP and diastolic blood pressure (DBP) were recorded with an electronic arm–type BP device on arrival in the emergency department. The primary outcome was death or disability (defined by a modified Rankin Scale score of 3–6) at 3 months. The secondary outcome was survival rate at 1 month.

Etiological subtypes of ICH were classified according to SMASH-U criteria.[15] Structural lesion subtype was defined as vascular structural abnormalities at the bleeding sites verified by imaging or pathological findings. Medication-related ICH was defined as warfarin use with international normalized ratio ≥2, novel oral anticoagulant use within 3 days, full-dose heparin, or thrombolytic agent use. Cerebral amyloid angiopathy (CAA) was defined as lobar, cortical, or subcortical hemorrhage among patients aged ≥55 years, according to the Boston criteria. The systemic disease subtype was defined by the presence of thrombocytopenia or liver cirrhosis as conventionally, or alternatively by the presence of non–drug-induced coagulopathy or renal failure (stage 5 chronic kidney disease or kidney disease requiring dialysis), both of which are risk factors for spontaneous ICH. Hypertensive angiopathy (HA) subtype was defined as deep or infratentorial hemorrhage with preexisting hypertension history. Hypertension was defined as any recorded hypertension diagnosis or preexisting BP ≥140/90 mm Hg on at least 3 measurements at rest on at least 2 separate healthcare visits for >1 month before ICH onset, either on or off antihypertensive therapy.

Statistical Analysis

Categorical variables are presented as counts (%), and continuous or discrete variables are presented as mean (SD) or median (interquartile range). All statistical analyses were performed in R Core Team (2017) unless noted otherwise. Two-sided *P* values are reported, and $P<0.05$ was considered significant unless noted otherwise; for multiple comparisons, this level was correlated according to modified Bonferroni correction ($P=0.0472\times K^{-0.6598}$). When appropriate, data are reported as odds ratios (ORs) or hazard ratios and 95% CIs. To systematically identify potential confounders in the multivariable model, we selected variables using a "least absolute shrinkage and selection operator" regularizer. The least absolute shrinkage and selection operator calculation was conducted using the *glmnet* algorithm in R. Age, sex, Glasgow Coma Scale, National Institutes of Health Stroke Scale, hematoma volume, urea nitrogen, intraventricular extension, and surgical interventions were identified as confounding variables in the entire cohort, which were adjusted in all multivariable models. Multivariable logistic regression was used to calculate the ORs and their *P* values of the potential association of clinical characteristics with death. Cox

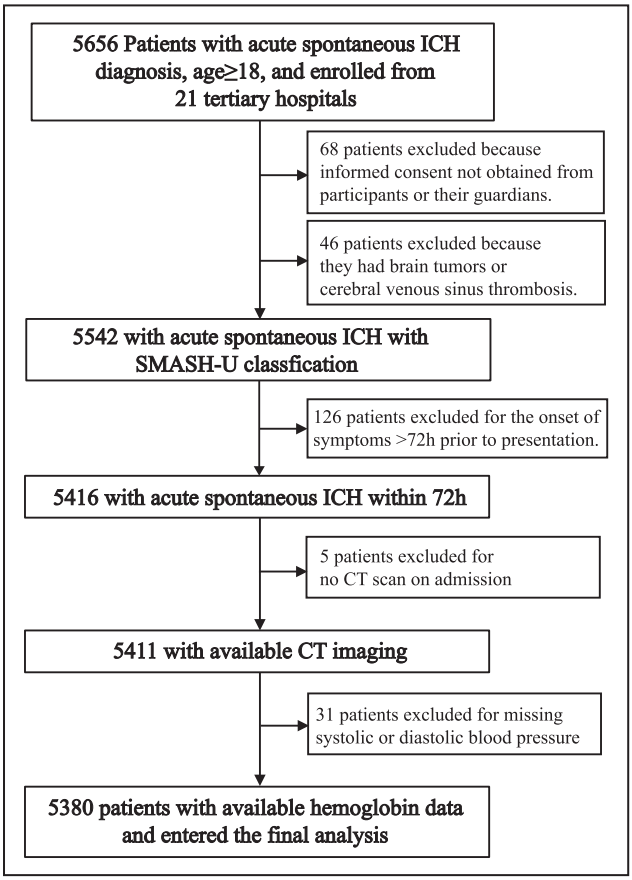

Figure 1. Flow chart of patients screened, included and excluded from the study.
CT indicates computed tomography; ICH, intracerebral hemorrhage; and SMASH-U classification, includes 7 etiologic categories: structural lesion, medication, amyloid angiopathy, systemic/other disease, hypertension, and undetermined.

Table 1. Baseline Characteristics of Study Population, According to Etiological ICH Subtypes

Characteristics	Total n=5380	HA n=2262	CAA n=593	Structural lesion n=768	Medication n=122	Systemic Disease n=263	Undetermined n=1372
Demographics							
Age, y	57.8±15.3	60.3±12.6	69.2±9.4	44.7±16.6	63.4±13.3	55.7±14.9	56.0±15.3
Male, n (%)	3451 (64.1)	1431 (63.3)	400 (67.5)	422 (54.9)	80 (65.6)	187 (71.1)	931 (67.9)
Medical history, n (%)							
HD history	375 (7.0)	158 (7.0)	47 (7.9)	11 (1.4)	112 (91.8)	9 (3.4)	38 (2.8)
Anticoagulants	137 (2.5)	9 (0.4)	5 (0.8)	1 (0.1)	122 (100.0)	0 (0.0)	0 (0.0)
Antiplatelet	76 (1.4)	43 (1.9)	10 (1.7)	1 (0.1)	20 (16.4)	0 (0.0)	2 (0.1)
Alcohol	1107 (20.5)	493 (21.8)	101 (17.0)	118 (15.1)	53 (43.4)	45 (17.1)	297 (21.6)
Vascular risk factors, n (%)							
Hypertension	3015 (55.9)	2262 (100)	322 (54.5)	133 (17.0)	84 (68.9)	157 (59.7)	183 (13.3)
Diabetes mellitus	448 (8.3)	264 (11.7)	49 (8.3)	18 (2.3)	36 (29.5)	30 (11.4)	51 (3.7)
Hyperlipidemia	1781 (38.9)	869 (45.2)	159 (32.4)	193 (27.0)	58 (49.2)	85 (37.4)	417 (37.4)
Smoking	1364 (25.3)	570 (25.2)	140 (23.6)	191 (24.4)	50 (41.0)	56 (21.3)	357 (26.0)
Clinical status							
GCS	13 (8–15)	13 (8–15)	14 (9–15)	15 (11–15)	12 (11–14)	12 (6–15)	13 (7–15)
NIHSS	8 (3–16)	10 (4–17)	6 (2–13)	3 (0–11)	11 (7–16)	10 (4–24)	9 (3–20)
SBP, mm Hg	161.8±31.4	171.2±26.9	159.3±27.7	135.3±26.5	168.8±29.9	168.9±34.1	160.6±33.1
DBP, mm Hg	94.9±18.2	99.8±16.7	90.6±15.6	81.8±15.2	95.1±15.6	98.9±19.0	95.2±19.0
Platelet count, 10^9/L	168.1±68.3	170.5±65.3	159.4±57.5	179.7±68.0	180.2±60.4	114.4±93.2	170.6±67.9
INR	1.1±0.30	1.0±0.13	1.0±0.13	1.1±0.24	2.5±0.76	1.1±0.17	1.0±0.11
Urea nitrogen, mmol/L	5.2 (4.0–6.6)	5.2 (4.1–6.6)	5.5 (4.2–6.8)	4.6 (3.7–6.0)	5.8 (4.8–7.4)	7.0 (5.0–16.1)	5.2 (4.0–6.6)
Hematoma volume, mL	13 (5–28)	11 (5–23)	21 (10–36)	13 (5–26)	8 (28–110)	16 (5–35)	14 (6–30)
ICH score	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)
Hematoma location, n (%)							
Lobar	1748 (32.5)	183 (8.1)	593 (100.0)	482 (62.8)	30 (24.6)	84 (31.9)	374 (27.3)
BG or thalamus	3115 (57.8)	1869 (82.6)	43 (7.3)	139 (18.1)	79 (64.8)	165 (62.7)	860 (62.7)
Brainstem	435 (8.1)	221 (9.8)	3 (0.5)	40 (5.2)	8 (6.6)	27 (10.3)	136 (9.9)
Cerebellar	314 (5.8)	148 (6.5)	34 (5.7)	46 (6.0)	10 (8.2)	11 (4.2)	65 (4.7)
IVH, n (%)	1841 (34.2)	703 (31.1)	140 (23.6)	336 (43.8)	36 (29.5)	105 (39.9)	521 (38.0)
SAH, n (%)	511 (9.5)	110 (4.9)	56 (9.4)	210 (27.3)	8 (6.6)	21 (8.0)	106 (7.7)
Examinations and therapies, n (%)							
Vascular examination	4353 (80.9)	1709 (75.6)	476 (80.3)	757 (98.6)	107 (87.7)	207 (78.7)	1097 (80.0)
CTA	2833 (52.7)	1032 (45.6)	317 (53.5)	700 (91.1)	87 (71.3)	105 (39.9)	592 (43.1)
MRA	728 (13.5)	291 (12.9)	102 (17.2)	122 (15.9)	19 (15.6)	23 (8.7)	171 (12.5)
DSA	1036 (19.3)	311 (13.7)	82 (13.8)	361 (47.0)	19 (15.6)	24 (9.1)	239 (17.4)
Surgical interventions	1450 (27.0)	427 (18.9)	120 (20.2)	537 (69.9)	21 (17.2)	30 (11.4)	315 (23.0)
Antihypertension	3020 (56.1)	1574 (69.6)	331 (55.8)	222 (28.9)	68 (55.7)	145 (55.1)	692 (50.4)

BG indicates basal ganglia; CAA, cerebral amyloid angiopathy; CTA, computed tomography angiography; DBP, diastolic blood pressure; DSA, digital subtraction angiography; GCS, Glasgow Coma Scale; HA, hypertensive angiopathy; HD, heart disease; INR, International normalized ratio; IVH, intraventricular hemorrhage; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

proportional hazard modeling was used to calculate hazard ratios and their *P* values of hypertension and 1-month survival among patients with CAA subtype of ICH. To investigate the differential association of SBP with 3-month mortality across ICH subtypes, adjusted multinomial logistic regression was performed in the patients who died by 3 months. In different ICH subtypes, the dose-responsive association between BP and outcome was determined based on tests for trend, modeling the ordered categories BP (140, 160, 180, and 200 mm Hg in SBP; 90, 100, 110 and 120 mm Hg in DBP) as a 1-degree-of-freedom linear

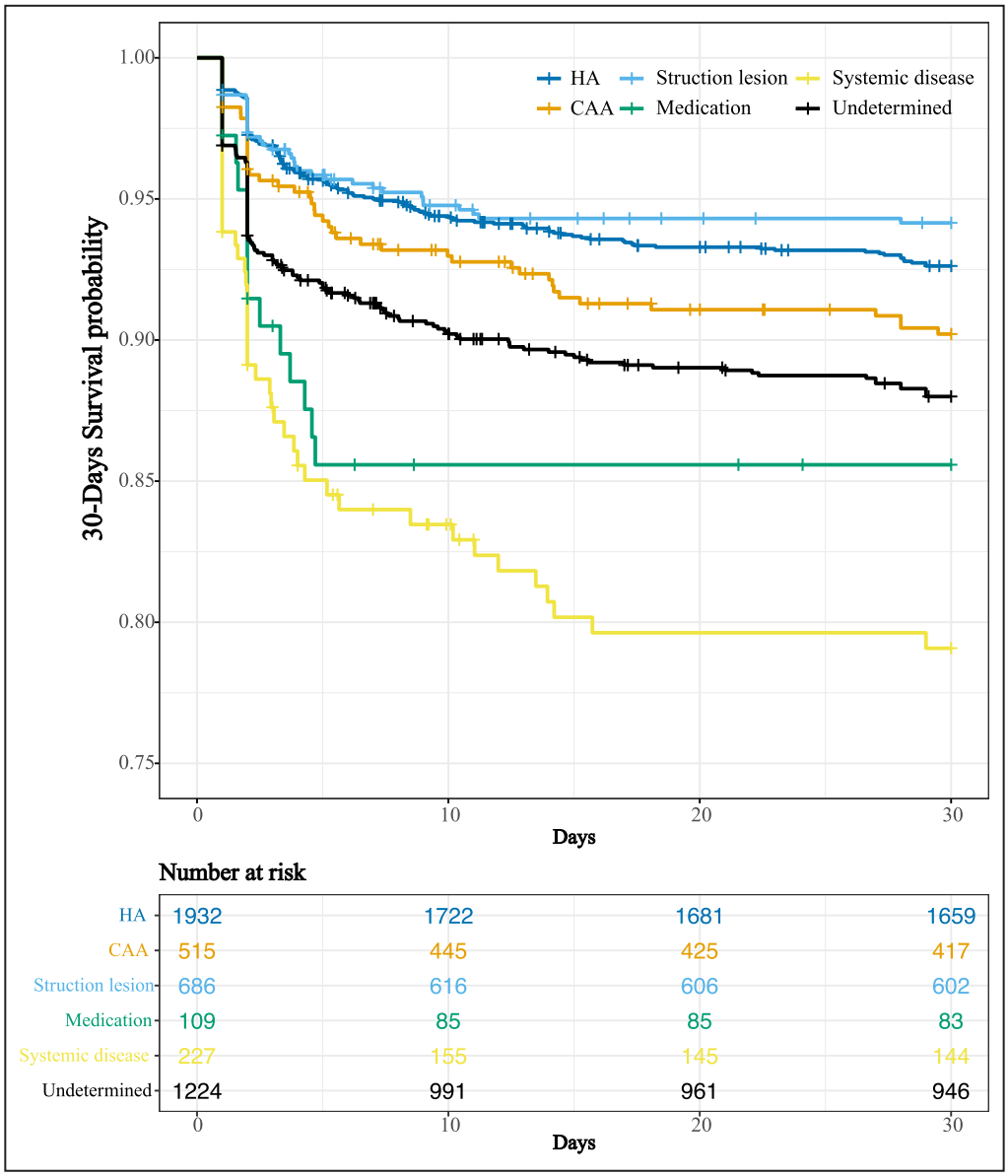

Figure 2. Kaplan–Meier analysis of 1-month survival by ICH subtypes.
The 1-month survival rate differences among the six subtypes are statistically significant (log-rank test, *P*<0.001). CAA indicates cerebral amyloid angiopathy; and HA, hypertensive angiopathy.

term in the multivariable logistic regression. Akaike information criterion was calculated using the –2log likelihood test. The area under the receiver operating characteristic curve of the binary logistic regression was calculated using the ROCR package of R language.

RESULTS

A total of 5656 patients with spontaneous ICH were screened, and 5380 patients with a mean age of 57.9 (15.1) years were included in the final analysis (Figure 1

). Of the 5380 patients, 3451 (64.1%) were male, 4052 (75.3%) had elevated SBP on admission, and 3015 (56.0%) had a history of hypertension (Table 1). Median hematoma volume in the entire cohort was 13.0 mL, ranging from 0 to 215 mL. Of the 5380 patients, 4762 (88%) completed follow-up at 3 months.

ICH Subtypes by SMASH-U Classification and Respective Outcomes

Table 1 presents the baseline characteristics of the patients with ICH stratified by the SMASH-U classification. The most common pathogenesis was HA (42%), followed by undetermined etiology (25%),

Table 2. Differential Association of SBP With Other ICH Subtypes Compared With HA Subtype, in the Patients Dead at 3 Months

ICH Subtypes	Variables	β	SE	OR (95% CI)	*P* Value
CAA	Age, y	0.056	0.011	1.06 (1.03–1.08)	<0.001
	Sex	0.197	0.288	1.22 (0.69–2.14)	0.495
	GCS	−0.034	0.051	0.97 (0.88–1.07)	0.507
	NIHSS	−0.053	0.018	0.95 (0.92–0.98)	0.004
	Hematoma volume, mL	0.021	0.004	1.02 (1.01–1.03)	<0.001
	Urea nitrogen, mmol/L	−0.014	0.048	0.99 (0.90–1.08)	0.769
	Surgical intervention	−0.193	0.358	0.83 (0.41–1.66)	0.590
	Intraventricular extension	−0.953	0.291	0.39 (0.22–0.68)	0.001
	SBP (per 20 mm Hg)	−0.021	0.004	0.66 (0.56–0.77)	<0.001
Structural lesion	Age, y	−0.033	0.011	0.97 (0.95–0.99)	0.002
	Sex	−0.56	0.312	0.57 (0.31–1.05)	0.072
	GCS	−0.037	0.059	0.96 (0.86–1.08)	0.523
	NIHSS	−0.046	0.022	0.96 (0.92–1.00)	0.037
	Hematoma volume, mL	0.007	0.006	1.01 (1.00–1.02)	0.235
	Urea nitrogen, mmol/L	0.052	0.043	1.05 (0.97–1.15)	0.229
	Surgical intervention	0.45	0.336	1.57 (0.81–3.03)	0.180
	Intraventricular extension	0.717	0.329	2.05 (1.07–3.90)	0.029
	SBP (per 20 mm Hg)	−0.021	0.005	0.66 (0.54–0.80)	<0.001
Medication and systemic disease	Age, y	−0.016	0.009	0.98 (0.97–1.00)	0.087
	Sex	−0.085	0.285	0.92 (0.53–1.60)	0.764
	GCS	0.001	0.053	1.00 (0.90–1.11)	0.986
	NIHSS	−0.022	0.019	0.98 (0.94–1.02)	0.245
	Hematoma volume, mL	0.017	0.004	1.02 (1.01–1.03)	<0.001
	Urea nitrogen, mmol/L	0.183	0.029	1.20 (1.13–1.27)	<0.001
	Surgical intervention	−0.13	0.348	0.88 (0.44–1.74)	0.708
	Intraventricular extension	0.186	0.281	1.21 (0.70–2.09)	0.507
	SBP (per 20 mm Hg)	−0.004	0.004	0.92 (0.79–1.08)	0.313
Undetermined	Age, y	−0.02	0.007	0.98 (0.97–0.99)	0.005
	Sex	0.154	0.203	1.17 (0.78–1.74)	0.449
	GCS	−0.014	0.038	0.99 (0.92–1.06)	0.716
	NIHSS	−0.014	0.014	0.99 (0.96–1.01)	0.313
	Hematoma volume, mL	0.011	0.003	1.01 (1.00–1.02)	0.002
	Urea nitrogen, mmol/L	−0.011	0.033	0.99 (0.93–1.05)	0.728
	Surgical intervention	−0.201	0.241	0.82 (0.51–1.31)	0.404
	Intraventricular extension	0.119	0.196	1.13 (0.77–1.65)	0.542
	SBP (per 20 mm Hg)	−0.009	0.003	0.84 (0.74–0.94)	0.003

HA subtype was used as reference subtype. CAA indicates cerebral amyloid angiopathy; GCS, Glasgow Coma Scale; HA, hypertensive angiopathy; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and SBP, systolic blood pressure.

structural lesions (15%), CAA (11%), systemic disease (5%), and medication (2%). Further etiologic investigations, including magnetic resonance imaging, magnetic resonance angiography, computed tomography angiography, or digital subtraction angiography, were performed in 2295 (43%) patients; 1450 (27%) patients had surgical interventions, and 3020 (56%) received antihypertensive therapy during hospitalization. The overall mortality rate at 1 month was 8.8%, and 1-month survival curves were differentiated among the ICH subgroups, with medication (13.5%) and systemic disease (18.7%) subtypes being significantly worse (P<0.001, Figure 2). Three-month mortality also varied among ICH subgroups: systemic disease (38.3%), medication (24.3%), undetermined (24.0%), CAA (21.0%), HA (15.9%), and structural vascular lesions (12.7%) (P<0.001).

Relationship Between BP on Admission and Outcomes in Different ICH Subtypes

Both SBP and DBP on admission were significantly different among the 6 SMASH-U subtypes (all $P<0.001$; Table 1). Among the patients who died by 3 months, compared with the HA subtype, SBP was significantly different in CAA ($P<0.001$), structural lesion ($P<0.001$), and undetermined subtype ($P=0.003$), but not in the medication or systemic disease subgroups ($P=0.313$) (Table 2). In different ICH subtypes, we observed differential associations for higher 3-month mortality and increasing levels of SBP (Table 3 and Tables S1 and S2). In both the HA and undetermined subtypes, the elevated SBP was dose-responsively related with 3-month mortality ($P_{trend}=0.013$ and 0.005, respectively), which was not observed in other ICH subtypes. In addition, as continuous variables, SBP was linearly associated with increased 3-month mortality in HA ($P=0.019$) and undetermined subtypes ($P=0.010$). Similar results were also observed with DBP. Comparably, survival rate at 1 month varied significantly with SBP levels in the HA, structural lesion, medication and undetermined subtypes (all $P<0.001$), but not in the CAA ($P=0.090$) or systemic disease subtypes ($P=0.096$; Figure S2).

Relationship Between Hypertension and Outcomes in Different ICH Subtypes

To investigate the correlation between hypertension history and outcomes in different ICH subtypes, we performed subgroup analysis in all subtypes except HA, in which hypertension is present in all cases. Hypertension was present in 332 patients (54.5%) with CAA, 133 (17.0%) with structural lesion, 241 (62.6%) with medication/systemic disease, and 183 (13.3%) with undetermined ICH causes. In univariable analysis, 3-month mortality rate differed significantly between hypertensive and nonhypertensive patients only in the subtypes CAA and structural lesion. In CAA, patients with hypertension had higher SBP (165 versus 153 mm Hg) and DBP (94 versus 87 mm Hg) (Table 4).

Multivariable analysis showed that CAA patients with hypertension were at a 73% lower risk of death than CAA patients without hypertension (unadjusted OR, 0.46; 95% CI, 0.30–0.70; $P<0.001$; adjusted OR, 0.37; 95% CI, 0.20–0.65; $P<0.001$; Table 5 and Tables S1 and S2). The shift analysis showed a significant favorable shift in the distribution of scores on the modified Rankin scale with a hypertension history (adjusted OR for shift to higher mRS, 0.66; 95% CI, 0.47–0.94; $P=0.021$; Figure 3). Similarly, adjusted Cox regression indicated decreased risk of 1-month survival in the presence of hypertension (unadjusted hazard ratio, 0.45; 95% CI, 0.25–0.81; $P=0.008$; adjusted hazard ratio, 0.47; 95% CI, 0.24–0.92; $P=0.027$; Figure 4 and Table S1).

Table 3. Dose-Responsive Association Between BP on Admission and 3-Month Mortality in Different ICH Subtypes

	HA		CAA		Structural Lesion		Medication and Systemic Disease		Undetermined	
	OR (95% CI)	*P* Value*	OR (95% CI)	*P* Value*	OR (95% CI)	*P* Value*	OR (95% CI)	*P* Value*	OR (95% CI)	*P* Value*
SBP										
<140 mm Hg	1.00 (ref)	0.013	1.00 (ref)	0.316	1.00 (ref)	0.667	1.00 (ref)	0.566	1.00 (ref)	0.005
140–159	1.68 (0.80–3.70)		0.80 (0.36–1.78)		0.61 (0.21–1.58)		0.71 (0.20–2.40)		1.13 (0.64–1.99)	
160–179	1.90 (0.94–4.07)		1.29 (0.61–2.79)		1.00 (0.38–2.47)		0.35 (0.10–1.09)		1.14 (0.63–2.09)	
180–199	1.61 (0.80–3.42)		0.77 (0.28–2.00)		2.24 (0.55–8.63)		0.78 (0.29–2.08)		2.14 (1.19–3.90)	
≥200	2.93 (1.46–6.16)		2.03 (0.70–5.80)		1.69 (0.40–6.73)		1.49 (0.51–4.34)		1.99 (1.10–3.61)	
Per 20 mm Hg	1.14 (1.02–1.28)	0.019	1.05 (0.86–1.28)	0.620	1.07 (0.84–1.37)	0.580	1.01 (0.83–1.24)	0.893	1.16 (1.03–1.29)	0.010
DBP										
<90 mm Hg	1.00 (ref)	0.001	1.00 (ref)	0.558	1.00 (ref)	0.817	1.00 (ref)	0.943	1.00 (ref)	0.012
90–99	1.16 (0.71–1.90)		1.14 (0.55–2.29)		0.76 (0.29–1.83)		0.59 (0.22–1.52)		1.62 (0.98–2.69)	
100–109	1.17 (0.72–1.91)		1.09 (0.49–2.33)		0.81 (0.27–2.17)		0.37 (0.13–0.99)		2.04 (1.22–3.42)	
110–119	2.62 (1.47–4.64)		1.05 (0.33–3.00)		1.23 (0.16–5.92)		0.54 (0.15–1.70)		1.94 (1.01–3.70)	
≥120	2.63 (1.46–4.72)		1.36 (0.27–5.72)		1.45 (0.27–7.47)		1.58 (0.53–4.70)		1.69 (0.88–3.22)	
Per 10 mm Hg	1.20 (1.09–1.32)	<0.001	1.04 (0.87–1.25)	0.670	0.89 (0.80–1.21)	0.880	0.96 (0.79–1.17)	0.930	1.13 (1.02–1.25)	0.015

CAA indicates cerebral amyloid angiopathy; DBP, diastolic blood pressure; HA, hypertensive angiopathy; OR, odds ratio; and SBP, systolic blood pressure.
*P_{trend} or *P* value. All models were adjusted for age, sex, Glasgow Coma Scale, National Institutes of Health Stroke Scale, hematoma volume and urea nitrogen, intraventricular extension, and surgical interventions.

Table 4. Clinical Features Based on Hypertension History in CAA, Structural Lesion, and Undetermined Subtypes

Hypertension History	CAA			Structural Lesion			Medication and Systematic Disease			Undetermined		
	−	+		−	+		−	+		−	+	
	n=271	n=322	*P* Value	n=635	n=133	*P* Value	n=144	n=241	*P* Value	n=1189	n=183	*P* Value
Age, y	69.8 (9.7)	68.7 (9.1)	0.132	42 (16.3)	58.1 (10.7)	<0.001	54.2 (16.0)	60.5 (13.6)	<0.001	55.9 (15.5)	57 (13.7)	0.385
Male	189 (69)	211 (65.5)	0.316	359 (55.3)	63 (47.4)	0.114	101 (70.1)	166 (68.9)	0.880	808 (68.0)	123 (67.2)	0.908
SBP	153 (26.3)	165 (27.7)	<0.001	131 (23.7)	158 (28)	<0.001	155.7 (33.2)	176.7 (29.9)	<0.001	158 (32.7)	174 (32.5)	<0.001
DBP	87 (14.9)	94 (15.5)	<0.001	80 (14.1)	92 (15.8)	<0.001	92.5 (19.5)	100.8 (16.5)	<0.001	94 (18.7)	102 (19.1)	<0.001
BUN	5.3 (4.3–6.7)	5.6 (4.2–7.0)	0.570	4.4 (3.3–5.8)	5.5 (4.2–6.9)	<0.001	5.5 (4.2–7.3)	7.3 (5.3–15.4)	<0.001	5.2 (4.1–6.5)	5.4 (4.1–6.9)	0.581
GCS	14 (9–15)	14 (10–15)	0.621	15 (12–15)	13 (9–15)	<0.001	13 (7–15)	12 (6–14)	0.262	13 (7–15)	13 (7–15)	0.827
NIHSS	7 (2–15)	6 (2–12)	0.265	2 (0–10)	6 (1–14)	0.012	9 (3–17)	12 (6–24)	0.009	9 (3–20)	9 (2–20)	0.671
Hematoma	24 (12–38)	20 (9–35)	0.605	13 (5–26)	15 (5–31)	0.038	13 (5–35)	14 (7–31)	0.990	14 (5–30)	21 (10–40)	0.006
3-mo death	68 (27.9)	42 (15.0)	<0.001	64 (11.1)	25 (20.5)	0.007	44 (34.4)	71 (33.3)	0.937	261 (24.1)	37 (23.3)	0.902

Male and 3-month death were presented as counts (%). Age, SBP, DBP, was presented as mean (SD), years. SBP and DBP were presented as mean (SD) mm Hg. BUN was presented as median (interquartile range) mmol/L. GCS and NIHSS were presented as median (interquartile range). Hematoma volume were presented as median (interquartile range), mL. BUN indicates blood urea nitrogen; CAA, cerebral amyloid angiopathy; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; HA, hypertensive angiopathy; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

DISCUSSION

To our knowledge, this is the largest multicenter cohort study to investigate the association between BP and outcomes among different etiological subtypes of ICH. The etiology of ICH in nearly 53% of our patients were hypertensive or CAA. In our study, the highest SBP or DBP was observed in the HA subtype, which was associated with the second good outcomes among these subtypes. This suggests that the influence of BP on outcomes is moderated by other factors in ICH, such as age, severity, and other factors related to the underlying ICH pathogenesis. Consistent with this idea, we found that the relationship of BP with outcomes varied with ICH subtypes. Elevated BP on admission was associated with worse outcomes in the subtypes HA and undetermined, whereas the hypertension history was associated with better outcomes in the subtype CAA. These results suggest a differential contribution of BP and its differential underlying pathological mechanism in different ICH subtypes.

ICH classification systems are either anatomic or mechanistic. Representatives of mechanistic classification systems are SMASH-U and H-ATOMIC (hypertension, cerebral amyloid angiopathy, tumor, oral anticoagulants, vascular malformation, infrequent causes, and cryptogenic),[15,18] both of which present high interrater reliability. H-ATOMIC, which includes 7 etiologic categories, uses a complicated set of definitions for each category and a subclassification if possible, which requires an expanded workup of ICH etiology study and a further diagnostic plan. SMASH-U is a simple system that is completed within 1 minute by experienced emergency physicians and neurologists. Although the SMASH-U classification has limitations, especially for the cases with uncertain and multiple overlapping mechanisms, its easy-to-use algorithm is suitable for rapid etiologic classification and initiation of time-sensitive therapy like BP lowering in the emergency department.

The most common pathogenesis of ICH in our cohort was HA, consistent with findings in other studies in both White and Asian cohorts.[15,19–21] In this study, more than half of ICH patients were the HA and CAA subtypes, indicating high prevalence of ICH related to cerebral small vascular disease in Asian, consistent with previous studies. Nevertheless, the constituent ratio of different etiologies was generally comparable between Whites and Asians (Table S3). Hypertension is the most important risk factor in ICH, yet recent large trials assessing the effects of lowering BP during the acute phase of ICH demonstrated that it was safe but showed no significant benefit on mortality.[8,9] We hypothesized that the individualized BP lowering in ICH cases stratified by etiology might

Table 5. Multiple Adjusted Logistic Regression of the Potential Associations of Different Variables With 3-Month Death in the ICH Subtypes CAA, Structural Lesion, Medication, Systemic Disease, and Undetermined

Variables	CAA		Structural Lesion		Medication & Systemic Disease		Undetermined	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, y	1.04 (1.00–1.07)	0.027	1.03 (1.00–1.06)	0.024	1.02 (0.99–1.04)	0.221	1.02 (1.00–1.03)	0.014
Sex	1.97 (1.07–3.78)	0.035	0.74 (0.35–1.54)	0.414	0.33 (0.15–0.69)	0.004	0.90 (0.58–1.42)	0.648
Hypertension	0.37 (0.20–0.65)	<0.001	0.55 (0.21–1.37)	0.217	0.84 (0.39–1.82)	0.653	0.76 (0.36–1.54)	0.455
GCS	0.82 (0.73–0.92)	<0.001	0.69 (0.56–0.84)	<0.001	0.75 (0.64–0.87)	<0.001	0.73 (0.67–0.80)	<0.001
NIHSS	1.02 (0.98–1.06)	0.266	0.95 (0.88–1.03)	0.195	0.98 (0.92–1.05)	0.601	1.01 (0.98–1.05)	0.377
Hematoma volume, mL	1.01 (1.00–1.03)	0.015	1.02 (1.00–1.04)	0.019	1.05 (1.03–1.07)	<0.001	1.01 (1.01–1.02)	0.001
Urea nitrogen, mmol/L	1.05 (0.94–1.17)	0.347	1.30 (1.10–1.55)	0.003	1.06 (1.01–1.11)	0.012	1.08 (1.00–1.17)	0.060
Intraventricular extension	1.26 (0.63–2.45)	0.497	2.04 (1.00–4.23)	0.052	1.89 (0.90–3.96)	0.092	1.93 (1.27–2.93)	0.002
Surgical intervention	0.39 (0.18–0.81)	0.014	0.20 (0.09–0.42)	<0.001	0.22 (0.07–0.60)	0.005	0.18 (0.11–0.30)	<0.001

Age, sex, GCS, NIHSS, hematoma volume, urea nitrogen, plus intraventricular extension and surgical interventions were identified as confounding variables in the total cohort, which were adjusted in all multivariable models. CAA indicates cerebral amyloid angiopathy; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

increase the efficiency of the treatment. A significant dose-response association between BP and poor outcomes was found in the HA and undetermined subtypes, but not for the others. The similar result observed for HA and undetermined cases might result from the unrecognized hypertension in those with undetermined ICH.[22,23]

Regarding the time from symptom onset to hospitalization, 74.8% of patients were within 24 hours and 100% within 72 hours. We found that the time from

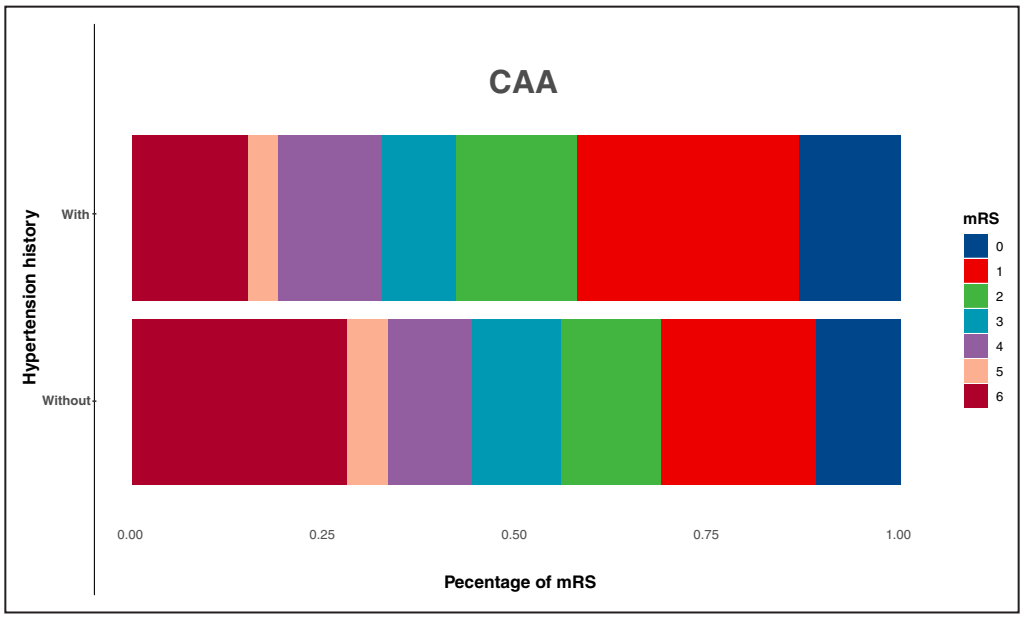

Figure 3. Distribution of scores on the Modified Rankin Scale (mRS), according to hypertension history in CAA patients.
Modified Rankin Scale (mRS) evaluates global disability and handicap: scores range from 0 (no symptoms or disability) to 6 (death). The data presented only patients whose score on mRS was obtained at 3 months in ICH patients with CAA (cerebral amyloid angiopathy). Multivariable ordinal analysis was performed after adjustment for potential confounders including age, sex, Glasgow Coma Scale, National Institutes of Health Stroke Scale, hematoma volume and urea nitrogen, intraventricular extension and surgical interventions. CAA indicates cerebral amyloid angiopathy.

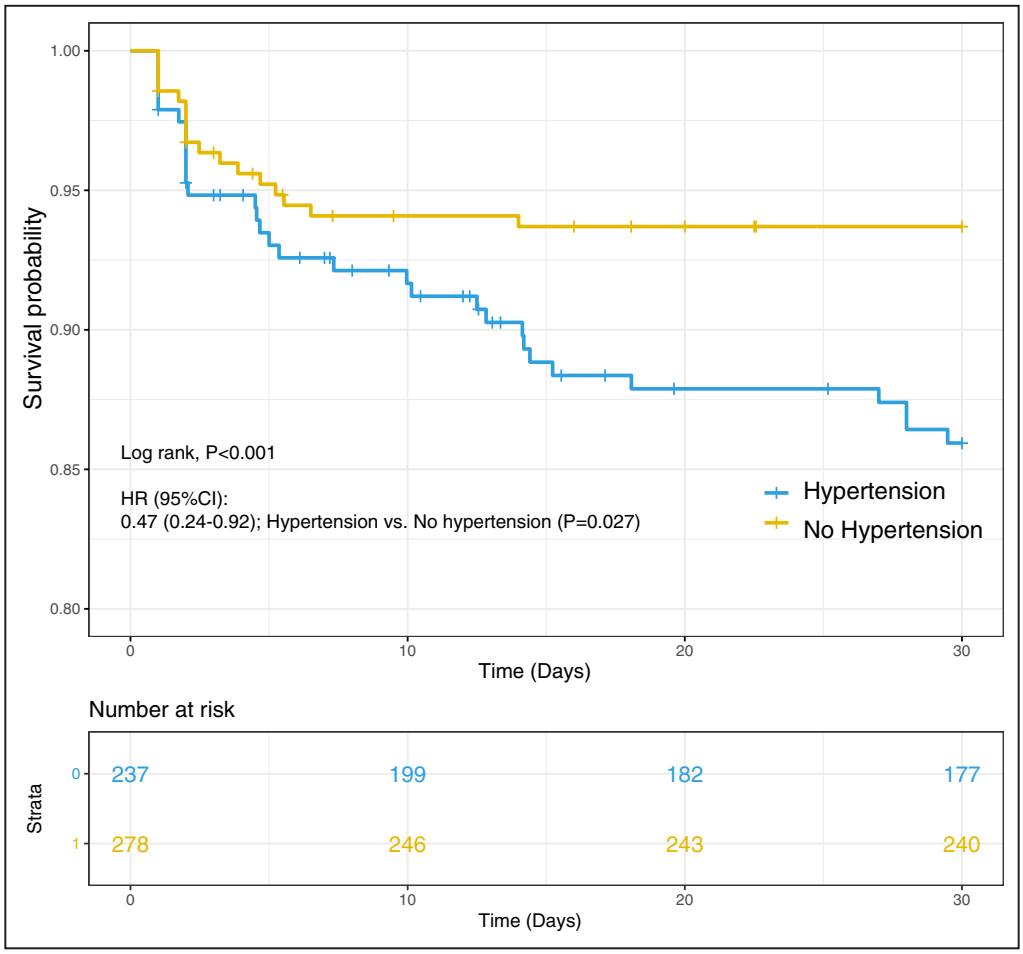

Figure 4. Cox proportional hazards regression curves for 1-month survival rate according to hypertension history in CAA subtype.
Hazard ratio (HR) was calculated using cox proportional hazard modeling with adjustment for potential confounders including age, sex, Glasgow Coma Scale, National Institutes of Health Stroke Scale, hematoma volume and urea nitrogen, intraventricular extension and surgical interventions; CAA indicates cerebral amyloid angiopathy; and HR, hazard ratio.

symptom onset to hospitalization was significantly correlated with hematoma volume (OR, 0.88; 95% CI, 0.86–0.91; *P*<0.001) and systolic blood pressure (OR, 0.73; 95% CI, 0.70–0.75; *P*<0.001; Figure S3). However, interaction analysis demonstrated that the time from symptom onset to hospitalization influenced neither the relationship between hematoma volume and outcomes (*P* for interaction=0.840) or that between SBP and outcomes (*P* for interaction=0.078). According to these results, the time from symptom onset to hospitalization was correlated with main variables like hematoma volume and SBP, but not significantly interact with their association with outcomes. We speculated that hematoma volume may have changed in cases of rebleeding, but it was not enough to influence the relationship between the main variables and outcomes.

Median hematoma volume in the entire cohort was 13.0 mL, ranging from 0 to 215 mL, 21.4% patients with hematoma >30 mL, which was comparable to the median volume of 9.8 or 15 mL in another 2 ICH etiology cohort studies.[15,21] Admittedly, the hematoma volume was an important determinant of the outcomes, which was included as a potential confounder and adjusted in all multivariable models. Besides, hematoma volume did not influence the relationship between SBP and outcomes (*P* for interaction=0.306). Drinking was confirmed if the patients drank alcohol at least once per week during the past 12 months. The frequency of drinking was 20.5% in the whole cohort, compared with 18.4% of one Asian cohort.[21] Drinking was associated with elevated SBP on admission (adjusted OR, 1.34; 95% CI, 1.19–1.51; *P*<0.001 per 20 mm Hg increase of SBP) and hypertension history (adjusted OR, 1.19; 95% CI, 1.01–1.40; *P*=0.035). However, in multivariable model, drinking was not significantly associated with 3-month death (*P*=0.513).

The incidence of CAA increases markedly beyond 60, and it is almost always associated with lobar ICH. There are no specific preventive therapies for CAA-related ICH. Control of hypertension may reduce the incidence of this type of ICH,[24] but whether elevated BP or hypertension is related with worse outcomes after CAA-related ICH is unclear. We found that hypertension was significantly associated with better outcome at 3 months among patients with CAA, and that CAA patients with hypertension showed >50% lower risk of 3-month death than those without hypertension. CAA patients with mildly elevated BP on admission also showed higher rates of 1-month survival than normotensive patients. These findings are interesting, given that hypertension is generally considered an adverse factor in most cardiovascular conditions. Nevertheless, one study of lobar ICH found subarachnoid extension of the hematoma to be significantly more frequent among nonhypertensive patients,[25] and a population-based study also found no association between hypertension and risk of lobar cerebral microbleeds.[26] Our findings, together with those previous studies, pose a challenge to the concept that hypertension is a risk factor in all subtypes of ICH.[27] One potential explanation is that hypertension and atherosclerosis restructure thicken the small vessels, limiting hematoma size. Another explanation is that the long-term use of antihypertensive drugs in hypertension patients protect against the pathological mechanism underlying CAA subtype. Future studies should verify and explore the mechanisms behind the findings.

Strengths of our study include its large, heterogeneous patient population, which was prospectively recruited and systematically analyzed early after the onset of acute ICH. Nevertheless, some limitations need to be mentioned. First, we included only tertiary hospitals, which may have missed patients with less severity. Second, recent studies suggested that patients with mixed ICH (lobar and deep bleeds), was possibly driven by the vascular mechanism similar to hypertensive ICH.[28] It is possible that a proportion of patients of undetermined subtype were HA related. Finally, BP was based on a single measurement on admission and thus prone to regression attenuation bias as well as some misclassification bias with respect to hypertension status because this was based only on a history of the condition at presentation. However, the random measurement error results in underestimation of the association between the elevated BP and worse outcomes of ICH.[28] In the future, BP estimates based on repeated readings are needed to reduce random error and to validate the findings.

In summary, this large study indicates that there is an etiology-specific association between BP and 3-month mortality in ICH patients. Elevated BP on admission might be more strongly associated with higher mortality in HA and undetermined subtypes of ICH, while hypertension might be associated with better outcomes in the CAA subtype. This study suggests that the association between BP and ICH outcomes might specifically depend on its subtypes and CAA might be pathologically distinctive from other subtypes of ICH.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S3
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Summary of the unadjusted ORs and HRs of associations between blood pressure or hypertension and 3-month mortality or survival.

Factor	Subtypes	OR (95% CI)	P
SBP for trend	HA	1.32 (1.19-1.47)	<0.001
	CAA	1.10 (0.93-1.30)	0.256
	Structural lesion	1.71 (1.42-2.05)	<0.001
	Medication and Systemic disease	1.21 (1.03-1.44)	0.022
	Undetermined	1.39 (1.26-1.54)	<0.001
SBP per 20mmHg	HA	1.29 (1.18-1.41)	<0.001
	CAA	1.04 (0.89-1.21)	0.611
	Structural lesion	1.61 (1.38-1.88)	<0.001
	Medication and Systemic disease	1.18 (1.02-1.36)	0.022
	Undetermined	1.31 (1.21-1.42)	<0.001
DBP for trend	HA	1.16 (1.06-1.27)	0.001
	CAA	1.02 (0.85-1.22)	0.840
	Structural lesion	1.40 (1.14-1.72)	0.001
	Medication and Systemic disease	1.05 (0.89-1.23)	0.560
	Undetermined	1.24 (1.12-1.36)	<0.001
DBP per 10mmHg	HA	1.13 (1.05-1.21)	<0.001
	CAA	0.96 (0.83-1.09)	0.502
	Structural lesion	1.27 (1.11-1.45)	<0.001
	Medication and Systemic disease	1.03 (0.91-1.17)	0.653
	Undetermined	1.14 (1.07-1.22)	<0.001
Hypertension	CAA	0.46 (0.30-0.70)	<0.001
	Structural lesion	2.07 (1.23-3.41)	0.005
	Medication and Systemic disease	0.95 (0.60-1.52)	0.844
	Undetermined	0.96 (0.64-1.40)	0.824
Factor	**Subtypes**	**HR (95% CI)**	**P**
Hypertension	CAA	0.45 (0.25-0.81)	0.008

HA, hypertensive angiopathy; CAA, cerebral amyloid angiopathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; OR, odds ratio; CI, confidence interval; HR, hazard ratio; P, p value.

Table S2. Summary of AIC and AUC of the ROC curves in both univariable and multivariable models.

Factor	Subtypes	AIC		AUC of ROC curve	
		Univariable model	Multivariable model	Univariable model	Multivariable model
SBP for trend	HA	1437.5	995.8	0.6102	0.8711
	CAA	449.4	351.5	0.6102	0.8637
	Structural lesion	364.2	255.4	0.6102	0.8509
	Medication and Systemic disease	354.2	239.4	0.6102	0.8532
	Undetermined	995.8	685.2	0.6102	0.8699
SBP per 20mmHg	HA	1437.5	996.3	0.6183	0.8705
	CAA	449.4	352.2	0.6183	0.8635
	Structural lesion	364.2	255.3	0.6183	0.8511
	Medication and Systemic disease	354.2	239.7	0.6183	0.8508
	Undetermined	995.8	686.6	0.6183	0.8697
DBP for trend	HA	1437.5	992.2	0.5513	0.8721
	CAA	449.4	352.2	0.4486	0.8648
	Structural lesion	364.2	255.6	0.5513	0.8513
	Medication and Systemic disease	354.2	239.6	0.5513	0.8483
	Undetermined	995.8	686.7	0.5513	0.8708
DBP per 10mmHg	HA	1437.5	989.8	0.5580	0.8719
	CAA	449.4	352.2	0.4419	0.8641
	Structural lesion	364.2	255.6	0.5580	0.8522
	Medication and Systemic disease	354.2	239.6	0.5580	0.8471
	Undetermined	995.8	686.8	0.5580	0.8702
Hypertension	CAA	449.4	341.4	0.4961	0.8444
	Structural lesion	364.2	254.0	0.5038	0.8444
	Medication and Systemic disease	354.2	239.3	0.5038	0.8524
	Undetermined	995.8	693.6	0.4961	0.8681

HA, hypertensive angiopathy; CAA, cerebral amyloid angiopathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; AUC, area under curve; AIC, Akaike information criterion; ROC, receiver operating characteristic.

Table S3. Comparison of the studies of SMASH-U classification in ICH.

SMASH-U classification	Total	HA	CAA	Structural lesion	Medication	Systemic Disease	Undetermined
Studies							
Meretoja et al., 2012 [15]	n=1013	35.0%	20.0%	5.0%	14.0%	5.0%	21.0%
Palm et al., 2013 [20]	n=152	51.0%	31.0%	3.0%	11.0%	-	4.0%
Yeh et al., 2014 [21]	n=3785	55.0%	12.0%	8.0%	3.0%	12.0%	10.0%
3-month mortality							
Meretoja et al., 2012 [15]	31.30%	31.3%	20.9%	4.0%	53.8%	43.8%	29.6%
Palm et al., 2013 [20]	44.10%	50.0%	35.5%	0.0%	11.3%	-	3.2%
Yeh et al., 2014 [21]	22.10%	14.2%	22.0%	5.4%	54.5%	55.9%	28.0%

Figure S1. Minimum diagnostic flow diagram for intracerebral hemorrhage.

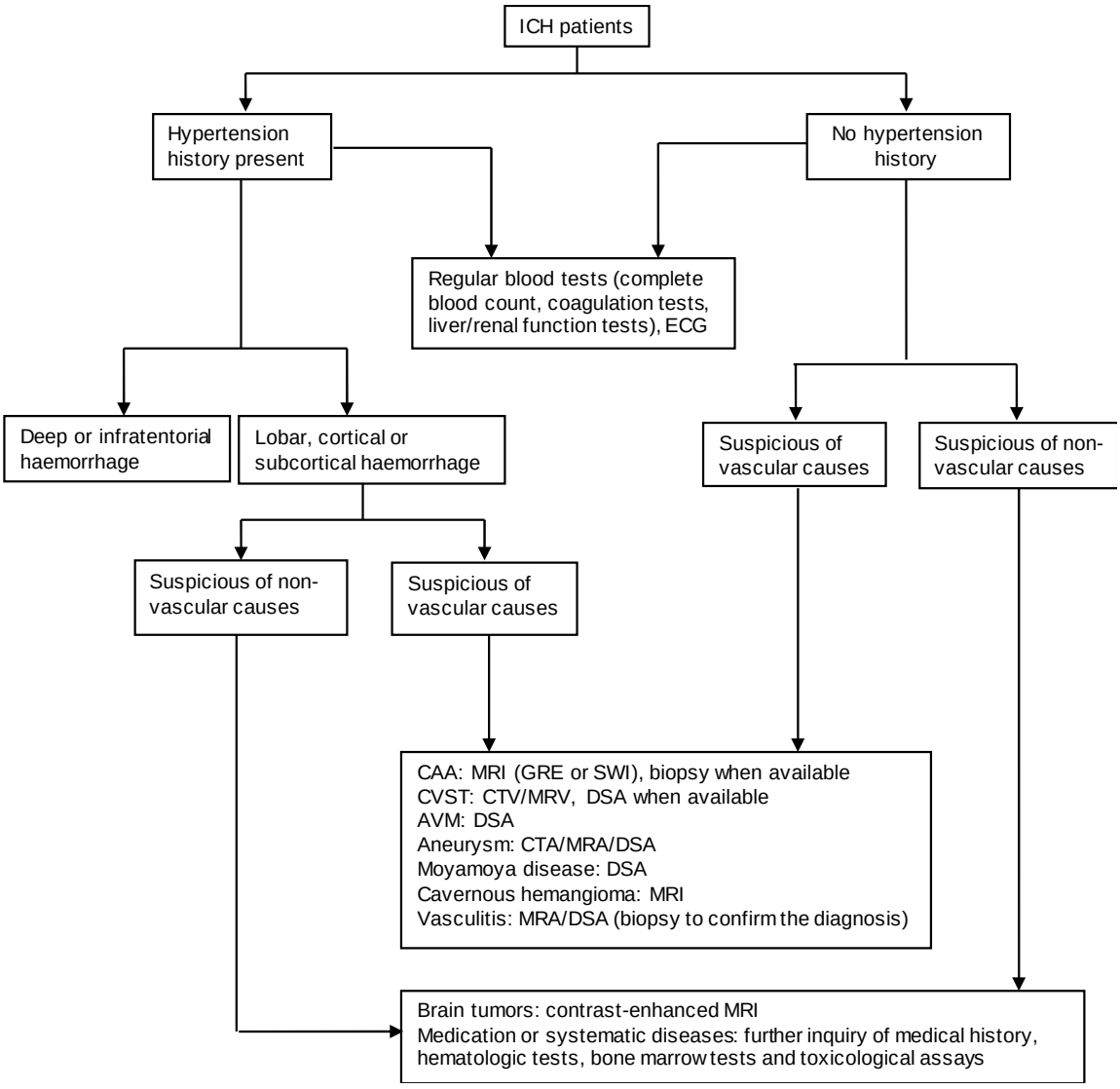
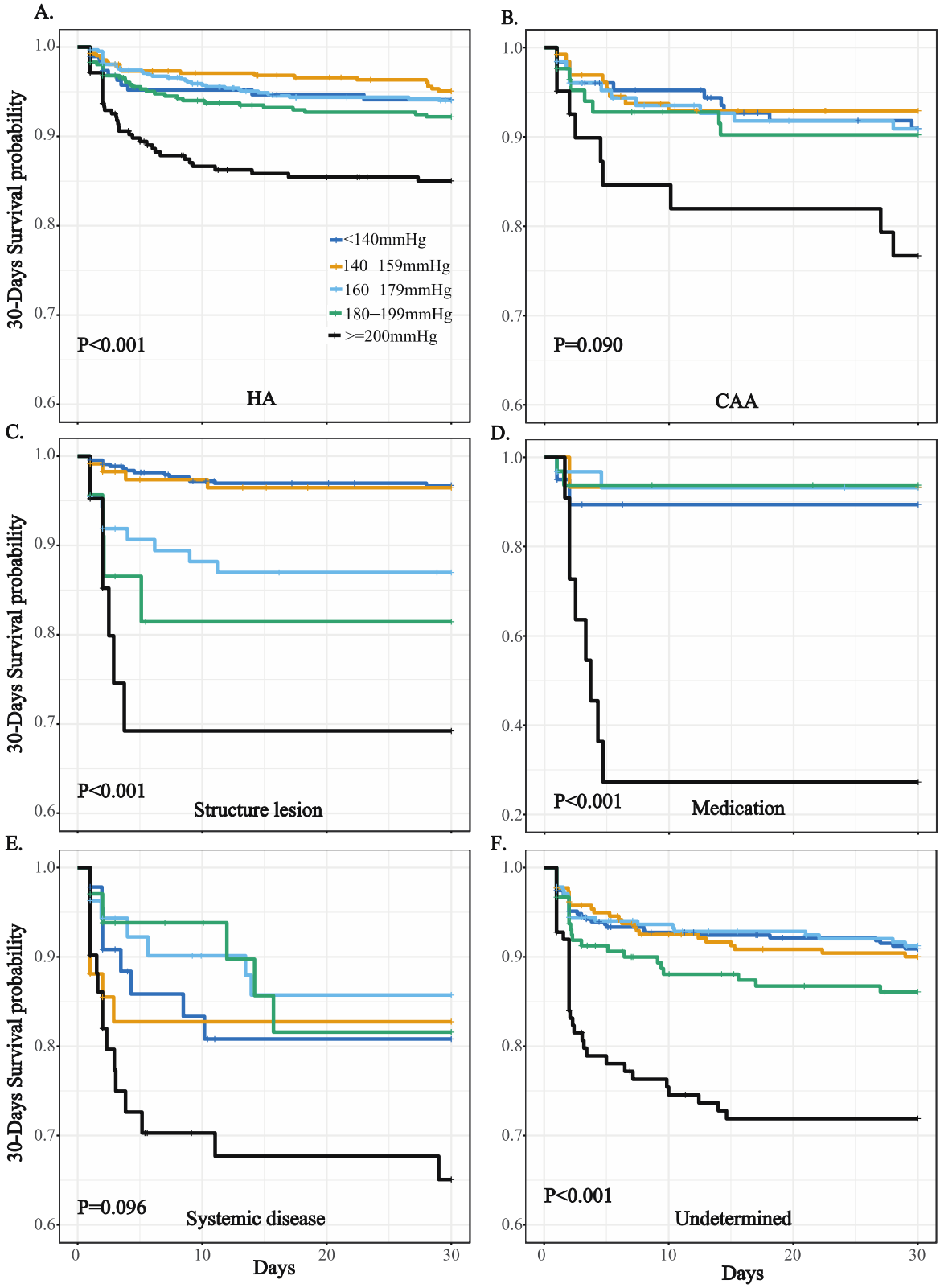
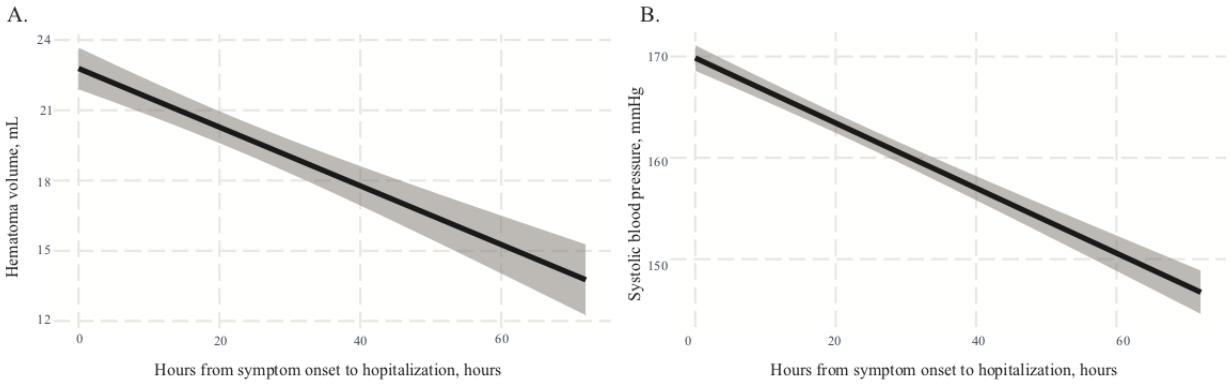


Figure S2. Kaplan-Meier analysis of 1-month survival of ICH patients according to five systolic blood pressure levels in different subtypes.



SBP, systolic blood pressure; HA, hypertensive angiopathy; CAA, cerebral amyloid angiopathy. The difference among five SBP levels in each ICH subtype was analyzed by log-rank test.

Figure S3. Relationship between the time from symptoms onset to hospitalization and hematoma volume or systolic blood pressure (SBP).



(A) The time from symptoms onset to hospitalization was significantly correlated with hematoma volume (OR 0.88, 95%CI 0.86-0.91, P<0.001); (B) The time from symptoms onset to hospitalization was significantly correlated with systolic blood pressure (OR 0.73, 95%CI 0.70-0.75, P<0.001).