Original Article

Blood Pressure Variability and Outcome in Patients with Acute Nonlobar Intracerebral Hemorrhage following Intensive Antihypertensive Treatment

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Abstract

Background: Blood pressure (BP) variability has been associated with stroke risk. We elucidated the association between systolic BP (SBP) variation and outcomes in patients with nonlobar intracerebral hemorrhage (ICH) following intensive antihypertensive treatment upfront.
Methods: We screened consecutive patients with spontaneous ICH who underwent intensive antihypertensive treatments targeting BP <140 mmHg between 2008 and 2016. SBPs were monitored hourly during the acute period (≤7 days after symptom onset) in the intensive care unit. SBP variability was determined in terms of range, standard deviation (SD), coefficient of variation (CoV), and mean absolute change (MAC). The primary outcomes included hematoma growth and poor clinical outcome at 3 months (modified Rankin Scale [mRS] score ≥3. The secondary outcome was an ordinal shift in mRS at 3 months.
Results: A total of 104 individuals (mean age, 63.0 ± 13.5 years; male, 57.7%) were included in this study. In multivariable model, MAC (adjusted odds ratio [*OR*], 1.11; 95% confidence interval [*CI*]: 1.02–1.21; *P* = 0.012) rather than the range of SD or CoV, was significantly associated with hematoma growth even after adjusting for mean SBP level. Sixty-eight out of 104 patients (65.4%) had a poor clinical outcome at 3 months. SD and CoV of SBP were significantly associated with a 3-month poor clinical outcome even after adjusting for mean SBP. In addition, in multivariable ordinal logistic models, the MAC of SBP was significantly associated with higher shift of mRS at 3 months (adjusted *OR*, 1.08; 95% *CI*: 1.02–1.15; *P* = 0.008).
Conclusions: The MAC of SBP is associated with hematoma growth, and SD and COV are correlated with 3-month poor outcome in patients with supratentorial nonlobar ICH. Therefore, sustained SBP control, with a reduction in SBP variability is essential to reinforce the beneficial effect of intensive antihypertensive treatment.

Key words: Blood Pressure; Hemorrhage; Outcome

Introduction

Primary intracerebral hemorrhage (ICH) is associated with higher mortality and disability than ischemic stroke. More than one-third of all patients experienced mortality, and 68% of survivors showed poor clinical outcome at 1-month follow-up.[1] High blood pressure (BP) is a well-known risk factor for hematoma growth[2] and poor clinical outcome.[3] Because acute hypertensive response (defined as systolic BP [SBP] over 140 mmHg or diastolic BP over 90 mmHg in two recorded BP measurements taken 5 min apart within 24 h after symptom onset) has been reported up to 75% after ICH development,[4] intensive antihypertensive upfront is widely used. Most physicians tend to treat high BP based on systolic or mean BP. Sakamoto *et al*.[5] reported that mean SBP after standardized antihypertensive treatment was associated with poor outcomes (odds ratio [*OR*]: 2.03; 95% confidence

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interval [*CI*]: 1.24–3.33) and hematoma growth (*OR*: 1.86; 95% *CI*: 1.09–3.16). Nevertheless, an absolute parameter such as systolic or mean BP alone did not contribute to the beneficial effect of antihypertensive medication in terms of reduction of cardiovascular events.[3] Webb *et al*.[6] reported that stroke risk was also determined by variation in SBP as well as mean BP. Accordingly, interindividual variation of BP should be considered to estimate risk reduction of stroke.

Any study of the factors associated with clinical outcomes after ICH development should consider ICH location. The main causes of primary ICH include arterial hypertension and cerebral amyloid angiopathy (CAA).[7] Although hypertensive ICH has been reported to account for nearly 90% of the spontaneous ICH,[8] distinguishing hypertensive ICH from CAA is difficult based on radiologic examination alone, without pathological confirmation. Nevertheless, previous studies showed that CAA was associated with lobar ICH, especially in elderly patients.[9] Patients with lobar ICH appear to exhibit greater degree of hemorrhage and extension to subarachnoid or subdural space than nonlobar ICH.[10] Samarasekera *et al*.[10] reported that lobar ICH exhibited lower 1-year fatality rate than nonlobar ICH, although lobar ICH showed a higher frequency of recurrence. In addition, nonlobar ICH was significantly related to hypertension.[11] Therefore, the significance of BP variation in outcomes of ICH patients should be based on hematoma location. The aim of this study was to clarify the association between BP variability and outcomes in patients with nonlobar ICH following upfront and intensive antihypertensive treatment.

Methods

Ethical approval

This study was approved by the Chuncheon Sacred Heart Hospital Institutional Review Boards/Ethics Committee (IRB No. 2016_57), and the patient consent was waived due to retrospective nature of the study.

Clinical reviews were conducted with ICH patients identified in a prospective ICH database between January 2008 and December 2016 were done. The inclusion criteria of the study were: (1) adult patients aged 18 years and above presenting with spontaneous ICH; (2) high SBP, 150–220 mmHg at admission; (3) absence of contraindications to antihypertensive medication; (4) time from symptom onset to diagnosis ≤6 h; (5) supratentorial hematoma volume <60 ml;[12] and (6) patients who underwent intensive antihypertensive treatments targeting BP <140 mmHg within 4 h after diagnosis.[3,12] The exclusion criteria were as follows: (1) patients who had structural causes of ICH such as aneurysms, arteriovenous malformation, moyamoya disease, or dissections; (2) patients who did not have 3-month clinical outcome; (3) patients who underwent early surgery for hematoma evacuation to control intracranial pressure; and (4) lobar ICH of the frontal, parietal, temporal, and occipital cortex [Figure 1]. Continuous intravenous antihypertensive medication using nicardipine or labetalol was administered for 24 h. Oral BP-lowering medications were added after cardiology consultation. BP was monitored every 15 min during the first 2 h and hourly until the follow-up computed tomography (CT) scan and during the entire admission period in the intensive care units. The follow-up CT scan was performed immediately following a change in the patient's neurological status, and under stable conditions, it was repeated at 24–48 h from the initial scan. Hematoma growth was defined as hematoma expansion >33% on follow-up (CT).[5] Magnetic resonance imaging was used to assess underlying vascular abnormalities. Hematoma volume was measure by the ABC/2 method using DicomViewer software (OsiriX imaging software; http://www.osirix-viewer.com/) (A, greatest diameter of the hemorrhage; B, largest perpendicular diameter to A; and C, sum of the thickness).[13]

The primary outcomes were hematoma growth and poor clinical outcome at 3 months (defined as modified Rankin Scale [mRS] score ≥cOR The secondary outcome was an ordinal shift in mRS at 3 months.[3] Medical records including gender, age, hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, smoking, history of antithrombotic use, onset to diagnosis and treatment time, initial ICH volume, and laboratory results were reviewed. BP variability in the acute period (<7 days after diagnosis)[3] included range, standard deviation (SD), coefficient of variation (CoV), and mean absolute change (MAC).

Statistical analysis

The baseline characteristics of the participants were presented with mean ± standard deviation (SD) or median (interquartile range) for continuous variable and number (proportion) for categorical variables as appropriate. We performed Spearman's correlation test to assess the association between BP parameters including variability index (range, SD, CoV, and MAC), hematoma growth, and crude 3-month mRS. We used multivariable binary logistic regression analysis to evaluate the effect of BP parameters on hematoma expansion or poor clinical outcome at 3 months. In addition, we used multivariable ordinal logistic regression analysis to evaluate

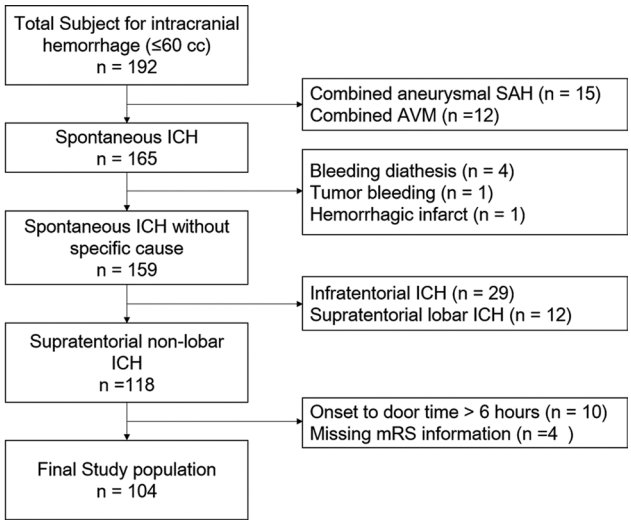

Figure 1: Flow diagram of the study. ICH: Intracerebral hemorrhage; SAH: Subarachnoid hemorrhage; mRS: Modified rankin scale.

the effect of BP parameters on 3-month mRS scores. All mRS scores were subgrouped into 0–1, 2, 3, 4, and 5–6, and entered into ordinal logistic regression model. We interpreted the *OR*s for the ordinal logistic regression as a common *OR* of shift in the 3-month mRS score to the higher (worsening of the clinical outcome) in association with the BP parameters. We entered mean glucose and all variables that were statistically significant at $P < 0.10$ in univariable analyses. We considered two-sided $P < 0.05$ statistically significant in multivariable analysis, which was performed using IBM SPSS 23.0 (SPSS Inc., Chicago, IL, USA) and R version 3.3.1 (R Foundation for Statistical Computing).

Table 1: Baseline characteristics of participating subjects with an acute nonlobar ICH (n = 104)

Variables	Value
Male	60 (57.7)
Age (years)	63.0 ± 13.5
Onset to visit time (min)	100 (53–218)
CT time interval (h)	22.0 (13.0–41.5)
Type of management	
Conservative	83 (79.8)
Burr hole trephination	19 (18.3)
Craniectomy	2 (1.9)
Comorbidities	
Hypertension	60 (57.7)
Diabetes mellitus	20 (19.2)
Coronary artery disease	7 (6.7)
Smoking	24 (23.1)
Chronic kidney disease	4 (3.8)
Previous antithrombotics use	
Aspirin	9 (8.7)
Clopidogrel	3 (2.9)
Aspirin + clopidogrel	3 (2.9)
Anticoagulants	4 (3.8)
Others	2 (1.9)
Laboratory parameters	
Albumin (g/L)	42 ± 5
LDL cholesterol (mmol/L)	2.59 ± 0.83
Glucose (mmol/L)	6.94 (5.88–8.88)
Hemoglobin (mmol/L)	8.69 ± 1.24
Platelet ($\times 10^9$/L)	232.4 ± 74.9
BUN (mmol/L)	4.91 (4.15–6.31)
Creatinine (μmol/L)	70.74 (61.89–88.42)
BP parameter (systolic)	
Number of measurement	23 (15–40)
Mean (mmHg)	134 (128–138)
Maximum (mmHg)	159 (149–171)
Minimum (mmHg)	110 (104–117)
Range (mmHg)	49 (36–60)
SD (mmHg)	11.9 (9.7–14.6)
CoV (%)	9.0 (7.0–11.0)
MAC (mmHg/n)	15.3 (12.3–20.5)

Data are presented as n (%) or mean ± SD or median (IQR). SD: Standard deviation; IQR: Interquartile range; LDL: Low-density lipoprotein; BUN: Blood urea nitrogen; BP: Blood pressure; CoV: Coefficient of variation; MAC: Mean absolute change; CT: Computed tomography; ICH: Intracerebral hemorrhage; SD:Standard deviation; IQR :Interquantile range.

Results

Baseline characteristics

A total of 104 individuals (mean age, 63.0 ± 13.5 years; male, 57.7%) were included in this study. The mean onset-to-visit time was 100 (53–218) min. A time interval from initial CT to follow-up was 22.0 (13.0–41.5) h. More than half of the patients had a history of hypertension, and one-fifth of the patients had diabetes mellitus. BP measurement was performed 23 (15–40) times during the interval between initial and follow-up CT scan, and the median of mean SBP was 134 (128–138) mmHg. Range, SD, CoV, and MAC of the SBP are shown in Table 1.

Hematoma growth

Table 2 shows the correlations between SBP parameters and hematoma growth and crude 3-month mRS scores. Mean SBP was not correlated with hematoma growth. Hematoma growth was not correlated with range, SD, CoV, and MAC of the SBP in Spearman's correlation analyses. In univariable logistic regression analysis [Table 3], female, hematoma volume at admission, hypertension, and low-density lipoprotein (LDL) cholesterol level were associated with hematoma growth. In multivariable model, MAC (adjusted *OR*, 1.11; 95% *CI*: 1.02–1.21; $P = 0.012$) rather than SD or CoV of the SBP was significantly associated with hematoma growth even after adjusting for mean SBP level [Table 4]. In addition, hematoma volume at admission and history of hypertension were significant predictors for hematoma growth in all multivariable models.

Functional outcome

Sixty-eight out of 104 patients (65.4%) showed a poor clinical outcome (mRS 3–6) at 3 months. Age, onset-to-visit time, hematoma volume at admission, and LDL cholesterol level were correlated with poor clinical outcomes [Table 5]. Among BP variability indices, SD and CoV of the SBP (but not the ranges of MAC) were positively associated with poor clinical outcome at 3 months in univariable binary logistic regression analysis. Diabetes mellitus had a marginal association with poor clinical outcome (*OR*, 3.67; 95% *CI*: 1.00–13.50, $P = 0.051$); therefore, it was entered into multivariable model as a covariate. Table 6 highlights the results of multivariable binary logistic regression analysis of predictors for poor clinical outcome at 3 months. Range and MAC of the SBP were not associated with 3-month poor clinical outcome. However, the SD and CoV of SBP were significantly correlated with poor clinical outcome even after adjusting for mean SBP. In addition, we performed a shift analysis of poor clinical outcome using ordinal logistic regression analysis, in which a shift to the higher score of mRS represented worsening clinical outcome at 3 months [Table 7]. In multivariable ordinal logistic models [Table 8], MAC of the SBP was significantly correlated with a higher shift of mRS (worsening clinical outcome) at 3 months (*OR*, 1.07; 95% *CI*: 1.01–1.14; $P = 0.051$). The SD or CoV of the SBP also showed a positive correlation with a higher shift of mRS, without statistical significance.

Table 2: Correlation between SBP parameters, Δ ICH, and crude 3M mRS score

Items	BP (*n*)	Mean	Range	SD	CoV	MAC	Δ ICH	3M mRS
BP (*n*)	–							
Mean	0.158	–						
Range	0.456†	0.263†	–					
SD	0.051	0.208*	0.805†	–				
CoV	0.046	0.024	0.779†	0.974†	–			
MAC	0.676†	0.106	0.031	0.439†	0.419†	–		
Δ ICH	0.026	0.119	0.067	0.099	0.068	0.123	–	
3M mRS	0.145	0.055	0.090	0.180	0.176	0.168	0.350†	–

Values are Spearman's correlation coefficients, *P<0.05; †P<0.01. SD: Standard deviation; CoV: Coefficient of variation; MAC: Mean absolute change; Δ ICH: Hematoma growth; 3M mRS: 3-month modified Rankin Scale score; BP: Blood pressure; –: No available data

Table 3: Univariable logistic regression analysis of Δ ICH

Variables	*OR* (95% *CI*)	*P*
Age	0.98 (0.95–1.01)	0.121
Female	0.44 (0.19–0.98)	0.045
Onset to visit time	1.00 (1.00–1.00)	0.625
Hematoma volume at admission	1.12 (1.05–1.18)	<0.001
CT interval time	1.01 (0.98–1.03)	0.464
Hypertension	2.29 (1.02–5.16)	0.045
Diabetes mellitus	0.50 (0.17–1.41)	0.188
Smoking	1.77 (0.71–4.44)	0.222
Antiplatelet usage	1.41 (0.55–3.63)	0.474
Albumin	1.04 (0.95–1.13)	0.420
LDL cholesterol	0.52 (0.31–0.88)	0.016
Glucose	1.11 (0.98–1.26)	0.115
Hemoglobin	1.17 (0.85–1.61)	0.328
Platelet count	1.00 (0.99–1.00)	0.116
BUN	1.01 (0.91–1.11)	0.926
Creatinine	0.99 (0.98–1.00)	0.228
BP (*n*)	1.00 (0.98–1.03)	0.718
Mean	1.03 (0.99–1.08)	0.197
Range	1.00 (0.98–1.02)	0.820
SD	1.03 (0.94–1.12)	0.585
CoV	1.02 (0.91–1.16)	0.719
MAC	1.05 (0.99–1.11)	0.119

OR: Odds ratio; LDL: Low-density lipoprotein; BUN: Blood urea nitrogen; BP: Blood pressure; SD: Standard deviation; CoV: Coefficient of variation; MAC: Mean absolute change; *CI*: Confidence interval; CT: Computed tomography; Δ ICH: Hematoma growth.

Discussion

Associations between SBP and outcomes yielded conflicting results. In patients with acute ICH and initial SBP >180 mmHg, hematoma growth and poor outcome were correlated with mean SBP.[5] Conversely, the Antihypertensive Treatment of Acute Cerebral Hemorrhage 2[14] trial found no beneficial effect of intensive treatment (SBP 110–139 mmHg) compared with standard reduction (SBP 140–179 mmHg (relative risk, 1.04; 95% *CI*: 0.85–1.27) in ICH patients with an initial hematoma volume <60 cm^3. A recent meta-analysis conducted by Boulouis *et al*. reported that intensive BP lowering failed to decrease the mortality and morbidity compared with standard antihypertensive treatment (*OR*: 0.91; 95% *CI*: 0.80–1.02; P = 0.106).[15] A significant increase in ICH occurred in standard treatment (*OR*: 0.82; 95% *CI*: 0.68–1.00, P = 0.056). Despite differences in the definition of poor outcome (mRS score >3 or >4),[14] hematoma volume at admission and its location yielded conflicting results, and future stroke risks were also determined by BP variability.[3,6] Therefore, the clinical significance of BP variability should be evaluated in ICH patients undergoing intensive antihypertensive treatment. Tanaka *et al*.[12] reported that SBP variability (SD and successive variation [SV]) during the first 24 h were associated with poor outcomes and early neurologic deterioration. In their study, SV variation of SBP increased the risk of poor outcomes (*OR*, 1.42; 95% *CI*: 1.04–1.97) and neurologic deterioration (*OR*, 2.37; 95% *CI*: 1.32–4.83). Manning *et al*.[3] investigated BP variables to predict outcomes of acute ICH patients in two phases of hyperacute (in the first 24 h after symptom onset) and acute (days 2–7 after symptom onset). Maximum SBP in the hyperacute phase and SD of SBP in the acute phase were significantly associated with poor clinical outcome at 3 months (mRS score ≥3). In contrast, Anderson *et al*.[16] did not find a significant improvement following intensive treatment (target SBP <140 mmHg within 1 h) or guideline-recommended treatment (target SBP <180 mm Hg) group (*OR*, 0.87; 95% *CI*: 0.75–1.01). However, the ordinal analysis showed a significantly lower mRS score in patients treated with intensive antihypertensive medication (*OR*, 0.87; 95% *CI*: 0.77–1.00). A *post hoc* analysis[17] of the two clinical trials, Continue or Stop Post-Stroke Antihypertensive Collaborative Study (COSSACS)[18] and Controlling Hypertension and hypotension immediately post stroke (CHHIPS)[19] showed no correlation between short-term BP variability (SD) and early outcome (2 weeks) after stroke onset (COSSACS, *OR*: 0.98, 95% *CI*: 0.78–1.23; CHHIPS, *OR*: 0.97, 95% *CI*: 0.90–1.11). However, their results were mainly derived from ischemic stroke patients, with relatively delayed recruitment time after symptom onset (within 36 h in CHHIPS and 48 h in COSSACS study) and short-term follow-up clinical outcomes (2 weeks).[3]

In addition to the different characteristics of the enrolled patients, the guidelines for BP management, the frequency of BP measurement and choice of antihypertensive drugs also resulted in conflicting results in acute ICH patients. The second Intensive Blood Pressure Reduction in the

Table 4: Predictors of Δ ICH in multivariable binary logistic regression analysis

Parameters	Model 1		Model 2		Model 3		Model 4	
	aOR (95% *CI*)	*P*	aOR (95% *CI*)	*P*	aOR (95% *CI*)	*P*	aOR (95% *CI*)	*P*
Female	0.51 (0.18–1.42)	0.196	0.47 (0.17–1.28)	0.138	0.46 (0.17–1.28)	0.136	0.45 (0.16–1.25)	0.126
Initial hematoma volume	1.13 (1.06–1.21)	<0.001	1.13 (1.06–1.20)	<0.001	1.12 (1.06–1.20)	<0.001	1.15 (1.07–1.24)	<0.001
Hypertension	3.67 (1.31–10.35)	0.014	3.78 (1.34–10.64)	0.012	3.78 (1.34–10.65)	0.012	5.42 (1.73–16.96)	0.004
LDL cholesterol	0.58 (0.30–1.05)	0.069	0.57 (0.31–1.06)	0.073	0.57 (0.31–1.06)	0.073	0.61 (0.32–1.16)	0.128
BP								
Mean	1.03 (0.97–1.09)	0.419	1.02 (0.96–1.08)	0.548	1.02 (0.97–1.08)	0.498	1.00 (0.95–1.06)	0.933
Range	1.00 (0.97–1.02)	0.740	–	–	–	–	–	–
SD	–	–	1.02 (0.91–1.13)	0.758	–	–	–	–
CoV	–	–	–	–	1.03 (0.89–1.19)	0.737	–	–
MAC	–	–	–	–	–	–	1.11 (1.02–1.21)	0.012

Covariates were adjusted for female, initial hematoma volume, hypertension, LDL cholesterol, mean BP, and range (model 1), SD (model 2), CoV (model 3) or MAC (model 4). aOR: Adjusted odds ratio; *CI*: Confidence interval; LDL: Low-density lipoprotein; SD: Standard deviation; CoV: Coefficient of variation; MAC: Mean absolute change; BP: Blood pressure; Δ ICH: Hematoma growth; –: Value of 1.0 (correlation).

Table 5: Results of univariable binary logistic regression analysis for poor clinical outcome at 3 months

Variables	Poor outcome (*n* = 68)	Good outcome (*n* = 36)	*OR* (95% *CI*)	*P*
Age (years)	64.9 ± 13.2	59.4 ± 13.6	1.03 (1.00–1.07)	0.049
Female (%)	26 (59.1)	18 (40.9)	1.62 (0.71–3.65)	0.249
Onset to visit time (min)	84 (46–165)	144 (60–320)	1.00 (0.99–1.00)	0.020
Hematoma volume at admission (ml)	13 (10–20)	10 (5–14)	1.08 (1.02–1.15)	0.011
CT interval time (h)	21.2 (14.6–42.6)	23.8 (12.1–40.6)	1.00 (0.98–1.02)	0.864
Hypertension (%)	43 (63.2)	17 (47.2)	1.92 (0.85–4.36)	0.118
Diabetes mellitus (%)	17 (25.0)	3 (8.3)	3.67 (1.00–13.50)	0.051
Smoking (%)	18 (26.5)	6 (16.7)	1.80 (0.64–5.04)	0.263
Antiplatelet usage (%)	15 (22.1)	7 (19.4)	1.17 (0.43–3.20)	0.756
Albumin (g/L)	42 ± 5	42 ± 4	1.01 (0.93–1.10)	0.842
LDL cholesterol (mmol/L)	2.45 ± 0.73	2.87 ± 0.91	0.51 (0.30–0.88)	0.015
Glucose (mmol/L)	6.94 (6.05–8.87)	6.88 (5.73–9.48)	0.99 (0.88–1.12)	0.894
Hemoglobin (mmol/L)	8.75 ± 1.24	8.56 ± 1.37	1.10 (0.80–1.52)	0.560
Platelet count ($\times 10^9$/L)	225 ± 72	246 ± 80	1.00 (0.99–1.00)	0.184
BUN (mmol/L)	5.32 (4.32–6.77)	4.71 (3.82–5.72)	1.03 (0.91–1.16)	0.631
Creatinine (μmol/L)	75.16 (61.89–88.42)	70.74 (55.26–86.21)	1.00 (1.00–1.00)	0.895
BP (*n*)	21 (15–40)	27 (13–42)	0.99 (0.97–1.02)	0.618
Mean (mmHg)	133.3 ± 9.1	133.8 ± 8.9	0.99 (0.95–1.04)	0.789
Range (mmHg)	52.0 ± 21.6	46.6 ± 18.8	1.01 (0.99–1.04)	0.206
SD (mmHg)	13.1 ± 4.7	11.1 ± 3.5	1.13 (1.01–1.26)	0.034
CoV (%)	9.8 ± 3.4	8.3 ± 2.5	1.20 (1.03–1.39)	0.022
MAC (%)	17.9 ± 7.9	15.9 ± 5.2	1.05 (0.98–1.12)	0.171

Data are shown as *n* (%), mean ± SD or median (IQR); *OR*: Odds ratio; *CI*: Confidence interval; LDL: Low-density lipoprotein; BUN: Blood urea nitrogen; SD: Standard deviation; CoV: Coefficient of variation; MAC: Mean absolute change; BP: Blood pressure; CT: Computed tomography; IQR: Interquantile range.

Acute Cerebral Hemorrhage Trial (INTERACT2)[3] assessed the predictive value of BP variability in outcomes for ICH patients (within 6 h after symptom onset) targeting BP levels to lower than 140 mmHg. BP was measured five times during the first 24 h and twice daily until day 7 after ICH onset. The Stroke Acute Management with Urgent Risk Factor Assessment and Improvement studies[12] included patients within 3 h after symptom onset with initial SBP exceeding 180 mmHg. The SBP was lowered to 120–160 mmHg. In our study, SBP was maintained intensively to a target level of <140 mmHg. In addition, about 22 BP measurements were performed in 22 h of repeated CT scan intervals. Therefore, our study presents a more accurate assessment of BP variability in ICH patients. Among acute ICH patients who underwent intensive antihypertensive treatment, BP variability was positively associated with poor functional outcome at 3 months of follow-up. Therefore, the benefits of intensive treatment can be reinforced with sustained control of SBP, and reducing BP variability. Liu-DeRyke *et al*.[20] reported that nicardipine provided superior therapeutic response than labetalol in terms of BP maintenance and lesser BP variability than labetalol in patients presenting with acute stroke. More specifically, SD of SBP was 15.0 (11.8–17.0) in nicardipine group and 19.0 (13.8–22.9) in labetalol group ($P = 0.006$). By contrast, such a difference was not observed in another cohort.[21] Ortega-Gutierrez *et al*.

Table 6: Results of multivariable binary logistic regression analysis of predictor of poor clinical outcome at 3 months

Parameters	Model 1		Model 2		Model 3		Model 4	
	aOR (95% *CI*)	*P*	aOR (95% *CI*)	*P*	aOR (95% *CI*)	*P*	aOR (95% *CI*)	*P*
Age	1.04 (0.99–1.08)	0.095	1.04 (0.99–1.08)	0.093	1.04 (0.99–1.08)	0.091	1.05 (1.00–1.09)	0.035
Onset to door time	0.99 (0.99–1.00)	0.002	0.99 (0.99–1.00)	0.003	0.99 (0.99–1.00)	0.002	0.99 (0.99–1.00)	0.006
Hematoma volume at admission	1.11 (1.04–1.19)	0.003	1.11 (1.04–1.19)	0.002	1.11 (1.04–1.19)	0.002	1.12 (1.04–1.20)	0.002
Diabetes mellitus	5.17 (1.01–26.41)	0.048	5.72 (1.14–28.64)	0.034	5.65 (1.13–28.17)	0.035	3.96 (0.87–18.13)	0.076
LDL cholesterol	0.41 (0.20–0.85)	0.017	0.42 (0.20–0.87)	0.020	0.42 (0.20–0.87)	0.019	0.44 (0.22–0.92)	0.028
BP								
Mean	0.95 (0.89–1.01)	0.119	0.95 (0.89–1.01)	0.090	0.96 (0.90–1.02)	0.198	0.97 (0.91–1.03)	0.304
Range	1.03 (1.00–1.06)	0.102	–	–	–	–	–	–
SD	–	–	1.19 (1.03–1.38)	0.019	–	–	–	–
CoV	–	–	–	–	1.27 (1.05–1.55)	0.016	–	–
MAC	–	–	–	–	–	–	1.06 (0.97–1.15)	0.197

Covariates were adjusted for age, onset to door time, hematoma volume at admission, diabetes mellitus, LDL cholesterol, mean BP, and range (model 1), SD (model 2), CoV (model 3) or MAC (model 4). aOR: Adjusted odds ratio; *CI*: Confidence interval; LDL: Low density lipoprotein; SD: Standard deviation; CoV: Coefficient of variation; MAC: Mean absolute change; –: Value of 1.0 (correlation).

Table 7: Results of univariable ordinal logistic regression analysis for higher shift of mRS score at 3 months

Variables	cOR (95% *CI*)	*P*
Age	1.04 (1.01–1.06)	0.006
Female	0.68 (0.34–1.36)	0.275
Onset to visit time	1.00 (0.99–1.00)	0.065
Hematoma volume at admission	1.06 (1.03–1.10)	0.002
CT interval time	1.00 (0.98–1.02)	0.782
Hypertension	1.76 (0.87–3.58)	0.116
Diabetes mellitus	2.41 (1.02–5.77)	0.046
Smoking	1.02 (0.46–2.25)	0.969
Antiplatelet usage	1.88 (0.79–4.56)	0.157
Albumin	1.00 (0.93–1.07)	0.940
LDL	0.54 (0.34–0.83)	0.006
Glucose	1.02 (0.91–1.14)	0.722
Hemoglobin	0.97 (0.73–1.28)	0.809
Platelet count	1.00 (0.99–1.00)	0.194
BUN	1.03 (0.92–1.17)	0.611
Creatinine	1.00 (1.00–1.00)	0.924
BP (*n*)	0.99 (0.97–1.01)	0.253
Mean	1.01 (0.97–1.05)	0.665
Range	1.01 (0.99–1.03)	0.326
SD	1.09 (1.00–1.17)	0.050
CoV	1.12 (1.00–1.25)	0.045
MAC	1.07 (1.01–1.13)	0.013

cOR: Common odds ratio; LDL: Low-density lipoprotein; BUN: Blood urea nitrogen; BP: Blood pressure; SD: Standard deviation, CoV: Coefficient of variation; MAC: Mean absolute change; mRS: Modified Rankin Scale; CT: Computed tomography.

showed that the median percentage of BP variability was not significantly different among patients with nicardipine, labetalol, or a combination of both.[21] Tachycardia alone was apparent in patients treated with a combination of nicardipine and labetalol together compared with those treated with nicardipine or labetalol ($P < 0.001$). Therefore, further studies are needed to focus on anti-hypertensive drug regiments and SBP variability, and its association with neurologic outcome in acute ICH patients.

ICH location was associated with clinical outcomes in ICH patients due to altered pathophysiology. In primary ICH, lobar ICH in elderly patients occurred more frequently associated with CAA than hypertensive small vessel disease.[22] Vascular structural changes such as basement membrane thickening and endothelial dysfunction in elderly patients increase susceptibility to hemodynamic stress.[23] Older age has been reported to be a risk factor for lobar ICH. According to Kremer *et al*.,[22] age was related to increased risk of lobar ICH (hazard ratio per 10 years 1.90; 95% *CI*: 1.17–3.10), but not nonlobar ICH.

Matsukawa *et al*.[24] reported that age above 70 years was related to lobar ICH (*OR*, 4.1; 95% *CI*: 2.1–8.2). Although baroreceptor reflex was affected by gender and age,[25] further studies investigating the relationship between baroreceptor sensitivity and ICH outcome according to type or location are required. Oral anticoagulation and male gender were significant risk factors for nonlobar ICH. Martini *et al*.[11] showed that hypertension increased the risk of nonlobar ICH (*OR*, 2.87; 95% *CI*: 2.13–3.86) but not lobar ICH. In addition, lobar ICH showed a higher recurrence rate compared with nonlobar ICH.[9] Compared with supratentorial ICH, infratentorial ICH resulted in poor outcome. Delcourt *et al*.[26] reported that infratentorial ICH increased the risk of death or major disability (*OR*, 3.04; 95% *CI*: 1.68–5.50). Accordingly, the significance of BP variability may be more accurately assessed according to ICH location (lobar vs. nonlobar ICH; supratentorial vs. infratentorial). Our study showed that MAC of SBP was associated with hematoma growth and SD, CV, or MAC were associated with poor clinical outcome in patients with supratentorial nonlobar ICH.

We suggest that BP variability in hematoma and poor functional outcome in patients with primary ICH may be attributed to the following factors. First, autonomic dysfunction such as baroreflex impairment and sympathetic overactivity may be related to poor outcome in ICH patients with increased BP variability.[12] Sykora *et al*.[27]

Table 8: Results of multivariable ordinal logistic regression analysis of higher shift of mRS score at 3 months

Parameters	Model 1		Model 2		Model 3		Model 4	
	aOR (95% *CI*)	*P*	aOR (95% *CI*)	*P*	aOR (95% *CI*)	*P*	aOR (95% *CI*)	*P*
Age	1.05 (1.01–1.08)	0.004	1.04 (1.01–1.07)	0.007	1.04 (1.01–1.07)	0.007	1.04 (1.02–1.08)	0.003
Onset to door time	1.00 (0.99–1.00)	0.008	1.00 (0.99–1.00)	0.010	1.00 (0.99–1.00)	0.009	1.00 (0.99–1.00)	0.017
Hematoma volume at admission	1.07 (1.04–1.12)	<0.001	1.08 (1.04–1.12)	<0.001	1.08 (1.04–1.12)	<0.001	1.09 (1.05–1.14)	<0.001
Diabetes mellitus	2.21 (0.85–5.85)	0.105	2.53 (0.97–6.76)	0.060	2.55 (0.98–6.82)	0.058	2.32 (0.90–6.12)	0.084
LDL	0.59 (0.37–0.92)	0.020	0.59 (0.37–0.93)	0.024	0.59 (0.37–0.93)	0.024	0.63 (0.40–1.00)	0.051
BP								
Mean	1.00 (0.96–1.05)	0.906	1.00 (0.95–1.04)	0.817	1.00 (0.96–1.04)	0.912	0.99 (0.95–1.04)	0.780
Range	1.00 (0.99–1.02)	0.694	–	–	–	–	–	–
SD	–	–	1.08 (0.99–1.18)	0.070	–	–	–	–
CoV	–	–	–	–	1.12 (1.00–1.26)	0.054	–	–
MAC	–	–	–	–	–	–	1.08 (1.02–1.15)	0.008

Covariates were adjusted for age, onset to door time, hematoma volume at admission, diabetes mellitus, LDL cholesterol, mean BP and range (model 1), SD (model 2), CoV (model 3) or MAC (model 4). aOR: Adjusted odds ratio; *CI*: Confidence interval; LDL: Low-density lipoprotein; SD: Standard deviation; CoV: Coefficient of variation; MAC: Mean absolute change; mRS: Modified Rankin Scale; –: Value of 1.0 (correlation).

reported that acute ICH patients had significantly decreased baroreflex sensitivity and increased mean beat-to-beat BP variation, suggesting that baroreflex impairment resulted in secondary brain injury through brain edema or and cerebral hypoperfusion.[27] Second, enhanced activity of sympathetic nervous system also triggered brain injury through increased inflammatory responses, headache-induced psychological stress, and blood–brain barrier permeability.[12,28,29] Third, lenticulostriate or thalamoperforating arteries are the most common sites of ICH development in the brain due to lack of capillaries, and therefore, susceptible to direct variation in systemic BP.[30] The additional disruption of ICH-induced blood–brain barrier may further enhance the effect of BP fluctuation on hematoma growth or clinical outcome. However, the impact of BP lowering on hematoma growth or clinical outcome in patients with spontaneous ICH was not identified, underscoring the need for prospective trials using standard BP parameters in clinically identical populations.

Nevertheless, the study limitations relate to concerns of possible selection bias, based on a retrospective design. Second, we could not generalize our results of BP variability and outcomes in all cases of ICH since patients with huge hematoma or delayed admission were excluded from our trials. Finally, retrospective observational studies failed to demonstrate a causal relationship between BP variability, hematoma growth, and poor clinical outcomes.

The investigation has a few strengths. First, we focused on supratentorial nonlobar ICH to reduce the innate risk due to hematoma location and different clinical characteristics in anterior and posterior circulation in ICH. Second, intensive antihypertensive treatment was maintained with hourly BP monitoring in the intensive care unit. Accordingly, the relationship between BP variability and outcome in patients who underwent antihypertensive treatment was better defined. Third, we analyzed dichotomizing ordinal outcome scales using binary logistic regression analysis as well as ordinal shift analysis of mRS, which represented a more sensitive method to identify differences in stroke outcome compared with dichotomization.[31] Fourth, we included diverse BP variability parameters such as range, SD, CoV, and MAC, which were associated with relatively similar impact on hematoma growth and poor functional outcomes.

In conclusion, BP variability, especially MAC of SBP was associated with hematoma growth, while SD and CoV correlated with poor functional outcome at 3 months in patients with supratentorial nonlobar ICH. Prospective trials of BP-lowering interventions monitored closely for BP parameters are needed to identify the precise mechanisms of BP variability and outcomes in patients with spontaneous ICH according to location (supratentorial vs. infratentorial) and type (lobar vs. nonlobar).

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Conflicts of interest

There are no conflicts of interest.

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