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
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.[4] 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 Board/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).[3] 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 hematomat growth and poor clinical outcome at 3 months (defined as modified Rankin Scale [mRS] score ≥3) OR. 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

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**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 ORs 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).

### RESULTS

#### Baseline characteristics

A total of 104 individuals (mean age, $63.0 \pm 13.5$ 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 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)              |
| Cranietomy                       | 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 ($\times 10^3$/L)       | 232.4 ± 74.9           |
| BUN (mmol/L)                     | 4.91 (4.15–6.31)       |
| Creatinine ($\mu$mol/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: Interquartile range.
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  | 0.263      | –          | 0.805     | –       | –       | –         | –         |
| Range                   | 0.456  | 0.779      | –          | 0.439     | 0.419   | –       | –         | –         |
| SD                      | 0.051  | 0.031      | 0.099      | 0.180     | 0.176   | 0.168   | 0.350     | –         |
| CoV                     | 0.046  | 0.106      | 0.067      | 0.035     | 0.132   |        |           |           |
| Δ ICH                   | 0.026  | 0.119      | 0.099      | 0.180     | 0.176   | 0.168   | 0.350     | –         |
| 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 (mmHg)                     | 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; 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.[8] Conversely, the Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 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 cm³. 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).[9] 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.[6] did not find a significant improvement following intensive treatment (target SBP <140 mmHg within 1 h) or guideline-recommended treatment (target SBP <180 mmHg) 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 after stroke onset (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...
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\[20\] 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 \[20\] et al 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\[21\].

### 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                |
| Female                      | 0.51 (0.18–1.42) | 0.196            | 0.47 (0.17–1.28) | 0.138            |
| Initial hematoma volume     | 1.13 (1.06–1.21) | <0.001           | 1.13 (1.06–1.20) | <0.001           |
| Hypertension                | 3.67 (1.31–10.35)| 0.014            | 3.78 (1.34–10.64)| 0.012            |
| LDL cholesterol             | 0.58 (0.30–1.05) | 0.069            | 0.57 (0.31–1.06) | 0.073            |
| BP Mean                     | 1.03 (0.97–1.09) | 0.419            | 1.02 (0.96–1.08) | 0.548            |
| Range                       | 1.00 (0.97–1.02) | 0.740            | –                | –                |
| SD                          | –                | –                | 1.02 (0.97–1.08) | 0.498            |
| CoV                         | –                | –                | 0.01 (0.95–1.06) | 0.933            |
| MAC                         | –                | –                | 1.13 (1.06–1.20) | <0.001           |

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) | 0.200 |
| 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 (1.10–13.50) | 0.051 |
| Smoking (%)                | 18 (26.3)             | 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 (×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 (mmHg)                  | 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: Interquartile range.
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.\(^\text{[22]}\) Vascular structural changes such as basement membrane thickening and endothelial dysfunction in elderly patients increase susceptibility to hemodynamic stress.\(^\text{[23]}\) Older age has been reported to be a risk factor for lobar ICH. According to Kremer et al.,\(^\text{[22]}\) 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.\(^\text{[24]}\) 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,\(^\text{[25]}\) 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.\(^\text{[26]}\) 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.\(^\text{[9]}\) Compared with supratentorial ICH, infratentorial ICH resulted in poor outcome. Delcourt et al.\(^\text{[27]}\) 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.\(^\text{[23]}\) Sykora et al.\(^\text{[27]}\)

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**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                        |
| Age                                     | 1.04 (0.99–1.08)         | 0.095                    | 1.04 (0.99–1.08)         | 0.093                    |
| Onset to door time                      | 0.99 (0.99–1.00)         | 0.002                    | 0.99 (0.99–1.00)         | 0.003                    |
| Hematoma volume at admission            | 1.11 (1.04–1.19)         | 0.001                    | 1.11 (1.04–1.19)         | 0.002                    |
| Diabetes mellitus                       | 5.17 (1.01–26.41)        | 0.048                    | 5.72 (1.14–28.64)        | 0.034                    |
| LDL cholesterol                         | 0.41 (0.20–0.85)         | 0.017                    | 0.42 (0.20–0.87)         | 0.020                    |
| BP                                      |                          |                          |                          |                          |
| Mean                                    | 0.95 (0.89–1.01)         | 0.119                    | 0.95 (0.89–1.01)         | 0.090                    |
| 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 (0.54–1.36) | 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 |
| Antithrombel plate 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 (\(\sigma\))        | 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.\(^\text{[21]}\) 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.
**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 |
|--------------------------------|---------|---------|---------|---------|
| Age                            | 1.05 (1.01–1.08) | 1.04 (1.01–1.07) | 1.04 (1.01–1.07) | 1.04 (1.02–1.08) |
| Onset to door time             | 1.00 (0.99–1.00) | 1.00 (0.99–1.00) | 1.00 (0.99–1.00) | 1.00 (0.99–1.00) |
| Hematoma volume at admission   | 1.07 (1.04–1.12) | <0.001   | 1.08 (1.04–1.12) | <0.001 |
| Diabetes mellitus              | 2.21 (0.85–5.85) | 0.105    | 2.53 (0.97–6.76) | 0.060 |
| LDL                            | 0.59 (0.37–0.92) | 0.020    | 0.59 (0.37–0.93) | 0.024 |
| BP                             | 1.00 (0.96–1.05) | 0.906    | 1.00 (0.96–1.04) | 0.912 |
| 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) |
| MAC                            | –                   | –       | –                   | 1.08 (1.02–1.15) |

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).

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