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Blood pressure variability and outcome in acute severe stroke: A post hoc analysis of CHASE—A randomized controlled trial

Jingjing Zhao PhD[1] | Fang Yuan PhD[1] | Feng Fu MSc[2] | Yi Liu MD[3] | Changhu Xue MSc[4] | Kangjun Wang MD[5] | Xiangjun Yuan MD[6] | Dingan Li MD[5] | Qiuwu Liu MD[7] | Wei Zhang PhD[8] | Yi Jia MD[9] | Jianbo He MD[10] | Jun Zhou MD[11] | Xiaocheng Wang MD[12] | Hua Lv MSc[13] | Kang Huo PhD[14] | Zhuanhui Li MD[15] | Bei Zhang MD[16] | Chengkai Wang MD[17] | Li Li PhD[1,18] | Hongzeng Li PhD[8] | Fang Yang PhD[1,18] | Wen Jiang PhD[1,18] | the CHASE Study Group

[1]Department of Neurology, Xijing Hospital, Fourth Military Medical University, Xi'an, China

[2]Department of Neurology, 215 Hospital of Shaanxi NI, Xianyang, China

[3]Department of Neurology, Ankang Central Hospital, Ankang, China

[4]Department of Neurology, Xianyang Central Hospital, Xianyang, China

[5]Department of Neurology, Hanzhong Central Hospital, Hanzhong, China

[6]Department of Neurology, Weinan Central Hospital, Weinan, China

[7]Department of Neurology, Xi'an 141 Hospital, Xi'an, China

[8]Department of Neurology, Tangdu Hospital, Fourth Military Medical University, Xi'an, China

[9]Department of Neurology, Xi'an Gaoxin Hospital, Xi'an, China

[10]Department of Neurology, Xi'an XD Group Hospital, Xi'an, China

[11]Department of Neurology, Shangluo Central Hospital, Shangluo, China

[12]Department of Neurology, Yulin No. 2 Central Hospital, Yulin, China

[13]Department of Neurology, Shaanxi Provincial People's Hospital, Xi'an, China

[14]Department of Neurology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

[15]Department of Neurology, 521 Hospital of NORINCO Group, Xi'an, China

[16]Department of Neurology, The First Affiliated Hospital of Xi'an Medical University, Xi'an, China

[17]Department of Neurology, Tongchuan People's Hospital, Tongchuan, China

[18]The Shaanxi Cerebrovascular Disease Clinical Research Center, Xi'an, China

Correspondence
Wen Jiang and Fang Yang, Department of Neurology, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China.
Emails: drjiangwen@hotmail.com (WJ) and fyangx@fmmu.edu.cn (FY)

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Abstract

The influence of blood pressure variability (BPV) on outcomes in patients with severe stroke is still largely unsettled. Using the data of CHASE trial, the authors calculated the BPV during the acute phase and subacute phase of severe stroke, respectively. The primary outcome was to investigate the relationship between BPV and 90-day modified Rankin scale (mRS) ≥ 3. The BPV was assessed by eight measurements including standard deviation (SD), mean, maximum, minimum, coefficient of variation (CV), successive variation (SV), functional successive variation (FSV), and average real

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[Correction added on February 8, 2021, after first online publication: The copyright line was changed.]

variability (ARV). Then, the SD of SBP was divided into quintiles and compared the quintile using logistic regression in three models. The acute phase included 442 patients, and the subacute phase included 390 patients. After adjustment, six measurements of BPV during the subacute phase rather than acute phase were strongly correlated with outcomes including minimum (odds ratio [OR]: 0.83, 95% confidence interval [CI]: 0.69-0.99, p = .037), SD (OR: 1.10, 95% CI: 1.03-1.17, p = .007), CV (OR: 1.12, 95% CI: 1.03-1.23, p = .012), ARV (OR: 1.13, 95% CI: 1.05-1.20, p < .001), SV (OR: 1.09, 95% CI: 1.04-1.15, p = .001), and FSV (OR: 1.12, 95% CI: 1.05-1.19, p = .001). In the logistic regression, the highest fifth of SD of SBP predicted poor outcome in all three models. In conclusion, the increased BPV was strongly correlated with poor outcomes in the subacute phase of severe stroke, and the magnitude of association was progressively increased when the SD of BP was above 12.

1 | INTRODUCTION

Severe stroke, accounting for 12%-55% of all acute strokes,[1-5] often leads to major neurological deficits and even death. High blood pressure (BP) was found to contribute to worse outcome in acute severe stroke.[5-7] Thus, the management of BP is a fundamental and crucial part in severe stroke management. However, the CHASE (Controlling Hypertension After Severe Cerebrovascular Event) trial showed no significantly improved functional outcome in patients who received individualized BP-lowering treatment (with a reduction of 10%-15% in systolic blood pressure [SBP] from baseline level) compared with standard treatment group,[8] which suggests that BP control should focus not only on absolute value of BP but also on other aspects of BP, such as variability.

There was no consensus of the impact of blood pressure variability (BPV) on stroke outcome. For patients with acute ischemic stroke (AIS), some studies suggested that increased BPV during acute period (within 24 or 72 h) was related to poor outcome,[9,10] while results from a large stroke registry showed that only BPV during subacute period (4-10 days after onset) predicted outcome.[11] As for patients with intracranial hemorrhage (ICH), several studies indicated that increased BPV during acute period was associated with poor outcome,[12-14] and the post hoc analysis of ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage II) showed that increased BPV contributed to worse outcome of ICH in both the acute and subacute periods.[15] As for studies including AIS and ICH, post hoc studies of CHHIPS (Controlling Hypertension and Hypotension Immediately Post-Stroke) and COSSACS (Continue Or Stop Post-Stroke Antihypertensives Collaborative Study) showed that short-term BPV had no significant association with poor outcomes,[16-18] while the post hoc analysis of HeadPoST (Head Positioning in Acute Stroke Trial) indicated that BPV over 24 h post-stroke had close association with adverse outcome.[19]

To be noted, all the previous studies excluded patients with severe stroke or included only a small portion of them. However, patients with severe stroke have worse outcome and higher mortality.[20-22] Thus, the management of BPV after severe stroke should attract more attention for its important clinical value. In the present study, we examined the impact of increased BPV in the acute phase and the subacute phase on 90-day functional outcome after severe stroke.

2 | EXPERIMENTAL PROCEDURES

2.1 | Study design and patients

This is a secondary analysis of CHASE study, a multicenter randomized controlled trial of patients with acute severe stroke (ClinicalTrials.gov Identifier: NCT02982655). The detailed design and main results of CHASE study have been published elsewhere.[8,23] In brief, the CHASE trial included 483 adult patients with severe stroke from 26 tertiary hospitals in the northwest of China between January 1, 2017, and August 31, 2018. Patients with available BP data at all of the monitoring timing were included in the present analyses. The CHASE trial was approved by the ethics committee at each hospital, and all participants or legal surrogates provided written informed consent.

2.2 | Procedures

In this study, two randomized groups of CHASE trial were merged into one cohort to determine the association between BPV and outcome at the following two early periods after severe stroke (Figure 1): acute phase (the first 24 h after enrollment) and subacute phase (days 2-7 after enrollment).

In CHASE trial, BP was recorded every 2 h during the first 24 h after randomization, every 4 h during days 2-3, every 8 h during days 4-7. Twelve BP measurements recorded from 2 to 24 h after randomization were collected to calculate the BPV during acute phase, and BP measurement at 0 h (baseline) was excluded. Eighteen BP measurements recorded from days 2 to 7 (at 8:00, 16:00, and 24:00 on each day) were taken to calculate BPV in the subacute phase.

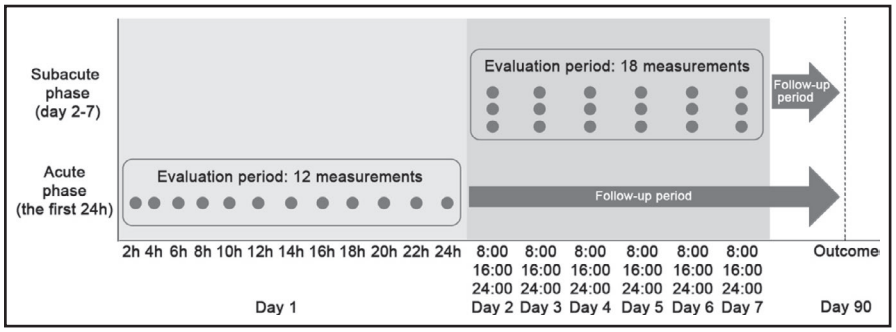

FIGURE 1 Measurements used to calculate blood pressure variability

TABLE 1 Baseline clinical data of included patients

	Acute phase (n = 442)	Subacute phase (n = 390)
Demographics		
Age (years)	66.7 ± 13.3	65.8 ± 13.4
Male	243 (55.0%)	220 (56.4%)
Qualifying stroke event		
Stroke type		
Ischemic stroke	217 (49.1%)	185 (47.4%)
Hemorrhagic stroke	225 (50.9%)	205 (52.6%)
Time from stroke onset to randomization (hours)	17 (6-36)	18 (6-36)
Severity		
Median NIHSS score[a]	15 (12-21)	15 (12-20)
Median GCS score[b]	11 (8-14)	11 (9-14)
Vital signs at presentation		
Systolic blood pressure (mmHg)	173.4 ± 17.5	173.2 ± 17.6
Diastolic blood pressure (mmHg)	96.8 ± 14.3	96.7 ± 14.8
Body temperature (°C)	36.5 ± 2.0	36.5 ± 2.1
Heart rate (beats per min)	79.3 ± 17.7	79.3 ± 17.5
Medical history		
Ischemic stroke	70 (15.8%)	62 (15.9%)
Hemorrhagic stroke	32 (7.2%)	28 (7.2%)
Coronary artery disease	121 (27.4%)	99 (25.4%)
Renal disease	7 (1.6%)	6 (1.5%)
Diabetes	81 (18.3%)	67 (17.2%)
Hypertension	357 (80.8%)	316 (81.0%)

[a]NIHSS (National Institutes of Health Stroke Scale) was used to evaluate the impairment caused by a stroke.

[b]GCS (Glasgow Coma Scale) was used to grade the conscious state.

Patients with missing BP recordings during the abovementioned time points were excluded. We calculated 8 measures of BP to measure the BPV: mean, maximum, minimum, SD, coefficient of variation (CV), successive variation (SV), functional successive variation (FSV), and average real variability (ARV). The calculation of FSV was computed by derivative of the continuous SBP curve.[24] SD was chosen as the key indicator for BPV because it is simple and commonly used in clinical practice.

2.3 | Study outcomes

The primary outcome was to investigate the relationship between BPV and 90-day poor outcome, defined as a score of 3-6 on modified Rankin scale (mRS).

2.4 | Statistical analysis

To examine the association between these 7 BPV measurements and 90-day outcome, three logistic regression models were built: Model 1 was unadjusted; Model 2 was adjusted for age, sex, time from stroke onset to randomization, and randomized group; and Model 3 was adjusted for all variables in Model 2 plus stroke type, National Institutes of Health Stroke Scale (NIHSS) score, and hematoma volume (for hemorrhagic stroke only) on admission. We divided SD of BP into quintiles (five equal groups) and estimated the odds ratio of SD for poor outcome in Model 1, Model 2, and Model 3, with the lowest quintile used as the reference. The associations between SBP variability and outcome in the acute phase and subacute phase in patients with severe AIS and ICH were later calculated separately. Two-sided p values < .05 were deemed significant. All the statistical analyses were conducted using SPSS version 22 software (SPSS Inc).

3 | RESULTS

Of the 483 participants in CHASE, the analysis of the acute phase included 442 (91.5%) patients and the analysis of the subacute phase included 390 (80.7%) patients (Figure S1). Demographics, stroke type, baseline severity, baseline vital signs, medical history, and BP-lowering treatment were all similar between patients in the acute phase and in the subacute phase (Tables 1 and 2). Variabilities of SBP and diastolic blood pressure (DBP) in two phases are presented in Table S1.

In the acute phase, SD and CV of SBP, mean SBP, maximal SBP, and minimal SBP were not significantly associated with poor outcome in any of the three models, and ARV, SV, and FSV were strongly related to stroke outcome only in Models 1 and 2 (Table 3). In the subacute phase, minimal SBP, SD, CV, ARV, SV, and FSV of SBP were significantly associated with poor outcome in all three models (Table 3). Variabilities of DBP showed the similar results in both the acute phase and subacute phase (Table S2).

In the subacute phase, the association between the highest fifth of SD of SBP and poor outcome was evident in all three models (Model 1: odds ratio [OR] = 2.96, 95% confidence interval [CI] = 1.40-6.28, p = .005; Model 2: OR = 3.66, 95% CI = 1.59-8.42, p = .002, and Model 3: OR = 3.40, 95% CI = 1.39-8.35, p = .008; Figure 2). The second fifth of SD of SBP was significantly related to stroke outcome only in Models 1 and 2 (Model 1: OR = 2.12, 95% CI = 1.05-4.31, p = .037; and Model 2: OR = 2.51, 95% CI = 1.17-5.39, p = .018; Figure 2). Figure 3 showed the distributions of mRS scores on five levels of SD of SBP in the subacute phase. When the SD of SBP in the subacute phase was above 12, the proportion of poor outcome rose as the SD increased, no matter the cutoff value of mRS for poor outcome was set at 3, 4, or 5. This pattern was not evident when the SD of SBP in the subacute phase was below 12.

The results of subgroup analyses of SBP variability in patients with severe AIS were consistent with the whole cohort of severe stroke in both the acute phase and subacute phase (Tables S3 and S4). In patients with severe ICH, the SBP variability in both the acute phase and subacute phase were all associated with the poor outcome (Tables S5 and S6). Also note that the association between minimal SBP in the subacute phase and outcome was significant in patients with severe AIS, while the association was not evident in patients with severe ICH (Tables S4 and S6).

TABLE 2 Blood pressure–lowering treatment in total

	Acute phase (n = 442)	Subacute phase (n = 390)
Blood pressure–lowering treatment		
Any BP-lowering treatment	319 (72.2%)	283 (72.6%)
Any intravenous treatment	146 (33.0%)	124 (31.8%)
Type of intravenous agent used		
Urapidil	85 (19.2%)	75 (19.2%)
Sodium nitroprusside	51 (11.5%)	40 (10.3%)
Nimodipine	34 (7.7%)	32 (8.2%)
Type of oral agent used		
Calcium channel blocker	227 (51.4%)	210 (53.8%)
ACE inhibitor	38 (8.5%)	34 (8.7%)
Angiotensin II receptor antagonist	58 (13.1%)	56 (14.4%)
Diuretic	20 (4.5%)	18 (4.6%)
β blocker	26 (5.9%)	24 (6.2%)

4 | DISCUSSION

Based on the data of CHASE trial, the present study evaluated the impact of BPV in the acute phase and subacute phase on 90-day outcome of patients with severe stroke. The BPV in the acute phase was not associated with the poor outcome of severe stroke. However, the BPV in the subacute phase of severe stroke was strongly correlated with poor outcome at 90 days. The impact of BPV on 90-day outcome in patients with severe AIS or ICH was consistent with the whole cohort.

The exact mechanism of how BPV affects outcome of stroke remains unknown. Previous studies suggested that ICH or AIS might impair cerebral autoregulatory control in microvascular channels and results in large fluctuations of BP, which will promote lesion expansion and aggravation of cerebral edema.[25,26] However, the INTERACT2 trial indicated that the BPV was not associated with hematoma growth, while the BPV was strongly associated with poor outcome.[27] In AIS patients treated with thrombolysis, the BPV after admission was independently correlated with greater lesion growth and worse three-month outcome.[28]

The results from INTERACT2, ATACH2, SAMURAI, and FAST-MAG trials indicated that the increased BPV in both the acute phase and subacute phase was all related to the poor three-month outcome for patients with ICH.[12,13,27,29] From the present study, the results of BPV in both phases were in accordance with previous studies. However, only ARV displayed the significant association between BPV and poor outcome in the acute phase after adjusted variables in Model 2, plus baseline NIHSS and hematoma volume. A recent study also stressed the association between BP reduction and outcomes varying with baseline hematoma volume.[30] In order to clarify the association between BPV in the acute phase and poor outcome for patients with ICH, it is necessary to design further studies that considering the severity of disease and hematoma volume.

In patients with AIS, Fukuoka Stroke Registry showed that the BPV in the subacute phase was independently associated with three-month poor outcomes, while no association was found in the acute phase.[11] A single-center study and a retrospective study noted that there were no significant associations between BPV during the first three days after onset and outcomes, while the BPV after the first three days strongly associated with the three-month outcome.[31,32] We also found the correlation between BPV and poor outcomes in the subacute phase rather than acute phase, which are similar to above studies. However, recent studies found that the BPV during the first 24 hours after AIS was significantly associated with functional outcome.[10,33] The differences may be partly attributed to that the above two studies focused on AIS patients after endovascular thrombectomy while our present study excluded those patients.

TABLE 3 Effects of systolic blood pressure variability on poor outcome at 90 days in total

	Model 1		Model 2		Model 3	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Acute phase						
Mean[a]	0.95 (0.82-1.11)	.520	0.95 (0.80-1.12)	.539	0.94 (0.78-1.13)	.488
Maximum[a]	1.00 (0.99-1.02)	.612	1.03 (0.90-1.18)	.636	0.99 (0.86-1.14)	.895
Minimum[a]	0.99 (0.98-1.0)	.083	0.90 (0.77-1.04)	.146	0.94 (0.80-1.11)	.459
SD	1.03 (0.99-1.08)	.139	1.03 (0.98-1.08)	.228	1.00 (0.95-1.06)	.937
CV	1.06 (0.99-1.13)	.125	1.05 (0.97-1.13)	.221	1.00 (0.93-1.09)	.875
ARV	1.07 (1.02-1.12)	**.005**	1.07 (1.02-1.12)	**.010**	1.05 (0.99-1.11)	.079
SV	1.05 (1.00-1.08)	**.017**	1.04 (1.00-1.08)	**.043**	1.03 (0.98-1.07)	.259
FSV	1.03 (1.01-1.06)	**.016**	1.03 (1.00-1.06)	**.047**	1.02 (0.99-1.05)	.213
Subacute phase						
Mean[a]	1.00 (0.83-1.22)	.980	1.03 (0.83-1.27)	.812	0.98 (0.78-1.23)	.839
Maximum[a]	1.16 (0.99-1.35)	.061	1.19 (1.01-1.41)	**.037**	1.14 (0.96-1.37)	.139
Minimum[a]	0.84 (0.72-0.98)	**.026**	0.83 (0.71-0.99)	**.032**	0.83 (0.69-0.99)	**.037**
SD	1.01 (1.03-1.15)	**.003**	1.11 (1.04-1.18)	**.001**	1.10 (1.03-1.17)	**.007**
CV	1.12 (1.04-1.20)	**.004**	1.14 (1.05-1.24)	**.003**	1.12 (1.03-1.23)	**.012**
ARV	1.12 (1.06-1.18)	**<.001**	1.14 (1.07-1.21)	**<.001**	1.13 (1.05-1.20)	**<.001**
SV	1.09 (1.04-1.14)	**<.001**	1.10 (1.05-1.16)	**<.001**	1.09 (1.04-1.15)	**.001**
FSV	1.11 (1.06-1.18)	**<.001**	1.13 (1.06-1.20)	**<.001**	1.12 (1.05-1.19)	**.001**

The bold values were used to emphasize the significant difference of the data.

Abbreviations: ARV, average real variability; CI, confidence interval; CV, coefficient of variation; FSV, functional successive variation; OR, odds ratio; SD, standard deviation; SV, successive variation.

[a]Every 10 mmHg increment in systolic blood pressure. Model 1 was unadjusted; Model 2 was adjusted for age, sex, time from stroke onset to randomization, and randomized group; and Model 3 was adjusted for all variables in Model 2 plus stroke type and National Institutes of Health Stroke Scale score on admission.

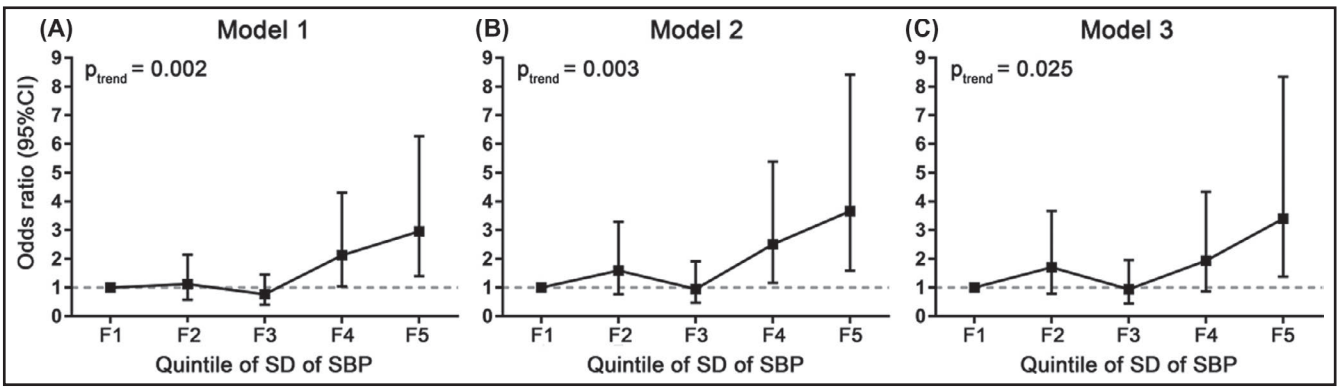

FIGURE 2 Association between quintiles of SD of systolic blood pressure in the subacute phase and poor outcome. Three models, with the lowest quintile as reference. SD, standard deviation

The post hoc studies of CHHIPS and COSSACS including both AIS and ICH, showed that short-term BPV had no significant association with early poor outcomes (2 weeks).[16-18] The post hoc analysis of HeadPoST indicated that BPV over 24 h post-stroke had close association with adverse outcome.[19] The above results were similar to the results of our cohorts including both AIS and ICH patients.

Another notable result was that the association between minimal SBP in the subacute phase of severe AIS and outcome was evident. By contrast, there was no significant association between the minimal SBP and poor outcome in mild-to-moderate stroke patients.[9,27,34] It implies that the benefits of early management of BP might be enhanced by sustained and smooth control, as well as by avoiding the extremely low value of SBP in patients with severe AIS.

The current post hoc analysis of CHASE trial has notable strengths as follows. Firstly, this study could be regarded as the largest

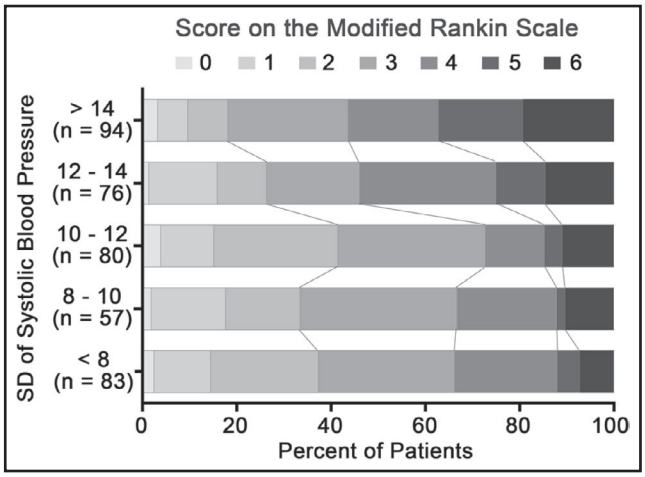

FIGURE 3 Distribution of modified Rankin scale, according to SD of systolic blood pressure in the subacute phase. SD, standard deviation

prospective cohort focused on the relationship between BPV and outcomes after severe stroke. Secondly, the multicenter data collection of CHASE trial increases the generalizability of the present results. Thirdly, we calculated twelve BP measurements in the acute phase and eighteen BP measurements in the subacute phase, eight measures of BPV, as well as multivariable models and graduated BPV, which increase the precision and reliability of the assessment of association.

There are some limitations of our present study. Firstly, patients with missing data of BP recordings at any of the abovementioned time points were excluded. Secondly, all the patients had elevated BP on admission, thus it is unknown whether the findings are applicable to severe stroke without high BP. Thirdly, the BPV may be affected by several factors, such as methods, frequency, and time points of measurements. Therefore, it is difficult to determine the exact range of BPV for the optimal BP management.

5 | CONCLUSIONS

In patients with severe stroke, the BPV in the acute phase was not associated with poor outcome at 90 days. In the subacute phase, the BPV was strongly correlated with an increased risk of poor 90-day outcome. In addition, the magnitude of the association between BPV and outcome was progressively increased when the SD of BP was above 12. In particular, the association between minimal SBP in the subacute phase of severe AIS and outcome was especially pronounced. Thus, in order to gain benefit of reducing BP, clinicians should pay more attention to the smooth BP in the subacute phase of severe stroke, and particularly avoid the low SBP in patients with AIS.

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Not applicable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

This study was conceived by WJ and F Yang. JJZ and F Yuan contributed to the data collection, interpretation, and analyzation, as well as wrote the first version of the manuscript. FF, YL, CX, KW, XY, DL, QL, WZ, YJ, JH, JZ, XW, HL, KH, ZL, BZ, CW, LL, and HL were the principal investigators who contributed to the design, recruiting patients, and revising the manuscript at each site. All of the authors are responsible for the final content of the manuscript.

DATA AVAILABILITY STATEMENT

The detailed data analyzed during the present study are available from the corresponding authors for reasonable request.

ORCID

Wen Jiang https://orcid.org/0000-0003-0612-2917

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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