Predicting prognosis in patients with stroke treated with intravenous alteplase through the 24-h trajectory of blood pressure changes

Kaiting Fan MS, RN# | Jie Zhao MS, RN, NVRN-BC# | Hong Chang MS, RN | Xiaojuan Wang BS, RN | Hui Yao BS, RN | Xiaoxia Yao BS, RN | Xin Yang BS, RN

Department of Neurology, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Disease, Beijing, China (Email: fakaiting@163.com)

Correspondence
Hong Chang, Department of Neurology, Xuanwu hospital, Capital Medical University, Changchun Street 45, Beijing 100053, China. Email: changhong19791111@126.com

# Kaiting Fan and Jie Zhao contributed equally to this work.

Abstract
Blood pressure (BP) monitored within 24 h from the beginning of intravenous thrombolysis (IVT) with alteplase, is one of the important factors affecting the prognosis of patients with acute ischemic stroke (AIS). This study aimed to explore longitudinal BP trajectory patterns and determine their association with stroke prognosis after thrombolysis. From November 2018 to September 2019, a total of 391 patients were enrolled consecutively during the study period, and 353 patients were ultimately analyzed. Five systolic (SBP) and four diastolic blood pressure (DBP) trajectory subgroups were identified. The regression analysis showed that when compared with the rapidly moderate stable group, the continuous fluctuation-very high level SBP group (odds ratio [OR]: 2.743, 95% confidence interval [CI]: 1.008–7.467) was associated with early neurological deterioration (END). Both the rapid drop-high level SBP (OR: 0.448, 95% CI: 0.219–0.919) and DBP groups (OR: 0.399, 95% CI: 0.219–0.727) were associated with early neurological improvement (ENI). Moreover, there was a U-shaped correlation between the OR value of SBP trajectory group and favorable outcome (the modified Rankin Scale [mRS] score 0–2) at 3 months: the slow drop-low level SBP group represent a well-established unfavorable outcome risk factor (OR:5.239, 95% CI: 1.271–21.595), and extremely high SBP—the continuous fluctuation-very high level SBP group, are equally associated with elevated unfavorable outcome risk (OR:3.797, 95% CI: 1.486–9.697). The continuous fluctuation-very high level DBP group was statistically significant in mRS (OR: 3.387, CI: 1.185–9.683). The BP trajectory groups show varying clinical features and risk of neurological dysfunction. The findings may help identify potential candidates for clinical BP monitoring, control, and specialized care.

KEYWORDS
acute ischemic stroke, blood pressure trajectory, follow-up, intravenous thrombolysis, neurological dysfunction

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J Clin Hypertens. 2021;23:1718–1730.
1 | INTRODUCTION

The clinical significance of monitoring and managing blood pressure (BP) during intravenous thrombolytic (IVT) therapy for the prevention of adverse prognosis in patients with acute ischemic stroke (AIS) remains an area of active investigation. Several observational studies have found that approximately 75%–80% of patients have elevated BP in response to stroke episodes, and a high BP during the thrombolysis period is a risk factor for poor clinical outcomes, such as poor rate of recanalization, intracerebral hemorrhage, and neurological dysfunction. Interventional studies that used antihypertensive drugs to maintain BP within 141–150 mmHg or 130–140 mmHg have not reached a consensus on whether this leads to an improved prognosis. In order to determine the ideal therapy, it is still necessary to accurately describe BP variations and their relationship with prognosis in patients undergoing venous thrombolysis.

In comparison, much less is known about the importance of changes in BP over time (ie, BP trajectories) in patients with AIS. A study on this topic showed that different BP trends were associated with the occurrence of cerebrovascular events. Unsupervised functional principal components analysis was used to characterize SBP trajectories in patients with spontaneous intracerebral hemorrhage over first 24 h and their relationship to the unfavorable shift on modified Rankin scale (mRS). The method used to analysis BP trajectory has gradually received researchers’ attention and has a broad research prospect.

For BP monitoring during IVT, current guidelines only indicate that BP should be maintained at < 180/105 mmHg within 24 h of treatment onset, mainly to prevent serious complications, such as symptomatic intracranial hemorrhage. Even if the ischemic penumbra is not affected by changes in infarction or massive hemorrhage, a varying BP trajectory causes unstable cerebral blood flow and cerebral perfusion pressure fluctuations, which will also affect the long-term prognosis. Moreover, it is unreasonable to use a single BP value, the average BP, or BP variation-related indicators at a single time point to represent the BP status within that time period. Studies describing the relationship between BP trajectories and early stroke outcomes in patients treated with IVT are lacking.

Hypertension is a heterogeneous condition in patients with AIS, and available data support the importance of both systolic (SBP) and diastolic (DBP) BP monitoring. We designed our analysis using an unsupervised cluster approach, group-based trajectory modeling (GBTM) approach that may provide an alternative method for summarizing long-term BP values accounting for the dynamic nature of BP over time, to group similar longitudinal BP response patterns. We then evaluated the associations of these clusters, or most commonly BP parameters in similar articles, with neurological function changes and status using a standard multivariate regression approach. Improved knowledge of BP trajectories is critical in understanding the role of BP as a risk factor for adverse outcomes.

WHAT IS ALREADY KNOWN ABOUT THE TOPIC?
- Stroke guidelines indicate that monitoring BP within 24 h from the beginning of IVT in patients with AIS is essential due to the high incidence of complications.
- Several studies have shown that high SBP or DBP levels are associated with the prognosis of patients with AIS, such as changes in neurological function, hemorrhaging-related complications, and mRS scores.
- In most similar studies, the BP values at a single time point, its mean value, the variation coefficient, and other indicators at multiple time points were used to describe BP and to explore the correlation between BP and stroke prognosis.

WHAT THIS PAPER ADDS
- According to BP data obtained at multiple time points in patients with AIS treated using thrombolysis, the group-based trajectory model can be used to assess patterns of BP fluctuations.
- SBP and DBP showed different patterns as the time to thrombolytic therapy increased.
- There were differences in clinical characteristics among patients with different patterns of BP changes as well as in the degree of correlation with stroke prognosis, which was one of the independent influencing factors.
- Compared with these parameters, the BP values at a single time point, its mean value, the variation coefficient, and other indicators at multiple time points, which were used to describe BP in similar articles, BP trajectories are equally important values for predicting stroke prognosis.

2 | METHODS

2.1 | Study sample

We prospectively identified 353 consecutive patients between November 2018 and September 2019 who were diagnosed with AIS and subsequently treated with IVT using alteplase, a thrombolytic medication, within 4.5 h after symptom onset and were then followed up for 3 months at one comprehensive stroke center (Xuanwu Hospital, Capital Medical University, Beijing, China). All patients were evaluated according to the American Heart Association guidelines
The secondary outcome events included early neurological deterioration (END) and improvement (ENI). END was defined as an increase in the National Institutes of Health stroke scale (NIHSS) score ≥4 points or as an increase ≥2 points in one sub-item that occurred at 24 h following alteplase infusion; these criteria were previously used to define significant deterioration. ENI was defined as an improvement in the NIHSS score ≥8 points or as a 0 or 1 score at 24 h following alteplase infusion.14

2.4 Covariates

Medical records were retrospectively reviewed by a nurse who was blinded to patients’ outcomes and the following information was retrieved: demographic data (sex, age), medical history (hypertension, diabetes, coronary heart disease [CHD], atrial fibrillation, hyperlipidemia, stroke, transient ischemic attack [TIA], antiplatelets before stroke, repetitive thrombolysis, and pre-stroke mRS score), vascular risk factors defined by our research team (body mass index [BMI], NIHSS score at admission [≤3 points was defined as mild stroke],15 gastric tube and catheterization after thrombolysis, pneumonia, using intravenous antihypertensive drugs, TOAST classification16), laboratory values (18 parameters from routine blood, biochemical, and coagulation tests), and characteristics of the thrombolytic procedure (onset to treatment time [OTT], door-to-needle time [DNT]).

2.5 Ethics statement

The study protocol was approved by the Ethical Committee of Xuanwu Hospital and conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.6 Group-based trajectory modeling

During the 24 h after thrombolysis, we adopted a group-based trajectory modeling approach using the traj procedure in SAS (SAS Institute, Cary, NC) to identify superior BP trajectories.17 Given the continuous measurement of BP value that belongs to censored continuous data, we used censored normal (CNORM) that is one of the three types of distributions provided by GBMT for our analysis. In a trajectory model, several regression models are estimated simultaneously through maximization of a likelihood that combines the information from all models. Specifically, based on individuals’ BP patterns over time, the probability of belonging to each potential BP group is modeled as a simple multinomial logistic regression. Each latent trajectory can be characterized by a starting value of impairment level (intercept) and possibly by a polynomial function (linear, quadratic, cubic), thereby capturing the start level and the shape of the BP course, respectively. For trajectories selection, the choice of the number of groups and the shape of each group are most important considerations. In our analysis, we first fit 2–6 group
Figure 1  Trajectory groups of 24-hour post-thrombolysis blood pressure measurement. (A) Systolic blood pressure trajectories. (B) Diastolic blood pressure trajectories

A. Systolic blood pressure trajectories:
- Group 1 (slow drop-low SBP group, 102–114 mmHg, n = 22, 6.2%)
- Group 2 (rapid drop-low SBP group, 120–128 mmHg, n = 76, 21.8%)
- Group 3 (rapid drop-medium SBP group, 134–143 mmHg, n = 124, 34.8%)
- Group 4 (rapid drop-high SBP group, 150–157 mmHg, n = 84, 24.0%)
- Group 5 (continuous fluctuation-very high SBP group, 162–173 mmHg, n = 47, 13.2%)

B. Diastolic blood pressure trajectories:
- Group 1 (slow drop-low DBP group, 56–62 mmHg, n = 45, 12.8%)
- Group 2 (slow drop-medium DBP group, 70–78 mmHg, n = 96, 27.2%)
- Group 3 (rapid drop-high DBP group, 80–89 mmHg, n = 112, 31.9%)
- Group 4 (continuous fluctuation-very high DBP group, 100–110 mmHg, n = 38, 10.8%)

2.7 Statistical analysis

Continuous data were reported as means ± standard deviation and were analyzed using one-way ANOVA or Kruskal-Wallis tests as appropriate. Categorical data were presented as frequency and percentages and were analyzed using the chi-square test. Logistic regression analysis and area under the curve (AUC) were used to determine the association between neurological damage and different BP trajectory groups, previous BP parameters. The strengths of the associations were determined by estimating the odds ratios (OR) and their 95% confidence interval (CI). To detect changes in associations between outcome and main exposures, the following multivariate logistic models were constructed: model 1 = no covariates; model 2 = statistical demographic indicators; model 3 = model 2 + all statistical indicators (p < .1). All statistical tests were two-sided, and statistical significance was considered at p < .05. Statistical analyses were performed using SPSS v.22.0 (SPSS Inc., Chicago, IL).

3 RESULTS

During the 11-month study period, 353 out of 391 patients met the study criteria and were enrolled in the study. Among the 12 patients with missing data, 1 patient was discharged from the hospital with the main diagnosis other than ischemic stroke, and 25 patients were lost to follow-up. Among the included patients, 257 (72.8%) were male, 96 (27.2%) were female, and the mean age was 62.49 ± 11.79 years.
fluctuated widely during the first 3 h. Groups 2, 3, and 4 showed stable BP after a rapid and steady decline within 1.5–2 h, whereas groups 2 and 3 had normal to high BP; the BP in group 4 remained stable at about 150 mmHg. In group 5, BP declined rapidly and steadily for the first 1.5 to 2 h, followed by wavy fluctuations.

Patients in these five SBP trajectory groups had distinct clinical profiles and laboratory results (Tables 1–2). Patients in group 1 were significantly younger by about 10 years on average and had a lower prevalence of hypertension and diabetes by 23.4%–57.1% and 11.6%–30.7%, lower than the other groups, respectively. Patients with high BP were more likely to have chronic diseases; those in groups 4 and 5 had high BP and a high prevalence of both intravenous antihypertensive treatment and large artery atherosclerosis TOAST subtype. Blood glucose, glycosylated hemoglobin, and erythrocyte sedimentation ratio showed an increasing trend from group 1 to 5, whereas triglycerides and total cholesterol levels showed a “W” and “V” pattern, respectively. Both the international normalized ratio and prothrombin time gener-

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ally appeared in group 5.

3.2 | Trajectory groups based on diastolic blood pressure

Four groups were identified based on the DBP trajectory (Figure 1B). Group 1 (rapid drop-low DBP group, 62–69 mmHg, n = 67, 19.3%); group 2 (slow drop-medium DBP group, 72–78 mmHg, n = 145, 40.8%); group 3 (rapid drop-high DBP group, 82–88 mmHg, n = 112, 31.9%); group 4 (continuous fluctuation-very high DBP group, 92–101 mmHg, n = 29, 8.0%). The only difference between groups 1–3 was the DBP level reached after the BP dropped.

Patients in these four DBP trajectory groups had distinct clinical profiles and laboratory results (Tables 1–2). Group 4 had a higher proportion of coronary heart disease, pneumonia, and catheter inser-
tion; higher NIHSS score at admission; and a greater likelihood of disease changes. The prevalence of drinking and repetitive thromboly-
sis decreased linearly among the four groups. White blood cell count, blood glucose, and total cholesterol levels increased from group 1 to 4, whereas the platelet count showed an inverted “U” shape. High-sensitivity C-reactive protein levels increased linearly in groups 1 to 3, whereas the values in group 4 decreased slightly.

The trend of the graph in Figure 2 and 3, which are drawn by calculating the average 24-hour blood pressure of each track group, is similar to the result after applying GBT grouping.

3.3 | Trajectory groups and stroke outcomes

After IVT, there were 67 (19.0%) cases of END, 131 (37.1%) cases of ENI, and 242 (68.6%) patients with an mRS score 0–2 at the 3-month follow-up. To examine the association between BP trajectory groups and outcomes, the groups were included as independent variables in a logistic regression model, and the moderate stable BP trajectory groups (SBP: group 3; DBP: group 4) were considered as the control groups (Table 3). Group 5 had a significantly increased risk of END (OR: 2.743, CI: 1.008–7.467) and the group 4 pattern was inversely associated with ENI (OR: 0.448, CI: 0.219–0.919). It is worth noting that there was a U-shaped correlation between SBP trajectories and the mRS score at 90 days (low SBP: [OR: 5.239, CI: 1.271–21.595]; fluctuating high SBP: [OR: 3.797, CI: 1.486–9.697]). The rapid drop-high level DBP group was inversely associated with ENI (OR: 0.399, CI: 0.219–0.727) and group 4 showed an association with unfavorable outcome (OR: 3.387, CI: 1.185–9.683).

3.4 | Previous BP parameters and stroke outcomes

Blood pressure variability and stroke outcome in acute stroke patients, whether in patients with internal carotid artery occlusion or endovas-
cular thrombectomy, which had shown that maximum values, max–min, SD and SV of systolic or diastolic BP resulted significantly higher in patients with poor outcome compared to those with good outcome after adjusting for potential confounders.16,19 More parameters used to describe BP showed an association with END than ENI or mRS scores, which is one of the more important predictors of the risk of END. Moreover, the OR value of SBP or DBP on admission or immedi-
ate completion of thrombolysis was shown to be one of the better pre-
dictors of END than BP trajectory. Secondly, regardless of any param-
eter used to describe BP within 24 h, the diagnostic value of END was low (0.5 < AUC < 0.7). In the case of ENI, only BP trajectory and 24-h SBP related indicators showed statistically significant correlation with ENI (p < .05). At the same time, the diagnostic value of SBP trajectory is not inferior to other BP parameters. With regard to the 3-month mRS score, only BP trajectory showed a strong correlation with it. Other BP parameters could not be used as an indicator to predict the stroke func-
tional status after 3 months; however, the mean and maximum values at any time point were more valuable for its diagnosis (Tables 4–5). In conclusion, BP trajectory, as one of the main indicators for predicting and diagnosing the stroke outcome, is of equal significance compared with previous BP parameters.

4 | DISCUSSION

Five SBP and four DBP trajectory subgroups were identified in the first 24 h after initiating IVT using the group-based trajectory model. In these groups, BP was classified according to its level as low, medium, and high and according to its changes as slow decline, rapid decline, and persistent fluctuation. Each trajectory group had different clinical char-
acteristics, which were correlated with END, ENI, and mRS scores at 3 months. The continuous fluctuation-very high SBP/DBP groups had the highest risk of having adverse events within 3 months. More impor-
tantly, the mean BP in these groups was similar, but they differed in the post-stroke prognosis.

The mechanisms for acute BP response after stroke differ. The sensitivity of vascular baroreceptors decreased, and the ischemic
| Variables                  | SBP trajectories | p value | DBP trajectories | p value |
|----------------------------|------------------|---------|------------------|---------|
| Age                        | 53.41±14.77      | 62.25±12.34 | 63.21±11.48 | .004 |
| Male sex                   | 14 (63.6%)       | 59 (77.6%) | 89 (71.8%) | .728 |
| Hypertension               | 5 (22.7%)        | 35 (46.1%) | 84 (79.8%) | <.001 |
| Diabetes                   | 4 (18.2%)        | 25 (32.9%) | 52 (41.9%) | .041 |
| Dyslipidemia               | 16 (72.7%)       | 62 (81.6%) | 93 (75.0%) | .622 |
| CHD                        | 2 (9.1%)         | 22 (28.9%) | 24 (19.4%) | .728 |
| Atrial fibrillation        | 1 (4.5%)         | 10 (13.2%) | 11 (8.9%) | .041 |
| Stroke                     | 4 (18.2%)        | 23 (30.3%) | 26 (21.0%) | .285 |
| TIA                        | 0 (0)            | 3 (3.9%) | 5 (4.0%) | .652 |
| Pneumonia                  | 0 (0)            | 2 (2.6%) | 3 (2.4%) | .887 |
| BMI (Kg/m²)                | 23.47±4.50       | 25.32±3.60 | 25.04±3.44 | .222 |
| Antiplatelets therapy      | 3 (13.6%)        | 15 (19.7%) | 20 (16.1%) | .904 |
| Smoking                    | 10 (45.5%)       | 39 (51.3%) | 51 (41.1%) | .853 |
| Alcohol drinking           | 7 (31.8%)        | 33 (43.4%) | 44 (35.5%) | .688 |
| repetitive thrombosis      | 0 (0)            | 2 (2.6%) | 5 (4.0%) | .585 |
| OTT (min)                  | 163.6±73.70      | 146.5±63.00 | 158.6±64.60 | .700 |
| DNT (min)                  | 30.79±12.47      | 26.9±12.36 | 30.6±14.71 | .350 |
| Minor stroke               | 8 (36.4%)        | 26 (34.2%) | 49 (39.5%) | .228 |
| Past mRS scores (0–2)      | 22 (100%)        | 76 (100%) | 123 (99.2%) | 1000 |
| Gastric tube               | 0 (0)            | 3 (3.9%) | 1 (0.8%) | .108 |
| Catheterization            | 3 (13.6%)        | 3 (3.9%) | 2 (1.6%) | .103 |
| Antihypertensive therapy   | 0 (0)            | 2 (2.6%) | 10 (8.1%) | <.001 |
TABLE 2  Comparison of laboratory parameters after thrombolysis (n = 353)

| variables |   | SBP trajectories |   |   | DBP trajectories |   |   |
|-----------|---|------------------|---|---|------------------|---|---|
|           |   | 1               | 2 | 3 | 4               | 5 | p value |
| WBCa (×10^9/L) | 7.53±2.21 | 7.44±2.15 | 7.95±2.52 | 8.13±2.61 | 7.78±2.02 | .447 | 6.99±1.94 | 7.99±2.47 | 7.97±2.38 | 8.43±2.56 | .007 |
| RBCb (×10^{12}/L) | 4.3±0.68  | 4.33±0.45 | 4.42±0.50 | 4.39±0.54 | 4.43±0.50 | .833 | 4.36±0.43 | 4.44±0.50 | 4.37±0.54 | 4.35±0.60 | .718 |
| PLTc (×10^9/L)  | 202.55±56.27 | 214.91±58.31 | 217.17±50.76 | 221.38±65.03 | 208.49±47.70 | .579 | 202.30±54.32 | 214.97±54.12 | 220.95±55.55 | 203.00±66.19 | .076 |
| Ureaa (mmol/L) | 5.49±1.78 | 5.10±1.82 | 4.92±1.38 | 5.03±1.71 | 5.21±2.11 | .698 | 5.00±1.36 | 5.06±1.69 | 4.92±1.46 | 5.75±2.78 | .506 |
| Glucose (mmol/L) | 5.93±2.75 | 6.45±2.76 | 6.64±2.73 | 6.92±3.16 | 8.22±3.53 | .004 | 6.23±2.59 | 6.66±2.96 | 7.18±3.04 | 7.75±3.69 | .023 |
| UAa (mmol/L) | 310.91±91.09 | 318.26±91.26 | 316.18±84.96 | 325.61±90.36 | 328.06±78.02 | .744 | 323.73±82.77 | 323.80±86.61 | 313.77±83.53 | 317.97±110.15 | .882 |
| TGa (mmol/L) | 1.86±2.46 | 1.40±1.04 | 1.69±1.20 | 1.40±1.06 | 2.04±2.55 | .070 | 1.44±0.96 | 1.61±1.56 | 1.62±1.50 | 2.02±2.12 | .673 |
| Cholesterol (mmol/L) | 3.97±0.85 | 3.90±0.94 | 4.10±1.05 | 4.09±1.11 | 4.92±3.10 | .039 | 4.08±0.92 | 4.06±1.06 | 4.06±1.02 | 5.20±3.89 | .094 |
| LDL-Cb (mmol/L) | 244±0.80 | 2.34±0.80 | 2.48±0.87 | 2.43±0.89 | 2.76±1.00 | .259 | 2.46±0.79 | 2.46±0.85 | 2.38±0.84 | 2.92±1.21 | .121 |
| PTAc (%) | 86.55±17.06 | 90.95±18.33 | 93.35±14.06 | 91.12±14.70 | 95.51±13.95 | .034 | 94.97±16.17 | 91.34±16.70 | 91.51±13.35 | 92.34±14.93 | .780 |
| INRd | 1.12±0.14 | 1.13±0.39 | 1.08±0.21 | 1.08±0.15 | 1.04±0.11 | .028 | 1.08±0.19 | 1.10±0.30 | 1.08±0.20 | 1.07±0.12 | .939 |
| PT (s) | 14.28±1.36 | 14.00±3.74 | 13.86±3.61 | 13.97±1.58 | 13.46±1.07 | .016 | 13.68±4.71 | 14.04±2.73 | 13.84±1.84 | 13.77±1.22 | .676 |
| FIBb (g/l) | 0.6±0.61 | 0.52±0.94 | 0.52±0.64 | 0.56±0.75 | 0.27±0.65 | .137 | 0.62±0.70 | 0.44±0.69 | 0.55±0.79 | 0.70±0.83 | .197 |
| HbA1ca (%) | 5.72±0.62 | 6.65±1.93 | 6.77±1.98 | 6.40±1.58 | 7.01±1.64 | .028 | 6.37±2.03 | 6.51±1.67 | 6.88±1.79 | 7.21±2.28 | .149 |
| HCYg (mmol/L) | 18.65±13.48 | 15.11±8.05 | 18.13±14.36 | 15.81±7.76 | 20.98±15.09 | .287 | 17.08±11.96 | 17.33±12.09 | 17.41±12.27 | 19.68±12.85 | .839 |
| D-dimers (mg/ml) | 1.74±0.07 | 3.57±5.66 | 2.22±3.44 | 4.40±12.20 | 2.07±3.25 | .139 | 3.60±12.08 | 3.05±4.75 | 2.60±4.39 | 3.89±5.12 | .176 |
| Hs-CRP (mg/L) | 273±41.18 | 6.02±1.105 | 4.24±6.19 | 5.85±8.87 | 3.66±4.57 | .228 | 2.89±3.84 | 4.85±9.66 | 5.76±10.08 | 5.32±9.26 | .092 |
| ESRh (%) | 420±3.63 | 8.74±12.77 | 7.53±6.64 | 8.63±6.21 | 9.46±11.96 | .036 | 7.61±6.57 | 6.74±5.15 | 8.95±10.71 | 12.96±15.62 | .323 |

aWhite blood cell count.
bRed blood cell count.
cPlatelet count.
dUrea nitrogen, urea.
eUric acid, UA.
fTriglyceride.
gLow-density lipoprotein.
hProthrombin time activity.
iInternational normalized ratio.
jProthrombin time.
kFibrinogen.
lGlycated hemoglobin.
mHomocysteine.
nHypersensitive C-reactive protein.
pErythrocyte sedimentation rate.
penumbra partially or completely lost its ability to regulate the reflex autonomic modulation. The improvement of perfusion pressure was directly related to systemic BP. In addition, increased intracranial pressure, elevated concentrations of circulating plasma catecholamine and inflammatory cytokine, stress from critical illness and hospitalization, unrecognized or uncontrolled pre-existing hypertension, the Cushing phenomenon, dehydration, pain or discomfort, nausea, and hypoxia are the potential pathogeneses or critical influences that contribute to the acute BP change in patients with AIS. Then, persistent lower BP level, insufficient blood oxygen supply to brain tissue, increased mitochondrial permeability and overexpression of inducible aquaporin may aggravate cerebral edema. Persistent higher BP level, the pressure
### TABLE 3  Results of the association between trajectory groups of 24 hours blood pressure and stroke outcomes

| Stroke outcomes                        | Systolic blood pressure Trajectory groups |  |  |  |  | Diastolic blood pressure Trajectory groups |  |  |  |  |
|----------------------------------------|------------------------------------------|---|---|---|---|--------------------------------------------|---|---|---|---|
|                                        | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Reference | Group 1 | Group 2 | Group 3 | Group 4 |
| Early neurological deterioration (within 24 h) | | | | | | | | | | |
| Model 1                                | 0.263 (0.033,2.075) | 1.140 (0.527,2.467) | Reference | 1.507 (0.738,3.079) | 2.852 (1.312,6.200) | 0.885 (0.397,1.973) | Reference | 1.449 (0.776,2.704) | 1.921 (0.762,4.842) |
| Model 2                                | 0.328 (0.041,2.646) | 1.241 (0.564,2.731) | Reference | 1.503 (0.725,3.113) | 3.175 (1.429,7.051) | 0.884 (0.392,1.994) | Reference | 1.490 (0.788,2.815) | 1.795 (0.690,4.670) |
| Model 3                                | 0.995 (0.106,9.331) | 1.343 (0.518,3.483) | Reference | 1.407 (0.594,3.334) | 2.743 (1.008,7.467) | 0.851 (0.294,2.466) | Reference | 1.243 (0.576,2.684) | 1.289 (0.355,4.680) |
| Early neurological improvement (within 24 h) | | | | | | | | | | |
| Model 1                                | 0.841 (0.335,2.111) | 1.152 (0.650,2.042) | Reference | 0.379 (0.205,0.701) | 0.288 (0.128,0.645) | 0.693 (0.383,1.254) | Reference | 0.446 (0.263,0.755) | 0.443 (0.184,1.066) |
| Model 2                                | 0.815 (0.316,2.098) | 1.125 (0.633,1.999) | Reference | 0.380 (0.205,0.703) | 0.282 (0.125,0.634) | 0.686 (0.378,1.246) | Reference | 0.442 (0.260,0.751) | 0.443 (0.183,1.071) |
| Model 3                                | 0.548 (0.155,1.932) | 0.694 (0.327,1.472) | Reference | 0.448 (0.219,0.919) | 0.550 (0.214,1.409) | 0.612 (0.309,1.214) | Reference | 0.399 (0.219,0.727) | 0.516 (0.181,1.474) |
| Modified Rankin scale score (3–6) (3 months) | | | | | | | | | | |
| Model 1                                | 0.963 (0.327,2.838) | 1.251 (0.651,2.402) | Reference | 2.228 (1.220,4.068) | 2.883 (1.420,5.851) | 0.924 (0.477–1.791) | Reference | 1.452 (0.851–2.478) | 3.345 (0.851–2.478) |
| Model 2                                | 1.277 (0.448,4.235) | 1.284 (0.659,2.502) | Reference | 2.222 (1.203,4.102) | 3.096 (1.503,6.380) | 0.891 (0.455–1.744) | Reference | 1.508 (0.874–2.605) | 3.146 (1.361–7.273) |
| Model 3                                | 5.239 (1.271,21.595) | 1.969 (0.866,4.477) | Reference | 2.030 (0.967,4.262) | 3.797 (1.486,9.697) | 1.473 (0.652,3.327) | Reference | 1.253 (0.655,2.396) | 3.387 (1.185,9.683) |

Note: In addition to SBP trajectory, high glucose levels also increased the risk of END (OR: 1.193, 95% CI: 1.049–1.356, \( p = .007 \)). Intravenous use of antihypertensive drugs was also associated with ENI (OR: 0.429, 95% CI: 0.187–0.983, \( p = .046 \)). Except for the systolic blood pressure trajectory, the occurrence of all three stroke outcomes was related to blood glucose. (END: [OR: 1.125, 95% CI: 1.036–1.222, \( p = .005 \)], ENI: [OR: 0.916, 95% CI: 0.842–0.996, \( p = .039 \)], mRS: [OR: 1.103, 95% CI: 1.009–1.205, \( p = .031 \)]. Urinary catheter indwelling within 24 h of thrombolysis was also one of the independent influencing factors of MRS (OR: 8.869, 95% CI: 1.613–48.772, \( p = .012 \)).
### TABLE 4  Results of the association between previous BP parameters and stroke outcomes

| Variables                  | Early neurological deterioration | Early neurological improvement | Modified Rankin scale score (3–6) |
|----------------------------|---------------------------------|---------------------------------|----------------------------------|
|                            | OR 95%CI p                       | OR 95%CI p                       | OR 95%CI p                       |
| **SBP on admission**       |                                 |                                 |                                 |
| max                        | 1.021 (1.002, 1.041)             | 0.979 (0.962, 0.996)             | 0.991 (0.978, 1.003)             |
| min                        | 1.028 (1.004, 1.052)             | 0.977 (0.959, 0.995)             | 0.993 (0.978, 1.009)             |
| range                      | 1.003 (0.978, 1.027)             | 0.990 (0.971, 1.009)             | 0.994 (0.978, 1.014)             |
| SD                         | 1.077 (1.003, 1.157)             | 0.934 (0.882, 0.988)             | 0.972 (0.921, 1.019)             |
| SV                         | 0.998 (0.686, 1.452)             | 0.747 (0.555, 1.005)             | 0.871 (0.667, 1.177)             |
| **24h SBP**                |                                 |                                 |                                 |
| max                        | 1.019 (0.987, 1.052)             | 0.971 (0.936, 1.006)             | 0.990 (0.970, 1.010)             |
| min                        | 1.022 (1.004, 1.052)             | 0.980 (0.950, 1.012)             | 0.996 (0.962, 1.030)             |
| range                      | 1.004 (0.975, 1.034)             | 1.000 (0.976, 1.024)             | 0.994 (0.940, 1.047)             |
| SD                         | 1.051 (0.915, 1.206)             | 0.907 (0.808, 1.019)             | 0.972 (0.912, 1.038)             |
| SV                         | 1.036 (0.694, 1.546)             | 1.088 (0.789, 1.502)             | 0.867 (0.673, 1.173)             |
| **SBP in daytime**         |                                 |                                 |                                 |
| max                        | 1.015 (0.997, 1.035)             | 0.986 (0.966, 1.005)             | 0.990 (0.970, 1.010)             |
| min                        | 1.021 (1.001, 1.040)             | 0.991 (0.975, 1.008)             | 0.995 (0.975, 1.013)             |
| range                      | 1.024 (1.002, 1.046)             | 0.985 (0.967, 1.004)             | 0.990 (0.970, 1.013)             |
| SD                         | 1.004 (0.979, 1.029)             | 1.004 (0.983, 1.025)             | 0.986 (0.963, 1.031)             |
| SV                         | 1.002 (0.920, 1.092)             | 0.976 (0.913, 1.043)             | 0.945 (0.904, 0.985)             |
| **DBP in daytime**         |                                 |                                 |                                 |
| max                        | 1.018 (0.988, 1.049)             | 0.969 (0.937, 1.002)             | 0.985 (0.950, 1.021)             |
| min                        | 0.998 (0.965, 1.032)             | 0.983 (0.957, 1.010)             | 0.983 (0.950, 1.012)             |
| range                      | 1.020 (0.982, 1.059)             | 0.980 (0.952, 1.010)             | 0.998 (0.968, 1.032)             |
| SD                         | 0.977 (0.938, 1.018)             | 1.000 (0.973, 1.028)             | 0.983 (0.938, 1.043)             |
| SV                         | 0.949 (0.826, 1.089)             | 0.970 (0.873, 1.078)             | 0.963 (0.910, 1.019)             |
| **SBP in nighttime**       |                                 |                                 |                                 |
| max                        | 0.999 (0.947, 1.054)             | 0.976 (0.859, 1.058)             | 0.925 (0.925, 1.037)             |
| min                        | 1.073 (0.883, 1.304)             | 0.896 (0.758, 1.059)             | 0.925 (0.925, 1.035)             |
| range                      | 1.101 (0.909, 1.332)             | 0.888 (0.753, 1.047)             | 0.944 (0.932, 0.956)             |
| SD                         | 1.122 (0.932, 1.352)             | 0.869 (0.736, 1.026)             | 0.942 (0.921, 0.963)             |
| SV                         | 1.130 (0.939, 1.361)             | 0.871 (0.738, 1.029)             | 0.940 (0.918, 0.962)             |
| **DBP in nighttime**       |                                 |                                 |                                 |
| max                        | 1.137 (0.945, 1.367)             | 0.880 (0.745, 1.039)             | 0.952 (0.923, 0.982)             |
| min                        | 1.119 (0.928, 1.349)             | 0.879 (0.744, 1.040)             | 0.940 (0.910, 0.971)             |
| range                      | 1.134 (0.943, 1.364)             | 0.871 (0.736, 1.029)             | 0.923 (0.892, 0.954)             |
| SD                         | 1.132 (0.940, 1.362)             | 0.869 (0.736, 1.026)             | 0.948 (0.918, 0.978)             |
| SV                         | 1.130 (0.938, 1.360)             | 0.867 (0.734, 1.023)             | 0.951 (0.919, 0.983)             |
| variables | early neurological deterioration | early neurological improvement | modified Rankin scale score (3-6) |
|-----------|---------------------------------|-------------------------------|----------------------------------|
|           | AUC    | 95%CI | p     | AUC    | 95%CI | p     | AUC    | 95%CI | p     |
| SBP on admission | 0.582  | 0.529,0.634 | .039  | 0.612  | 0.559,0.663 | <.001 | 0.593  | 0.540,0.645 | .004  |
| DBP on admission | 0.612  | 0.559,0.663 | .005  | 0.571  | 0.518,0.624 | .022  | 0.654  | 0.601,0.703 | <.001 |
| Immediate SBP after thrombolysis | 0.586  | 0.533,0.638 | .038  | 0.586  | 0.532,0.638 | .006  | 0.575  | 0.521,0.627 | .019  |
| Immediate DBP after thrombolysis | 0.580  | 0.527,0.632 | .051  | 0.567  | 0.513,0.619 | .035  | 0.633  | 0.580,0.683 | <.001 |

### 24h BP

| variables | AUC    | 95%CI | p     |
|-----------|--------|-------|-------|
| mean      | 0.602  | 0.549,0.654 | .010  |
| max       | 0.603  | 0.550,0.654 | .007  |
| min       | 0.600  | 0.547,0.652 | .013  |
| Range     | 0.536  | 0.483,0.589 | .367  |
| SD        | 0.603  | 0.550,0.654 | .009  |
| SV        | 0.541  | 0.487,0.594 | .301  |

### 24h DBP

| variables | AUC    | 95%CI | p     |
|-----------|--------|-------|-------|
| mean      | 0.588  | 0.534,0.639 | .032  |
| max       | 0.583  | 0.529,0.635 | .048  |
| min       | 0.586  | 0.533,0.638 | .039  |
| range     | 0.528  | 0.474,0.581 | .502  |
| SD        | 0.588  | 0.535,0.640 | .031  |
| SV        | 0.524  | 0.470,0.577 | .564  |

### SBP in daytime

| variables | AUC    | 95%CI | p     |
|-----------|--------|-------|-------|
| mean      | 0.586  | 0.533,0.638 | .029  |
| max       | 0.591  | 0.538,0.643 | .025  |
| min       | 0.610  | 0.557,0.661 | .006  |
| range     | 0.518  | 0.464,0.571 | .669  |
| SD        | 0.509  | 0.455,0.562 | .832  |
| SV        | 0.511  | 0.458,0.574 | .781  |

### DBP in daytime

| variables | AUC    | 95%CI | p     |
|-----------|--------|-------|-------|
| mean      | 0.582  | 0.529,0.634 | .048  |
| max       | 0.564  | 0.510,0.616 | .116  |
| min       | 0.579  | 0.525,0.631 | .058  |
| range     | 0.506  | 0.452,0.559 | .893  |
| SD        | 0.507  | 0.453,0.560 | .873  |
| SV        | 0.525  | 0.472,0.578 | .426  |

### SBP in nighttime

| variables | AUC    | 95%CI | p     |
|-----------|--------|-------|-------|
| mean      | 0.612  | 0.559,0.663 | .004  |
| max       | 0.628  | 0.576,0.679 | .001  |
| min       | 0.576  | 0.523,0.628 | .057  |
| range     | 0.622  | 0.569,0.673 | .002  |
| SD        | 0.624  | 0.571,0.675 | .002  |
| SV        | 0.592  | 0.539,0.644 | .019  |

### DBP in nighttime

| variables | AUC    | 95%CI | p     |
|-----------|--------|-------|-------|
| mean      | 0.561  | 0.507,0.613 | .132  |
| max       | 0.583  | 0.529,0.635 | .043  |
| min       | 0.610  | 0.557,0.661 | .005  |
| range     | 0.524  | 0.470,0.577 | .563  |
| SD        | 0.536  | 0.482,0.589 | .382  |
| SV        | 0.537  | 0.483,0.590 | .357  |
| SBP trajectory | 0.606  | 0.553,0.657 | .007  |
| DBP trajectory | 0.566  | 0.513,0.618 | .092  |
difference between the cerebrovascular and brain interstitium, and the cracks in the vessel wall increases risk of brain edema and bleeding. As one of the common and interventionable indicators, BP is one of the main indicators with strong operability and practicability in clinical nursing work. By monitoring a patient’s BP and its fluctuations over time, known as BP variability, more and better information can be obtained for observation.

Each indicator described BP, either the traditional method or the group-based trajectory modeling, has its own advantages and limitations when considering the availability of appropriate data, ease of analysis, association with longer-term clinical outcomes. Of course, all reduce the dynamic and longitudinal nature of BP into measurements that can be assessed cross-sectionally at a single time point, which can lead to missed opportunities to understand BP course and potentially even misleading conclusions under certain circumstances. Emerging approach, group-based Trajectory Modeling, which is to longitudinally measure BP provide nuanced assessments that reveal unique insights into different BP changes at different time points over an individuals’ treatment. This method help meet the needs of the current scientific agenda for BP changes and reveal important opportunities for developing more tailored interventions that target the varied care challenges patients may face over the intravenous thrombolysis within 24 h. However, this method indicated that outcomes must be relatively complete, and trajectory grouping and course are not fixed because of basing on the best fit to the observed data, not actually an innate characteristic.

BP in SBP group 1 fluctuated only within 3 h of admission. Considering that these patients were younger and had fewer chronic diseases, we believe that they were more affected by psychological factors, such as nervousness, fear of disease progression, side effects, and drug-related complications. SBP group 5 had a higher NIHSS score at admission, indicating a greater influence of disease status. Meanwhile, with the highest proportion of intravenous use of antihypertensive drugs, patients in group 5 showed BP levels > 185/110 mmHg during admission and thrombolysis, which is likely to result in unstable BP over the 24-h period. Changes in other groups suggested that although the blood pressure was high at admission, it was safe to reduce it quickly and steadily to about 160 mmHg later and to subsequently stabilize it. Therefore, it is particularly important to monitor BP at multiple time points in the acute phase, and clinicians can more intuitively grasp the changes in patients’ condition according to the trajectory map.

Our study both confirms and expands on the findings of previous BP studies. First, a high BP level was prevalent in patients with AIS. Harper and coworkers found that 69.3%-82% of patients had BP > 140/90 mmHg and less than 5% of patients had a BP < 120 mmHg in the acute stage. In our study, 72% of patients had a higher-than-normal BP, and 6.2% of patients had a BP < 120 mmHg. Second, most patients’ BP levels gradually declined and stabilized over time within the acute phase and were associated with neurological deficits. The decrease in BP is faster within the first 8 h and lasts up to 36 h. Gill and coworkers found that an SBP decrease of 10 mmHg was related to a decrease of 0.51 points in the NIHSS scores. Zhang and coworkers and Tsou and coworkers et showed that SBP ≥160 mmHg or an increase of 15 mmHg could predict the risk of neurological deterioration. Leonardi-Bee and coworkers also found that the relationship between SBP and the 14-day mortality rate and 6-month mortality or disability rate was U-shaped rather than linear. The study showed that the risk of adverse prognosis increased by 5% for every 1-mmHg increase up to 90 mmHg. Third, current research on the association between BP and prognosis mainly focuses on data from single measurements, multiple measurements in a short time, or 24-h ambulatory blood pressure measurements. Current BP reporting methods may not adequately reflect individuals’ accurate BP levels. Group-based trajectory modeling considers BP variations over time and the heterogeneity within multiple BP measurements, thus providing an effective approach to describe the relationship between BP changes and stroke outcomes.

Our study had several limitations that should be acknowledged. First, the participants were recruited only from one hospital; our findings should be verified in other cohorts to determine generalizability to other ethnicities and populations with different backgrounds. Second, identifying stroke outcomes based on more objective indicators, such as imaging findings, is more accurate. Third, due to the observational study design, although BP management was carried out according to guidelines, how long and how much the individual patients’ BP was controlled was left at the discretion of primary stroke physicians; future studies should aim to standardize this management.

5 | CONCLUSION

Trajectory analysis models showed that the 24-h changes in BP in patients with AIS treated with alteplase can reflect the dynamic changes in BP over time. BP may effectively be grouped according to distinct trajectory patterns, which have differential clinical characteristics and risk of subsequent early neurological improvement or deterioration as well as different associations with mRS score at 3 months. Being classified into the continuous low SBP (102–114 mmHg), fluctuating high SBP/DBP (162–173/92–101 mmHg), or rapidly high stable SBP/DBP (150–157/82–88 mmHg) groups was an independent predictor of adverse events. The clinical significance of this study is that our findings may help identify patients at a high risk of future vascular events and those requiring intervention.

ACKNOWLEDGEMENTS

The authors wish to thanks all participants in XUANWU hospital capital medical university, including the physicians, nurses staff for their work with the follow-up assessments, and their expertise in medical statistics.

FUNDING

This study does not need any fund support, and all the work is completed within the normal work content and time. The data used in the study is also easy to access.

CONFLICT OF INTEREST

There are no conflict of interest.
AUTHOR CONTRIBUTIONS

Conceptualization: Kaiting Fan, Jie Zhao, Hong Chang, xin Yang.
Data curation: Kaiting Fan, Jie Zhao, Hong Chang.
Investigation: Kaiting Fan, Xiaojuan wang, Xiaoxia yao.
Methodology: Kaiting Fan, Jie Zhao.
Project administration: Kaiting Fan, Hong Chang, Hui Yao, xin Yang.
Supervision: Kaiting Fan, Hong Chang, Hui Yao. xin Yang.
Visualization: Kaiting Fan.
Writing – original draft: Kaiting Fan.
Writing – review & editing: Kaiting Fan, Jie Zhao, Hong Chang.

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How to cite this article: Fan K, Zhao J, Chang H, et al. Predicting prognosis in patients with stroke treated with intravenous alteplase through the 24-hour trajectory of blood pressure changes. J Clin Hypertens. 2021;23:1718–1730. https://doi.org/10.1111/jch.14331