CLINICAL TRIAL REPORT

# Association of Blood Pressure with Neurological Function Decline and Functional Outcome in Patients of Watershed Infarction

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**Background and Aims:** The association between acute-phase blood pressure (BP) and outcomes in watershed infarction (WI) remains unclear. This study aimed to investigate the relationships between BP and BP changes with neurological functional decline (NFD) and functional outcome at 90 days.

**Methods:** We included patients with WI from a prospective, observational, single-center study (Effect of Cardiac Function on Short-Term Functional Prognosis in Patients with Acute Ischemic Stroke, SPARK). We recorded data of systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the day of admission, as well as on day 2 and day 3. In logistic regression models, both the baseline BP and BP changes were assessed.

**Results:** Among the 207 patients with WI, 147 (71%) had concurrent cortical and internal infarcts. After adjusting for relevant factors, higher baseline SBP (OR:1.17; 95% CI:1.01–1.37) and DBP (OR:1.04; 95% CI:1.01–1.09) were associated with an increased risk of NFD. However, the restricted cubic spline (RCS) curve indicated that this association was statistically significant only when SBP was >180 mmHg or DBP was >100 mmHg. Additionally, an elevation in DBP of ≥4 mmHg on day 3 was associated with a reduced risk (OR:0.28; 95% CI: 0.08–0.97), whereas an elevation of DBP ≥10 mmHg was not. Neither baseline BP nor BP changes were associated with functional outcome.

**Conclusion:** In patients with WI, the risk of NFD increases when baseline SBP >180 mmHg or DBP >100 mmHg. However, raising DBP by ≥4 mmHg but <10 mmHg on day 3 is associated with a reduced risk of NFD. BP may not be associated with functional outcome.

**Trial Registration:** https://www.chictr.org.cn/, ChiCTR2300067696.

**Keywords:** watershed infarcts, neurological function decline, functional outcome, hypertension

## Introduction

Since 2015, stroke has become the leading cause of death and disability in China, with its prevalence continuing to rise.[1–3] As a major chronic non-communicable disease, it poses a significant threat to the health of Chinese citizens,[4] and the disease burden has been increasing annually.[5,6] Cerebral watershed infarction (WI) is an ischemic lesion that occurs in a characteristic location at the junction of the two major intracranial arteries, accounting for approximately 10% of all ischemic strokes. In most cases, WI is associated with carotid artery occlusive disease or impaired hemodynamics resulting from severe intracranial stenosis. While the pathology of WI has not been fully elucidated, the generally accepted

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hypothesis is that reduced perfusion to the distal portions of the arteries makes these areas particularly susceptible to infarction.

Among the subtypes of WI, cortical watershed infarction (CWI) is believed to result from microembolization due to cerebrovascular reactive injury and impaired oxygen metabolism.[7–9] In contrast, internal watershed infarction (IWI) typically presents in a linear or rosette pattern in the center of the semi-ovals and is primarily associated with hemodynamic deficits resulting from severe luminal stenosis.[7,10] This type of infarction is thought to occur due to supply from a distal arterial branch, which experiences the lowest perfusion pressure. Studies have also demonstrated that IWI arises from a combination of hemodynamic impairment and microembolism.[11] Treatment strategies vary based on the underlying pathophysiology, with arterial blood pressure (BP) being a critical factor.[12] Wabnitz et al[13] suggested that WI may be linked to poor collateral circulation. Whereas the presence of collateral flow may facilitate early spontaneous neurological improvement in acute ischemic stroke (AIS). Ois et al[14] found that BP fluctuations may accelerate neurological deterioration by altering hemodynamic homeostasis. Moreover, they noted that a reduction in cerebral hemodynamic reserve, coupled with the absence of collateral blood supply, might contribute to worse neurological outcomes. Therefore, managing BP is particularly crucial during the acute phase of ischemic stroke, especially in patients with WI.

Severe arterial stenosis or occlusion, combined with recurrent episodes of hypotension, can lead to hemodynamic compromise. Few studies have investigated the impact of acute-phase BP on the outcomes of WI. This study aims to examine the impact of after-admission BP or BP fluctuation on neurological function decline (NFD) and functional outcome in WI patients. It seeks to provide clinical thinking on the appropriate range of BP during the acute phase of WI.

## Materials and Methods

### Study Design and Participants

The SPARK study (Effect of Cardiac Function on Short-Term Functional Prognosis in Patients with Acute Ischemic Stroke) is a prospective, observational, single-center study. Its primary objective is to determine whether cardiac function influences the functional prognosis of patients with AIS. Data were consecutively collected from 1357 patients with AIS admitted to the Tianjin Huanhu Hospital, the largest National Stroke Center in northeastern China, from January 19th to March 20th of 2023. AIS was diagnosed based on assessable neurological deficits, which included speech impairment, motor dysfunction, cognitive impairment, gaze impairment, visual field impairment, and visual loss. The inclusion criteria consisted of patients aged 18 years and older who were hospitalized and underwent echocardiography within 7 days. Exclusion criteria included a transient ischemic attack, intracerebral hemorrhage, an expected survival time of less than six months, and participation in other interventional clinical studies. In the present study, we included only patients with WI. Ethical approval for this study was granted by the Medical Research Ethics Committee of Tianjin Huanhu Hospital and the Tianjin Municipal Health Bureau (approval number 2022–158), and informed consent was obtained from all participants or their legal guardians.

### Imaging Criterion for Watershed Infarcts

Neuroimaging was performed by specialized radiologists in this study. WI are classified into three types based on their location: CWI, IWI, and mixed-type watershed infarction (MWI). CWIs are characterized on imaging as ovoid or wedge-shaped infarcts located between the cortical regions of the anterior cerebral artery, middle cerebral artery, and posterior cerebral artery. In contrast, IWIs are defined by a series of three or more foci aligned in a linear pattern parallel to the lateral ventricles or the centers of the semiovals,[15] and MWI is a combination of both CWI and IWI occurrences.[7]

### Outcome Variables

The primary outcome was NFD, and the second outcome was poor functional outcome. NFD was defined as a progressive worsening of neurologic deficit symptoms within 7 days after admission, with an increase of at least 2 points on the NIHSS at the time of the patient's condition change,[16–20] excluding symptom exacerbation due to extracranial factors such as infection, aspiration pneumonia, dehydration, metabolic changes, or heart failure. Poor

functional outcome was determined using the mRS, assessed by a trained neurologist 90 days post-onset. A score between 0 and 1 indicated a good functional outcome, while scores between 2 and 6 indicated a poor functional outcome.

## Other Data Collection

We collected baseline demographic and clinical data from all study participants, including age, sex, admission SBP/DBP (referred to as first-day or baseline BP), pulse pressure difference, and BP measurements on the second and third days of hospitalization (all taken in the morning at the same time while patients were in a calm state). Cerebrovascular risk factors were also recorded, including hypertension (defined as reported hypertension history, or prior use of antihypertensive medications, or SBP ≥140 mmHg or DBP ≥90 mmHg during hospitalization), diabetes mellitus (defined as reported diabetes history, prior use of glucose-lowering medications or hemoglobin A1c ≥6.5%), coronary artery disease (including a history of myocardial infarction, angina pectoris, etc), and current smoking and alcohol consumption. Additionally, we gathered laboratory data, stroke characteristics, and imaging studies. Laboratory data included fasting plasma glucose, hemoglobin levels, and low-density lipoprotein cholesterol. Stroke characteristics recorded were the NIHSS score on admission and treatment details (whether antihypertensive therapy was administered during hospitalization or intravenous thrombolysis was performed). Imaging studies, including CT, MRI, magnetic resonance angiography, computed tomography angiography, and digital subtraction angiography were used to evaluate the type of WI and the degree of stenosis in the responsible vessel. Notably, no patients received antihypertensive therapy within the first 3 days of after-admission, and initial treatment consisted of dual antiplatelet therapy.

## Statistical Analysis

We analyzed BP as both a continuous and categorical variable. For SBP on the day of admission (SBP1), participants were categorized into three groups: Group 1 (≤139 mmHg), Group 2 (140 mmHg −159 mmHg), and Group 3 (≥160 mmHg) (Supplementary Table 1). DBP on the day of admission (DBP1), was similarly categorized into three groups: Group 1 (≤79 mmHg), Group 2 (80 mmHg −89 mmHg), and Group 3 (≥90 mmHg) (Supplementary Table 2). Changes in SBP between the first and third days of hospitalization (SBP3-SBP1) were also categorized by tertiles: Group 1 (≤-14 mmHg), Group 2 (−13 mmHg −0 mmHg), and Group 3 (≥1 mmHg). Similarly, changes in DBP between the first and third days of hospitalization (DBP3-DBP1) were categorized into tertiles: Group 1 (≤-10 mmHg), Group 2 (−9 mmHg −3 mmHg), and Group 3 (≥4 mmHg). Group 1 was used as the reference group for all analyses. Demographic characteristics were summarized as frequencies and percentages for categorical variables and as means or medians for continuous variables. Normality was assessed using the Shapiro–Wilk test, histograms, and Q-Q plots. Comparisons of continuous variables were performed using the independent samples $t$-test, Mann–Whitney $U$-test, or Kruskal Wallis test. Categorical data were compared using the Chi-square test or Fisher's exact test.

Multiple logistic regression was used to identify factors associated with two outcomes: an increase of ≥2 points from baseline in the NIHSS score and the mRS score of 2–6 at 90 days. Odds ratio (OR) and 95% confidence interval (CI) were calculated. We performed logistic regression analyses on the entire study population using two models: an unadjusted model and an adjusted model, the latter including additional covariates. Covariates were selected based on their correlation with the outcome and clinical relevance, with variables having a P-value <0.2 in Supplementary Tables 3 and 4 being considered. Statistical significance was defined as a P-value <0.05. The RCS curve was used to test the non-linear relationship between BP and outcomes. All analyses were performed using SPSS software (version 26.0) and R (revision 4.3.1) (https://www.r-project.org).

## Results

### Demographic and Clinical Characteristics of Included Patients

In this study, 100 patients lost to the 90-day follow-up were excluded from the initial cohort of 1,357 patients with AIS. A total of 207 patients with WI were screened, including 8 with CWI (3.9%), 52 with IWI (25.1%), and 147 with MWI (71%). (Figure 1) The median age of the cohort was 66 years (range: 54–72 years), with a male predominance. The median NIHSS score at admission was 6 (range: 3–8). A small percentage of patients received intravenous thrombolysis
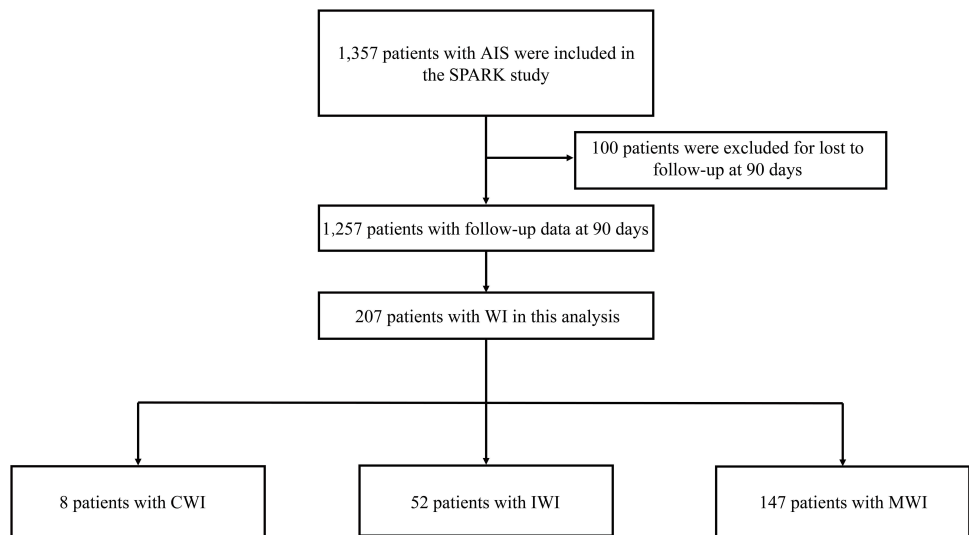
**Figure 1** Study flow of patients.
**Abbreviations**: AIS, acute ischemic stroke; CWI, cortical watershed infarction; IWI, internal watershed infarction; MWI, mixed-type watershed infarction.

(n=6, 2.9%) or endovascular treatment (n=1, 0.5%). Most patients had a history of hypertension (n=164, 79.2%), and a smaller proportion had diabetes (n=77, 37.2%). The majority were current smokers (n=125, 60.4%), while fewer were current alcohol drinkers (n=68, 32.9%). The median low-density lipoprotein cholesterol level was 2.80 mmol/L (range: 2.25 mmol/L-3.33 mmol/L) (Table 1). Patients with WI, regardless of hypertension status, had higher BP on the first day of after-admission compared to the second and third days (Figure 2).

**Table 1** The Baseline Characteristics of the Study Population (n=207)

| Variables | Values |
|---|---|
| Age, median (IQR), years | 66 (54–72) |
| Male, n (%) | 157 (75.8%) |
| Systolic Blood Pressure, mean (±SD), mmHg | 152 (±24) |
| Diastolic Blood Pressure, mean (±SD), mmHg | 86 (±13) |
| Fasting Plasma Glucose, median (IQR), mmol/L | 5.80 (4.92–7.61) |
| Hemoglobin, median (IQR), g/L | 144 (130–154) |
| Low Density Lipoprotein, median (IQR), mmol/L | 2.80 (2.25–3.33) |
| Left Ventricular Ejection Fraction, median (IQR), % | 60 (60–62) |
| Ventricular Rate, median (IQR), bmp | 65 (53–80) |
| Admission NIHSS Score, median (IQR) | 6 (3–8) |
| Medical History | |
| Atrial Fibrillation, n (%) | 8 (3.9%) |
| Hypertension, n (%) | 164 (79.2%) |
| Diabetes, n (%) | 77 (37.2%) |
| Ischemic Heart Diseases, n (%) | 31 (15%) |
| Habits | |
| Current Smoking, n (%) | 125 (60.4%) |
| Current Drinking, n (%) | 68 (32.9%) |
| Treatment During Hospitalization | |
| Intravenous Thrombolysis, n (%) | 6 (2.9%) |
| Endovascular Treatment, n (%) | 1 (0.5%) |
| Anticoagulant Therapy, n (%) | 61 (29.5%) |
| Antihypertensive Treatment, n (%) | 21 (10.1%) |

**Abbreviations**: SD, Standard Deviation; IQR, Interquartile Range; NIHSS, National Institutes of Health Stroke Scale.
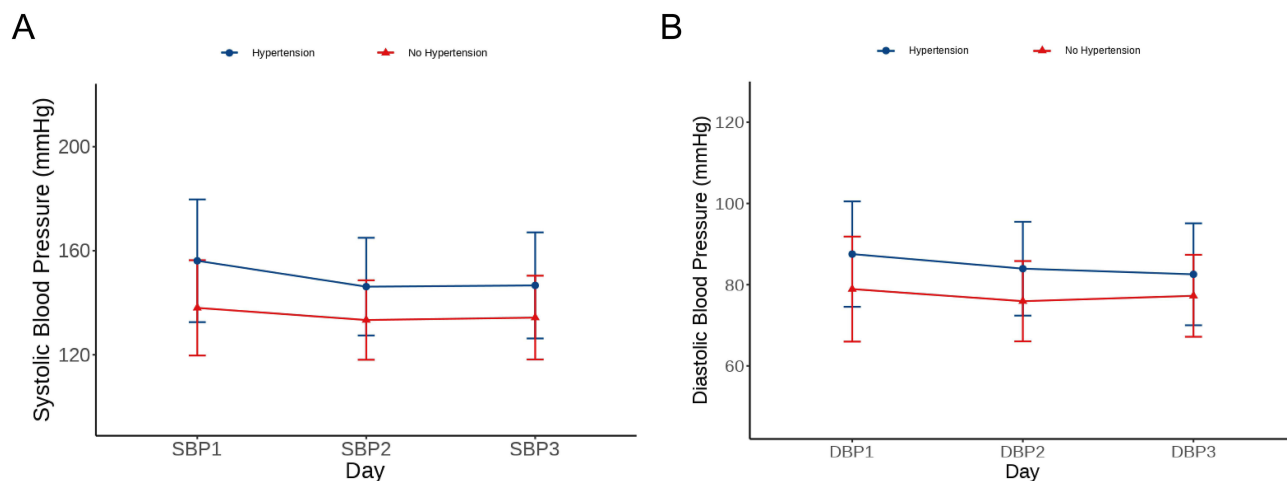
**Figure 2** The trajectory of blood pressure in the first 3 days after admission. (**A**): The SBP trajectory by hypertension in 3 days. (**B**): The DBP trajectory by hypertension in 3 days.
**Abbreviations**: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; SBP1, SBP on the first day; SBP2, SBP on the second day; SBP3, SBP on the third day; DBP1, DBP on the first day; DBP2, DBP on the second day; DBP3, DBP on the third day.

## Neurological Function Decline

The association between BP and NFD during hospitalization is presented in Figure 3. When SBP1 was analyzed as a continuous variable, higher SBP1 was associated with an increased risk of NFD [unadjusted model: OR 1.02

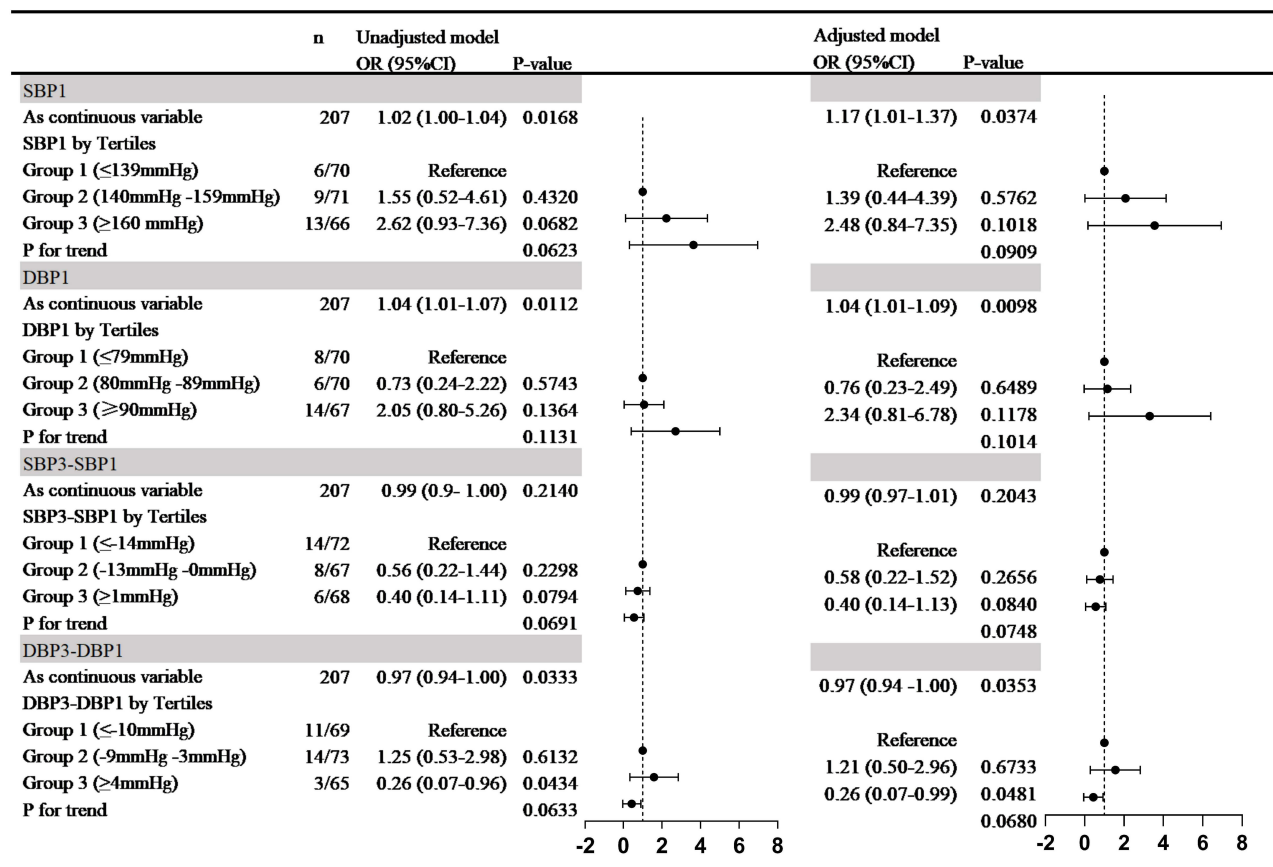| | n | Unadjusted model OR (95%CI) | P-value | | Adjusted model OR (95%CI) | P-value | |
|---|---|---|---|---|---|---|---|
| **SBP1** | | | | | | | |
| As continuous variable | 207 | 1.02 (1.00-1.04) | 0.0168 | | 1.17 (1.01-1.37) | 0.0374 | |
| **SBP1 by Tertiles** | | | | | | | |
| Group 1 (≤139mmHg) | 6/70 | Reference | | | Reference | | |
| Group 2 (140mmHg -159mmHg) | 9/71 | 1.55 (0.52-4.61) | 0.4320 | | 1.39 (0.44-4.39) | 0.5762 | |
| Group 3 (≥160 mmHg) | 13/66 | 2.62 (0.93-7.36) | 0.0682 | | 2.48 (0.84-7.35) | 0.1018 | |
| P for trend | | | 0.0623 | | | 0.0909 | |
| **DBP1** | | | | | | | |
| As continuous variable | 207 | 1.04 (1.01-1.07) | 0.0112 | | 1.04 (1.01-1.09) | 0.0098 | |
| **DBP1 by Tertiles** | | | | | | | |
| Group 1 (≤79mmHg) | 8/70 | Reference | | | Reference | | |
| Group 2 (80mmHg -89mmHg) | 6/70 | 0.73 (0.24-2.22) | 0.5743 | | 0.76 (0.23-2.49) | 0.6489 | |
| Group 3 (≥90mmHg) | 14/67 | 2.05 (0.80-5.26) | 0.1364 | | 2.34 (0.81-6.78) | 0.1178 | |
| P for trend | | | 0.1131 | | | 0.1014 | |
| **SBP3-SBP1** | | | | | | | |
| As continuous variable | 207 | 0.99 (0.9- 1.00) | 0.2140 | | 0.99 (0.97-1.01) | 0.2043 | |
| **SBP3-SBP1 by Tertiles** | | | | | | | |
| Group 1 (≤-14mmHg) | 14/72 | Reference | | | Reference | | |
| Group 2 (-13mmHg -0mmHg) | 8/67 | 0.56 (0.22-1.44) | 0.2298 | | 0.58 (0.22-1.52) | 0.2656 | |
| Group 3 (≥1mmHg) | 6/68 | 0.40 (0.14-1.11) | 0.0794 | | 0.40 (0.14-1.13) | 0.0840 | |
| P for trend | | | 0.0691 | | | 0.0748 | |
| **DBP3-DBP1** | | | | | | | |
| As continuous variable | 207 | 0.97 (0.94-1.00) | 0.0333 | | 0.97 (0.94 -1.00) | 0.0353 | |
| **DBP3-DBP1 by Tertiles** | | | | | | | |
| Group 1 (≤-10mmHg) | 11/69 | Reference | | | Reference | | |
| Group 2 (-9mmHg -3mmHg) | 14/73 | 1.25 (0.53-2.98) | 0.6132 | | 1.21 (0.50-2.96) | 0.6733 | |
| Group 3 (≥4mmHg) | 3/65 | 0.26 (0.07-0.96) | 0.0434 | | 0.26 (0.07-0.99) | 0.0481 | |
| P for trend | | | 0.0633 | | | 0.0680 | |

**Figure 3** Association of blood pressure with neurological function decline. Adjusted model: adjusting by age, diabetes, systolic blood pressure, diastolic blood pressure, responsible vascular stenosis greater than or equal to 50%, fasting plasma glucose, admission NIHSS score. (all variables with P < 0.2 in Supplementary Table 3).
**Abbreviations**: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; SBP1, SBP on the first day; SBP2, SBP on the second day; SBP3, SBP on the third day. DBP1, DBP on the first day; DBP2, DBP on the second day; DBP3, DBP on the third day. SBP3- SBP1, "SBP on the third day"- "SBP on the first day"; DBP3- DBP1, "DBP on the third day"- "DBP on the first day"; OR, Odd Ratio; CI, Confidence Interval; NIHSS, National Institutes of Health Stroke Scale.

(1.00–1.04), P =0.0168; adjusted model: OR 1.17 (1.01–1.37), P =0.0374]. However, the RCS curve indicated that this association was statistically significant only when SBP1 was >180 mmHg (Figure 4A). When SBP1 was analyzed by tertiles, no statistically significant differences were observed among the three SBP1 groups. In the adjusted model, compared to Group 1 with SBP1 of ≤139 mmHg (6/70), Group 2 with SBP1 of 140–159 mmHg (9/71, OR: 1.39; 95% CI: 0.44–4.39), and Group 3 with SBP1 of ≥160 mmHg (13/66, OR: 2.48; 95% CI: 0.84–7.35) showed no significant difference in the incidence of NFD.

When DBP1 was analyzed as a continuous variable, we found that higher DBP1 was associated with an increased risk of NFD [unadjusted model: OR 1.04 (1.01–1.07), P =0.0112; adjusted model: OR 1.04 (1.01–1.09), P =0.0098]. However, the RCS curve suggested this association was statistically significant only when DBP1 was >100 mmHg (Figure 4B). When we analyzed DBP1 by tertiles, we found that there was no statistically significant difference in the three DBP1 groups.
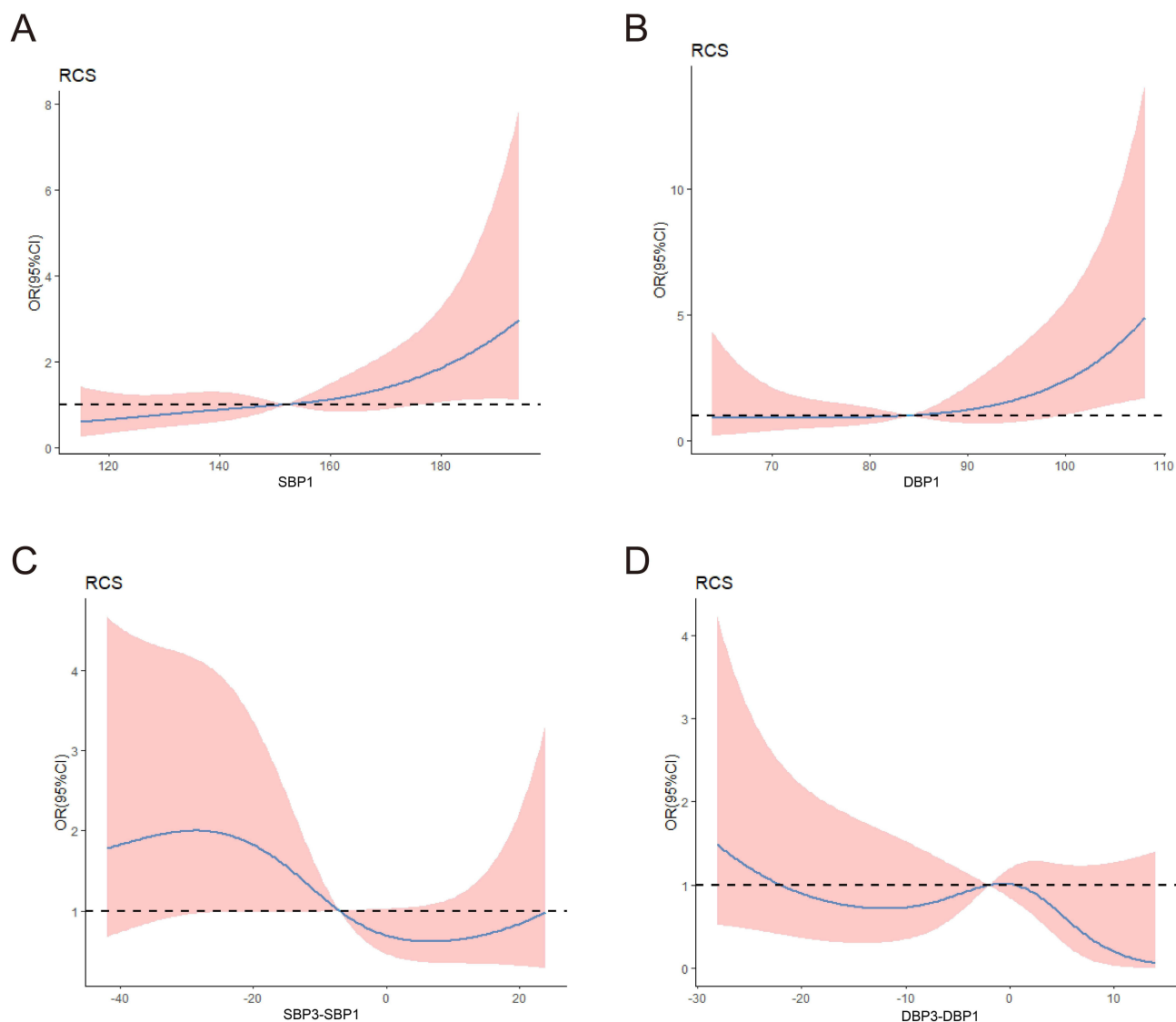


**Figure 4** Restricted cubic spline curve for the association of blood pressure with neurological function decline. (**A**) The association of "SBP1" with neurological function decline. (**B**) The association of "DBP1" with neurological function decline.(**C**) The association of "SBP3-SBP1" with neurological function decline.(**D**) The association of "DBP3-DBP1" with neurological function decline.

**Abbreviations**: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; SBP1, SBP on the first day; SBP2, SBP on the second day; SBP3, SBP on the third day. DBP1,DBP on the first day; DBP2, DBP on the second day; DBP3, DBP on the third day. SBP3- SBP1, "SBP on the third day"- "SBP on the first day"; DBP3- DBP1, "DBP on the third day"- "DBP on the first day"; OR, Odd Ratio; CI, Confidence Interval; NIHSS, National Institutes of Health Stroke Scale.

When we analyzed the change in SBP ("SBP3-SBP1") as either a continuous or categorical variable, no significant association with NFD was found. In contrast, when the change in DBP ("DBP3-DBP1") was analyzed as a continuous variable, higher baseline "DBP3-DBP1" was associated with a decreased risk of NFD [unadjusted model: OR 0.97 (0.94 −1.00), P =0.0333; adjusted model: OR 0.97 (0.94–1.00), P =0.0353]. When "DBP3-DBP1" was analyzed by tertiles, a statistically significant difference was observed. In the adjusted model, compared to Group 1 with "DBP3-DBP1" ≤-10 mmHg (11/69), Group 3 with "DBP3-DBP1" ≥4 mmHg (3/65, OR: 0.26; 95% CI: 0.07–0.97, P =0.0456) showed a decreased risk of NFD. However, no significant differences were found in the RCS curve (Figure 4C and D).

When SBP on day 3 (SBP3) was analyzed either as a continuous or categorical variable, no significant differences were found between SBP3 and NFD. Similarly, when DBP on day 3 (DBP3) was analyzed in both forms, no statistically significant differences were found between DBP3 and NFD (Supplementary Figure 1 and Supplementary Figure 2A and B).

## Poor Functional Outcome

The association between BP and poor functional outcome is presented in Figure 5. When SBP1 was analyzed as a continuous variable, higher SBP1 was associated with an increased risk of poor functional outcome; however, this association was no longer significant in the adjusted model. [unadjusted model: OR 1.02 (1.01–1.03), P =0.0020; adjusted model 3: OR 1.01 (1.00–1.03), P =0.2757]. The RCS curve further suggested that SBP1 was not associated with a 90-day functional outcome (Figure 6A). When SBP1 was analyzed by tertiles, compared to Group 1 with SBP ≤139 mmHg, higher SBP1 in Group 3 with SBP
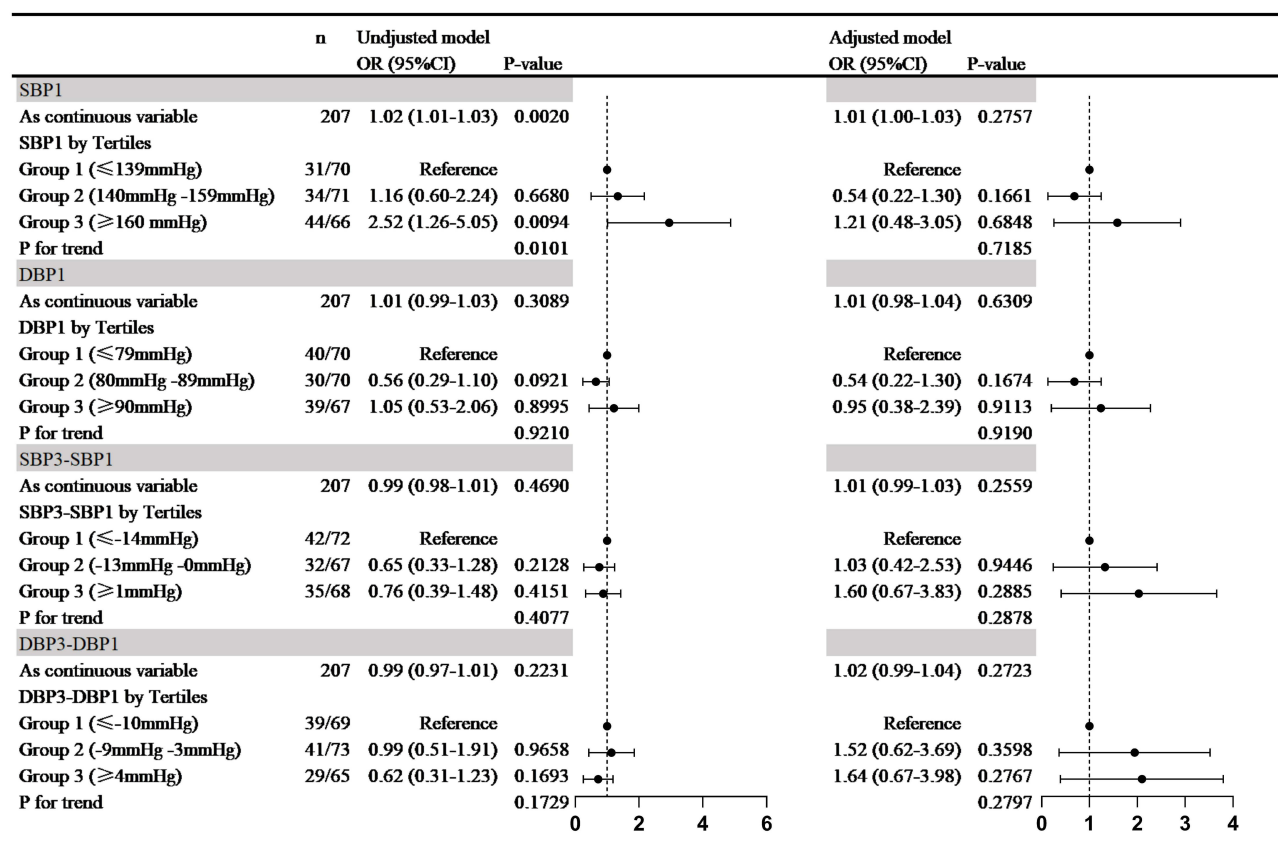
| | n | Undjusted model OR (95%CI) | P-value | Adjusted model OR (95%CI) | P-value |
|---|---|---|---|---|---|
| **SBP1** | | | | | |
| As continuous variable | 207 | 1.02 (1.01-1.03) | 0.0020 | 1.01 (1.00-1.03) | 0.2757 |
| **SBP1 by Tertiles** | | | | | |
| Group 1 (≤139mmHg) | 31/70 | Reference | | Reference | |
| Group 2 (140mmHg -159mmHg) | 34/71 | 1.16 (0.60-2.24) | 0.6680 | 0.54 (0.22-1.30) | 0.1661 |
| Group 3 (≥160 mmHg) | 44/66 | 2.52 (1.26-5.05) | 0.0094 | 1.21 (0.48-3.05) | 0.6848 |
| P for trend | | | 0.0101 | | 0.7185 |
| **DBP1** | | | | | |
| As continuous variable | 207 | 1.01 (0.99-1.03) | 0.3089 | 1.01 (0.98-1.04) | 0.6309 |
| **DBP1 by Tertiles** | | | | | |
| Group 1 (≤79mmHg) | 40/70 | Reference | | Reference | |
| Group 2 (80mmHg -89mmHg) | 30/70 | 0.56 (0.29-1.10) | 0.0921 | 0.54 (0.22-1.30) | 0.1674 |
| Group 3 (≥90mmHg) | 39/67 | 1.05 (0.53-2.06) | 0.8995 | 0.95 (0.38-2.39) | 0.9113 |
| P for trend | | | 0.9210 | | 0.9190 |
| **SBP3-SBP1** | | | | | |
| As continuous variable | 207 | 0.99 (0.98-1.01) | 0.4690 | 1.01 (0.99-1.03) | 0.2559 |
| **SBP3-SBP1 by Tertiles** | | | | | |
| Group 1 (≤-14mmHg) | 42/72 | Reference | | Reference | |
| Group 2 (-13mmHg -0mmHg) | 32/67 | 0.65 (0.33-1.28) | 0.2128 | 1.03 (0.42-2.53) | 0.9446 |
| Group 3 (≥1mmHg) | 35/68 | 0.76 (0.39-1.48) | 0.4151 | 1.60 (0.67-3.83) | 0.2885 |
| P for trend | | | 0.4077 | | 0.2878 |
| **DBP3-DBP1** | | | | | |
| As continuous variable | 207 | 0.99 (0.97-1.01) | 0.2231 | 1.02 (0.99-1.04) | 0.2723 |
| **DBP3-DBP1 by Tertiles** | | | | | |
| Group 1 (≤-10mmHg) | 39/69 | Reference | | Reference | |
| Group 2 (-9mmHg -3mmHg) | 41/73 | 0.99 (0.51-1.91) | 0.9658 | 1.52 (0.62-3.69) | 0.3598 |
| Group 3 (≥4mmHg) | 29/65 | 0.62 (0.31-1.23) | 0.1693 | 1.64 (0.67-3.98) | 0.2767 |
| P for trend | | | 0.1729 | | 0.2797 |

**Figure 5** Association of blood pressure with poor functional outcome. Adjusted model: adjusting by age, gender, atrial fibrillation, hypertension, ischemic heart diseases, current smoking, current drinking, involvement of subcortical watershed area, systolic blood pressure, fasting plasma glucose, hemoglobin content, and admission NIHSS score. (all variables with P < 0.2 in Supplementary Table 4).
**Abbreviations**: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; SBP1, SBP on the first day; SBP2, SBP on the second day; SBP3, SBP on the third day. DBP1,DBP on the first day; DBP2, DBP on the second day; DBP3, DBP on the third day. SBP3- SBP1, "SBP on the third day"- "SBP on the first day"; DBP3- DBP1, "DBP on the third day"- "DBP on the first day"; OR, Odd Ratio; CI, Confidence Interval; NIHSS, National Institutes of Health Stroke Scale.
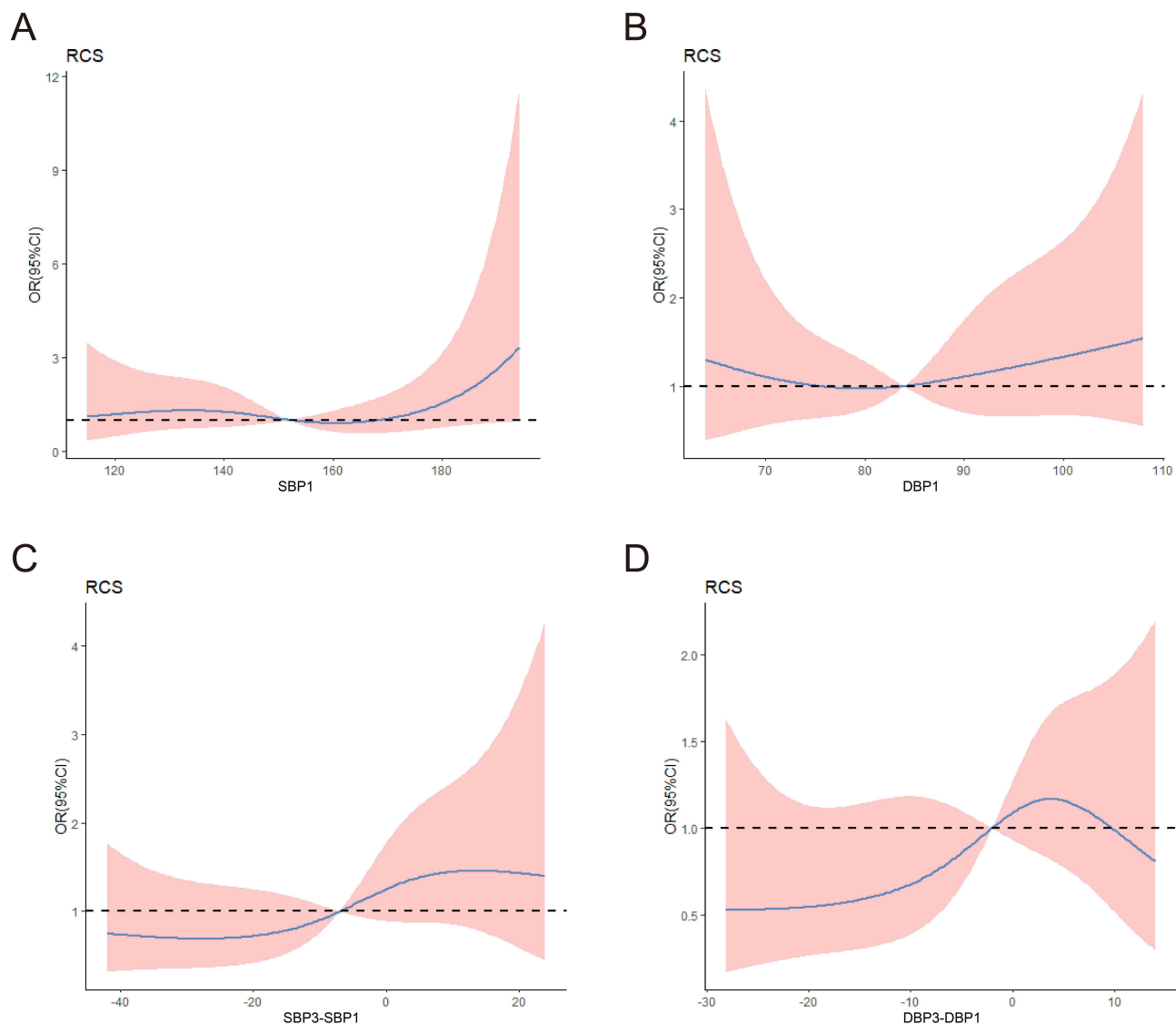
**Figure 6** Restricted cubic spline curve for the association of blood pressure with functional outcome. (**A**) The association of "SBP1" with functional outcome. (**B**) The association of "DBP1" with functional outcome.(**C**) The association of "SBP3-SBP1" with functional outcome.(**D**) The association of "DBP3-DBP1" with functional outcome. **Abbreviations**: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; SBP1, SBP on the first day; SBP2, SBP on the second day; SBP3, SBP on the third day. DBP1,DBP on the first day; DBP2, DBP on the second day; DBP3, DBP on the third day. SBP3- SBP1, "SBP on the third day"- "SBP on the first day"; DBP3- DBP1, "DBP on the third day"- "DBP on the first day"; OR, Odd Ratio; CI, Confidence Interval; NIHSS, National Institutes of Health Stroke Scale.

≥160 mmHg was associated with an increased risk of poor functional outcome; however, this difference was also not significant in the adjusted model. [unadjusted model: OR 2.52 (1.26–5.05), P =0.0094; adjusted model 3: OR 1.21 (0.48–3.05), P =0.6848].

When DBP1 was analyzed as either a continuous or categorical variable, no statistically significant differences were found between baseline DBP1 and poor functional outcome. The RCS curve also indicated that baseline DBP1 did not affect 90-day functional outcome (Figure 6B). In the adjusted model, compared to Group 1 with DBP1 ≤79 mmHg (40/70), Group 2 with DBP1 80–89 mmHg (30/70, OR: 0.54; 95% CI: 0.22–1.30), and Group 3 with DBP1 ≥90 mmHg (39/67, OR: 0.95; 95% CI: 0.38–2.39) showed no significant differences in the incidence of poor functional outcome.

When we analyzed the change in SBP ("SBP3-SBP1") or the change in DBP ("DBP3-DBP1") as continuous or categorical variables, no significant differences in poor functional outcome were found (Figure 6C and D).

When SBP3 was analyzed as a continuous variable, higher SBP3 might associated with an increased risk of poor functional outcome [Adjusted OR (95% CI): 1.02 (1.00–1.04), P = 0.0194]. However, when SBP3 was analyzed by tertiles, no statistically significant differences were observed among the three groups. Similarly, when DBP3 was
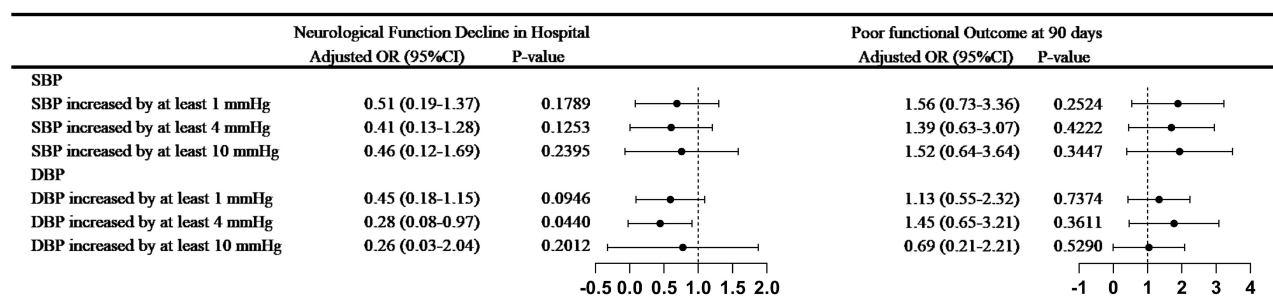
| | Neurological Function Decline in Hospital | | | Poor functional Outcome at 90 days | | |
|---|---|---|---|---|---|---|
| | Adjusted OR (95%CI) | P-value | | Adjusted OR (95%CI) | P-value | |
| **SBP** | | | | | | |
| SBP increased by at least 1 mmHg | 0.51 (0.19–1.37) | 0.1789 | | 1.56 (0.73–3.36) | 0.2524 | |
| SBP increased by at least 4 mmHg | 0.41 (0.13–1.28) | 0.1253 | | 1.39 (0.63–3.07) | 0.4222 | |
| SBP increased by at least 10 mmHg | 0.46 (0.12–1.69) | 0.2395 | | 1.52 (0.64–3.64) | 0.3447 | |
| **DBP** | | | | | | |
| DBP increased by at least 1 mmHg | 0.45 (0.18–1.15) | 0.0946 | | 1.13 (0.55–2.32) | 0.7374 | |
| DBP increased by at least 4 mmHg | 0.28 (0.08–0.97) | 0.0440 | | 1.45 (0.65–3.21) | 0.3611 | |
| DBP increased by at least 10 mmHg | 0.26 (0.03–2.04) | 0.2012 | | 0.69 (0.21–2.21) | 0.5290 | |

**Figure 7** Impact of baseline blood pressure elevated by 1 mmHg, 4 mmHg, and 10 mmHg on outcomes.
**Abbreviations**: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; SBP1, SBP on the first day; SBP2, SBP on the second day; SBP3, SBP on the third day. DBP1,DBP on the first day; DBP2, DBP on the second day; DBP3, DBP on the third day. SBP3- SBP1, "SBP on the third day"- "SBP on the first day"; DBP3- DBP1, "DBP on the third day"- "DBP on the first day"; OR, Odd Ratio; CI, Confidence Interval; NIHSS, National Institutes of Health Stroke Scale.

analyzed either as a continuous or categorical variable, no statistically significant differences were found between DBP and poor functional outcome (Supplementary Figure 1 and Supplementary Figure 2C and D).

## Impact of BP Elevated by 1 mmHg, 4 mmHg, and 10 mmHg on Outcomes

Figure 7 illustrates the association between fluctuations in SBP and DBP and the occurrence of NFD as well as poor functional outcome. Elevations in SBP by 1 mmHg, 4 mmHg, and 10 mmHg were not associated with NFD. Notably, the risk of NFD was lower in patients with a DBP increase of ≥4 mmHg on the third day (OR:0.28; 95% CI:0.08–0.97, P = 0.0440) compared to those without such an increase. However, this difference was no longer significant when DBP was elevated by ≥10 mmHg on the third day. Similarly, no association was found between SBP or DBP elevations of 1 mmHg, 4 mmHg, or 10 mmHg and poor prognosis at 90 days.

## Discussion

Previous studies have not established an appropriate range for acute-phase BP control in patients with WI. In the study, we found that higher baseline SBP and DBP were associated with an increased risk of NFD. These findings suggest even in patients with WI, BP levels exceeding 180/100 mmHg require antihypertensive therapy. Ouyang et al[21] demonstrated a nonlinear "J-shaped" relationship between BP and poor prognosis: patients with low SBP had worse functional outcome compared to those with normal SBP. However, we did not observe a significant correlation between changes in baseline SBP/DBP or acute-phase SBP/DBP and functional outcome. This lack of association may be attributed to the relatively small sample size in our study.

The progression of cerebral WI may be due to the feeding arteries being primarily terminal vessels, located between cortical arteries, deep perforating branches, and their branches, with poorly developed collateral circulation. Systemic hypotension can lead to low-flow infarction in areas situated between large vascular territories, predisposing these regions to NFD when hemodynamic stability is compromised or perfusion is insufficient.[7] Furthermore, when stenosis or hypoperfusion occurs, blood flow slows, impairing the clearance of microemboli, which can result in the retention of microemboli in the watershed regions, ultimately leading to adverse outcomes.

The present study found that the majority of patients with WI had a history of hypertension (n=164, 79.2%). Chronic and severe hypertension can damage microcirculation and endothelial cells, impair vascular remodeling in both small and large arteries, reduce lumen diameter and vasodilatory reserve, and lead to stenosis of the cerebral small arteries. When cerebral infarction occurs, the ischemic penumbra may not be effectively perfused, increasing the risk of infarct expansion. Elevated BP during the acute phase of ischemic stroke has been shown to reduce stroke severity, as demonstrated in animal studies in which mild hypertension was induced.[22,23] Cho et al[24] suggested that untreated hypertensive patients had significantly better outcomes 3 months after ischemic stroke when the stroke was athero-sclerotic or cardioembolic with large vessel occlusion or stenosis. Although the role of hypertension treatment in acute ischemic stroke remains unclear,[25] current guidelines for BP management in acute stroke are largely empirical and

conservative, recommending antihypertensive treatment only in cases of severe hypertension.[26] In particular, for patients with WI and hemodynamic impairment (such as circulatory hypotension and hypovolemia), maintaining an appropriate BP to ensure intracranial hyperperfusion is critical during the acute phase of treatment.

Our study found that higher BP, particularly when it exceeds 180/100 mmHg, is associated with an increased risk of NFD. It may be due to BP in the acute phase of stroke reflecting both local and systemic mechanisms. When the infarct is large, BP can rise reflexively, and admission SBP may indicate the extent of the lesion, which is more likely to progress with a larger infarct. Additionally, peri-lesional brain edema can elevate intracranial pressure, further increasing BP to compensate for reduced perfusion in the ischemic area, leading to excessive SBP. Autoregulation of cerebral arteries is markedly impaired when BP ≥180/100 mmHg. If SBP exceeds the vascular autoregulation range, it can cause paralytic vasodilation, resulting in ischemia-reperfusion injury and worsening edema, ultimately contributing to NFD. Furthermore, impaired cerebral autoregulation increases the risk of cardiovascular complications and secondary brain injury, both of which may contribute to the development of NFD. In our study, we observed that patients with a DBP increase of ≥4 mmHg on the third day had a lower risk of NFD, likely due to improved collateral circulation. Based on the role of elevated BP in enhancing collateral circulation, some studies advocate for BP-boosting therapies in patients with AIS and large vessel occlusion to reduce the final infarct core.[27] However, we found that in patients with a DBP increase of ≥10 mmHg on the third day, the risk of NFD was not low. This may be due to the damaging effects of larger BP fluctuations on the vessel wall, which can lead to reduced hemodynamic stability, impaired endothelial function, and the formation of atherosclerotic plaques, ultimately negatively affecting prognosis. Therefore, special attention should be given to the early BP changes in patients with acute WI in clinical practice, both to prevent irrational BP reduction that may compromise brain tissue perfusion and expand infarct volume and to avoid exacerbating cerebral edema caused by excessively high BP.

Nasi et al found that in the AIS population, patients with a SBP between 161 and 180 mmHg had the best prognosis, after accounting for other factors.[28] Hu et al demonstrated a U-shaped relationship between mean SBP and functional outcome at 3 months following AIS, with both higher and lower SBP associated with poor prognosis.[29] However, early antihypertensive therapy did not reduce the risk of dependency or death at 90 days in patients with mild to moderate AIS, who did not receive intravenous thrombolysis and had an SBP between 140 mmHg and 220 mmHg.[30] In our study, statistical analysis revealed that BP and acute phase BP fluctuations did not significantly affect functional outcome. This may be due to the relatively short 3-month follow-up period, suggesting that the impact of acute-phase BP on functional outcome may require longer observation. Additionally, BP may have a more significant association with functional outcome in patients with IWI, which is strongly influenced by hemodynamics. In contrast, our study had a higher proportion of patients with MWI, which may explain why this association was not significant in our cohort.

## Strength and Limitation

This study was conducted in a real-world clinical setting with strict inclusion criteria, a thorough analysis of the data, and a careful review of the conclusions. However, the sample size was relatively small, and the number of patients in each WI subtype was limited. Additionally, only one BP measurement was recorded for each patient. Ideally, BP should be measured twice within 5 minutes to fully adhere to the International Society of Hypertension's definition of elevated BP in acute stroke (acute hypertensive response).[31] Finally, although all patients were within 7 days of AIS onset, some were admitted within 24 hours, while others were not. The exact time of admission was not entirely consistent, and BP may have had more clinical significance in patients admitted earlier.

## Conclusion

Our study highlights the significant association between acute-phase BP and outcomes in WI. While maintaining high intracranial perfusion pressure is crucial during the acute phase, our findings suggest that BP exceeding a certain threshold at admission increases the risk of NFD. In WI patients, the risk of NFD is elevated when baseline SBP >180 mmHg or DBP > 100 mmHg. Conversely, raising DBP by ≥4 mmHg but <10 mmHg on the third day after admission, compared to the first day, appears to reduce the risk of NFD. However, our study did not find a significant association between acute-phase BP management and functional outcome.

## Abbreviations

BP, blood pressure; WI, watershed infarction; NFD, neurological function decline; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; OR, odds ratio; CI, confidence interval; CWI, cortical watershed infarction; IWI, internal watershed infarction; MWI, mixed-type watershed infarction; AIS, acute ischemic stroke.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

The SPARK study was conducted by the Declaration of Helsinki and was approved by the Institutional Review Board of Tianjin Huanhu Hospital on December 16th, 2022. The number of the approval was 2022-158. Informed consents were obtained from all participants or their legal guardians.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest in this work.

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