Early blood pressure changes during systemic thrombolysis and its association with unexplained early neurological deterioration in small subcortical infarct

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Abstract
Early neurological deterioration (END), observed in the acute phase of small subcortical infarct treated with intravenous thrombolysis (IVT), is not uncommon in these patients. However, in over half of the END cases, the exact cause is yet incompletely understood, which is so-called unexplained END (unEND). Our aim was to investigate the association of early blood pressure (BP) changes with unEND in patients with small subcortical infarct in the perforator territory of middle cerebral artery treated with IVT. Consecutive patients with acute small subcortical infarct treated with IVT were enrolled in this study. unEND was defined as ≥2-point increase of NIHSS from baseline to 24 hours, without straightforward causes. BP excursions and BP variability were calculated and compared between patients with unEND and those without. A total of 168 patients with acute small subcortical infarct were included. Of them, there were 29 patients with unEND and 139 without END. During the first 24 hours following IVT, 66 (39.29%) patients had at least one BP excursion. Logistic regression analyses indicated that BP excursion presence (OR = 3.185, 95% CI: 1.238-8.198), SBP excursion presence (OR = 3.535, 95% CI: 1.366-9.143), and number of SBP excursion (OR = 1.466, 95% CI: 1.090-1.973) were independently associated with unEND. Although SBPSD (P < .001) and SBPCV (P < .001) were higher in patients with unEND than those without END, none of the parameters of BP variability predicted unEND in multivariate analyses. BP excursions above guideline thresholds during the first 24 hours following IVT for small subcortical infarct are common and are independently associated with unEND.

KEYWORDS
blood pressure variability, early neurological deterioration, excursions, outcome, small subcortical infarct, stroke
**1 | INTRODUCTION**

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator within 4.5 hours has been proven to be an effective medical treatment available for patients with acute ischemic stroke. However, individual differences in the effects of IVT therapy are significant. It is universally acknowledged that acute small subcortical infarcts in the territory of cerebral perforating arteries have fluctuating symptoms and higher risk of experiencing early neurological deterioration (END) even though treated with IVT. Previous studies have reported that END occurs in 20-30% of perforator territory infarctions, leading to poor functional outcomes. Symptomatic intracranial hemorrhage, malignant edema, early recurrent stroke, and post-stroke seizure were all the known causes of END, while in over half of END cases, the exact cause yet incompletely understood, which is so-called unexplained END. Thus, it is of great importance to identify relevant factors of unEND and conduct targeted interventions so as to improve the overall outcome in perforator territory infarction after IVT.

Systematic BP monitoring and treatment are still the subjects of discussion in acute stroke management. Current guidelines recommend that patients who are suitable for treatment with IVT should be maintained <185/110 mmHg before thrombolysis. However, it is reported that up to 70% of patients suffer BP changes response to acute ischemic stroke. And BP changes, including BP excursions and BP variability during the first 24 hours following IVT, are all reported to be associated with increased risk of END caused by symptomatic intracerebral hemorrhage, malignant edema, early recurrent stroke, and post-stroke seizure. However, no studies to date have evaluated the effect of BP changes during the first 24 hours following IVT on unEND in perforator territory infarction with higher risk of neurological deterioration.

In view of these considerations, we aimed to investigate the relationship between early changes of BP and unEND in patients with small subcortical infarcts in the perforator territory of middle cerebral artery treated with IVT.

**2 | MATERIALS AND METHODS**

**2.1 | Patients**

We conducted a retrospective review of the prospectively collected database between January 2018 and December 2021. All acute small subcortical infarcts in the perforator territory of middle cerebral artery were treated with IVT. Inclusion criteria were (1) age older 18 years; (2) acute isolated infarction located in the middle cerebral artery perforating territory; (3) the largest diameter of lesion on axial DWI ≤20 mm; (4) IVT was performed with intravenous recombinant tissue-type plasminogen activator (dose of 0.9 mg/kg, but not > 90 mg) within 4.5 hours of symptom onset and follow-up magnetic resonance imaging performed 24 hours after IVT. Exclusion criteria were (1) receiving further endovascular therapy; (2) patients with END due to symptomatic intracranial hemorrhage, malignant edema, early recurrent ischemic stroke (had stroke recurrence at 24 hours, defined as the occurrence of new neurological symptoms suggesting the involvement of initially unaffected vascular territories and evidence of corresponding ischemic lesions on follow-up cranial CT or MR) and post-stroke seizure, et al. (3) had inadequate data on baseline. The study has been approved by the ethics committee of Second Affiliated Hospital of Xuzhou Medical University and written informed consent was obtained from each patient.

**2.2 | Demographic and clinical assessment**

Detailed clinical profile, medical history, risk factors for stroke, acute management modalities, and laboratory findings were recorded on admission. Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria. Magnetic resonance imaging examination was performed during the first 24 hours after admission. The imaging protocol included T1-weighted imaging (T1-WI), T2-weighted imaging (T2-WI), diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR), and 3D time-of-flight magnetic resonance angiography (MRA). The diagnosis of infarct on the middle cerebral artery perforating territory was made with the use of a previously published template. The size of the infarction was analyzed and represented by the largest diameter of the lesion on axial DWI.

**2.3 | Blood pressure parameters**

In the stroke unit, BP was measured in the same side depending on the patient’s conditions, including paralysis and intravenous infusion and recorded automatically into the electronic medical record by using a noninvasive BP monitoring device. BP was first recorded at the time of IVT to begin, and recorded every 15 minutes for 2 hours from the start of IVT, then every 30 minutes for 6 hours, and then at least once an hour for 16 hours. We studied the systolic BP (SBP) and diastolic BP (DBP) data obtained during the first 24 hours after admission. The BP variability was described using various parameters for each of SBP and DBP: the mean (an average of values BP), SD (BPSD), and coefficient of variation (equal to $[SD \times 100]/\text{mean}$, BP_CV). BP excursion was defined as greater than 185 SBP or greater than 110 DB. The number of BP excursions was also analyzed in this study.

**2.4 | Outcomes**

Once patients had been admitted to the stroke unit, two certified investigators who were blinded to clinical and imaging information evaluated the neurological deficits by using the National Institutes of Health Stroke Scale (NIHSS) immediately and continued over the following 24 hours one to three times a day. END was defined as an increase of at least 2 points in NIHSS score or death between baseline and day 1 of the ischemic event. Causes for END were classified...
FIGURE 1  Patients flow chart: Abbreviations: IVT, intravenous thrombolysis; MCA, middle cerebral artery; END, early neurological deterioration; unEND, unexplained END

as symptomatic intracranial hemorrhage on day 1 imaging, malignant edema, early recurrent stroke, and post-stroke seizure, et al. In all other cases with unexplained causes for END, END was considered as unEND and constituted the primary end point of our study.10,11,17

2.5 Statistical analysis

Statistical analyses were performed using SPSS software package (version 24.0). To search for predictors of unEND, we compared patients without END to those with unEND. Categorical variables were compared using the Pearson’s χ2 tests or Fisher’s exact test and expressed as frequencies and percentages. Quantitative variables were compared using the t-test or Mann-Whitney U test and expressed as means (SD) or medians (interquartile range). To express the BP variability as a categorical variable, we classified the subjects into one of four groups, representing four quartiles of BP variability and considered the first quartile as reference groups. Logistic regression model was conducted to determine the independent association between BP changes and unEND by adjusting the following variables with a P value ≤ .01 in univariate analysis. P < .05 was considered statistically significant in this study.

3 RESULT

A total of 792 patients with acute ischemic stroke treated with IVT between January 2018 and December 2021 were analyzed in this study. Of them, 186 patients with small subcortical infarcts in the perforator territory of the middle cerebral artery were included in this study, and thereinto, 47 patients (24.86%) experienced END. Among the patients with END, five patients had symptomatic intracranial hemorrhage, nine patients early recurrent stroke, and one patient post-stroke seizure at 24 hours. None of the patients had early malignant edema. Three patients had inadequate data on baseline. Finally, 29 patients with unEND and 139 patients without END were included in analysis. Figure 1 is the patient flow chart.

Of the remaining 168 patients in this study, the average age was 67.41 ± 11.17 years. Hypertension was present in 107 patients (63.69%), diabetes mellitus in 39 patients (23.21%), atrial fibrillation in 16 patients (9.52%), current smoking in 63 patients (37.5%), and drinking in patients 49 (29.17%). Twenty-three patients (13.69%) had histories of stroke or transient ischemic attack.

Comparisons of main demographic, clinical, and imaging characteristics between patients with unEND and those without are presented in Table 1. Univariate analysis suggested that the age (P < .001), baseline
TABLE 1 Baseline and treatment characteristics in patients without END versus unexplained END

| Characteristics                        | END          | P       |
|----------------------------------------|--------------|---------|
|                                        | unEND (No. = 29) | No END (No. = 139) |
| General clinical characteristics       |              |         |
| Age, y, mean (SD)                      | 74.21 ± 7.93 | 66.04 ± 11.25 | <.001 |
| Female, No. (%)                        | 14 (48.3)    | 46 (33.1) | .121  |
| Hypertension, No. (%)                  | 21 (72.4)    | 86 (61.9) | .283  |
| Diabetes mellitus, No. (%)             | 11 (37.9)    | 28 (20.1) | .039  |
| Ischemic heart disease, No. (%)        | 5 (17.2)     | 15 (10.8) | .329  |
| History of TIA-S, No. (%)              | 6 (20.7)     | 17 (12.2) | .228  |
| Atrial fibrillation, No. (%)           | 3 (10.3)     | 13 (9.4)  | .868  |
| Smoking, No. (%)                       | 9 (31.0)     | 54 (38.8) | .429  |
| Drinking, No. (%)                      | 6 (20.7)     | 43 (30.9) | .270  |
| Initial NIHSS, median (IQR)            | 8 (5.5-9)    | 5 (4-7)   | <.001 |
| TOAST classification                   |              |         |
| Large-artery atherosclerosis, No. (%)  | 10 (34.5)    | 39 (28.1) | .302  |
| Small-artery disease, No. (%)          | 12 (41.4)    | 73 (52.5) |         |
| Cardioembolism, No. (%)                | 2 (6.9)      | 11 (7.9)  |         |
| Other, No. (%)                         | 5 (17.2)     | 16 (11.5) |         |
| Onset to treatment time (min, x±s)     | 106.25 ± 57.06 | 121.87 ± 64.28 | .227  |
| Door to needle time (min, x±s)         | 31.28 ± 25.63 | 30.76 ± 15.91 | .889  |
| Hematological parameters               |              |         |
| White blood cell, (×10⁹, x±s)         | 8.36 ± 2.25  | 8.17 ± 2.82 | .192  |
| Fasting blood-glucose, (mmol/L, x±s)   | 6.77 ± 2.61  | 6.30 ± 2.58 | .378  |
| Hemoglobin, (g/L, x±s)                 | 139.53 ± 12.15 | 141.97 ± 16.84 | .459  |
| Platelets, (x10⁹, x±s)                | 216.83 ± 54.01 | 213.96 ± 26.58 | .819  |
| C-reaction protein, (mg/L, x±s)       | 21.26 ± 28.22 | 18.98 ± 27.29 | .683  |
| Total cholesterol, (mmol/L, x±s)      | 4.52 ± 0.92  | 4.54 ± 0.99 | .904  |
| Triglycerides, (mmol/L, x±s)          | 1.49 ± 0.64  | 1.70 ± 1.00 | .270  |
| High density lipoprotein, (mmol/L, x±s)| 1.19 ± 0.28  | 1.19 ± 0.30 | .952  |
| Low-density lipoprotein, (mmol/L, x±s)| 2.99 ± 0.76  | 3.03 ± 0.88 | .798  |

Abbreviations: END, early neurological deterioration; unEND, unexplained END; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; TIA-S, transient ischemic attack and stroke.

NIHSS (P < .001), diabetes mellitus (P = .039), and the prestroke modified Rankin Scale score ≥ 2 (P = .004) were significantly associated with the presence of unEND.

In this study, the number of serial BP recordings was at least 30 in this study. BP variability parameters, including SBPmean, SBPSD, SBPV, DBPmean, DBPSD, DBPV were compared between patients with unEND and those without, and results suggested that SBPSD (P < .001) and SBPV (P < .001) were higher in patients with unEND than those without END (Table 2). We further regarded the BP variability as a categorical variable and classified the participants into one of four groups, representing four quartiles of BP variability. Cutoff values of quartiles for BP variability parameters and the number of patients in each quartile are shown in Table 3. The proportion of unEND was significantly different between quartiles of SBPSD (P = .042). While no differences were found in the proportion of unEND between quartiles of SBPmean, SBPV, DBPmean, DBPSD, and DBPV using a chi-square test (Figures 2 and 3). In the multivariable logistic regression analyses, we considered the lowest quartiles as the reference group and found that patients who fell in any other quartiles had not a significantly higher risk of END after adjusting the variables (age, baseline NIHSS, diabetes mellitus, and the prestroke modified Rankin Scale score ≥ 2) (Table 4).

Overall, 66 (39.29%) patients had at least one BP excursion during the first 24 hours following IVT in this study. Univariate analysis revealed that the proportion of total BP excursions (P = .001) and SBP excursion (P<.001), the number of SBP excursions (P < .001)
TABLE 2  Relationship between early changes in blood pressure and unEND

| BP parameters        | END (No. = 29) | No END (No. = 139) | P  |
|----------------------|----------------|-------------------|----|
| Admission BP         |                |                   |    |
| Admission SBP (mmHg, \( \bar{x} \pm s \)) | 152.21 ± 23.38 | 148.54 ± 21.26    | .407|
| Admission DBP (mmHg, \( \bar{x} \pm s \)) | 85.34 ± 11.29  | 86.40 ± 9.98      | .615|
| BP variability       |                |                   |    |
| SBP\(_{\text{mean}}\) | 144.43 ± 8.82  | 141.71 ± 10.66    | .200|
| SBP\(_{SD}\)         | 18.11 ± 5.53   | 13.43 ± 3.70      | <.001|
| SBP\(_{CV}\)         | 12.51 ± 3.59   | 9.49 ± 2.56       | <.001|
| DBP\(_{\text{mean}}\) | 80.80 ± 4.32   | 81.71 ± 4.17      | .292|
| DBP\(_{SD}\)         | 7.62 ± 2.17    | 6.98 ± 1.79       | .094|
| DBP\(_{CV}\)         | 9.45 ± 2.72    | 8.59 ± 2.36       | .084|
| BP excursions        |                |                   |    |
| Total BP excursions  | 19 (65.5)      | 47 (33.8)         | .001|
| SBP excursion presence | 19 (65.5)      | 42 (30.2)         | <.001|
| DBP excursion presence | 9 (31.0)       | 30 (21.6)         | .273|
| Number of SBP excursions | 1 (0.35)      | 0 (0, 1)          | <.001|
| Number of DBP excursions | 0 (0, 1)      | 0 (0, 0)          | .196|

Abbreviations: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation.

TABLE 3  Cutoff values of BP variability and number of patients in each quartile group

| Cutoff values (mmHg) | Number of each quartile group |
|----------------------|-----------------------------|
|                      | Q1  | Q2  | Q3  | Q4  |
| 25th Percentile     |     |     |     |     |
| SBP\(_{\text{mean}}\) | 137.76 | 143.28 | 148.92 | 41  | 42  | 44  | 41  |
| SBP\(_{SD}\)         | 11.12 | 13.39 | 16.89 | 42  | 43  | 41  | 42  |
| SBP\(_{CV}\)         | 7.79  | 9.53  | 11.78 | 41  | 43  | 42  | 42  |
| DBP\(_{\text{mean}}\) | 79.91 | 81.98 | 84.04 | 42  | 42  | 42  | 42  |
| DBP\(_{SD}\)         | 5.68  | 6.97  | 8.19  | 42  | 43  | 41  | 42  |
| DBP\(_{CV}\)         | 6.69  | 8.30  | 10.24 | 43  | 42  | 41  | 42  |

Abbreviations: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation; Q1, the first quartile; Q2, the second quartile; Q3, the third quartile; Q4, the fourth quartile.

was higher in patients with unEND than those without END. Logistic regression analyses indicated that BP excursion presence (OR = 3.185, 95% CI: 1.238-8.198), SBP excursion presence (OR = 3.535, 95% CI: 1.366-9.143), and number of SBP excursion (OR = 1.466, 95% CI: 1.090-1.973) were independently associated with unEND after adjust for the variables (age, diabetes mellitus, baseline NIHSS, and the prestroke modified Rankin Scale score ≥ 2) with P values < .01 in univariate analyses (Table 5).

4 | DISCUSSION

Our study suggested that BP excursions above guideline thresholds during the first 24 hours following IVT are common and independently associated with unEND for acute small subcortical infarcts in the per-
FIGURE 2  Proportions of patients developing unexplained early neurological deterioration (unEND) according to SBP parameters. Abbreviations: SBP, systolic blood pressure; SD, standard deviation; CV, coefficient of variation; unEND, unexplained early neurological deterioration; Q1: the first quartile; Q2: the second quartile; Q3: the third quartile; Q4: the fourth quartile

Tisserand and associates carried out an exploratory study and found that 90% (9/10) unEND was caused due to the initial DWI lesion growth beyond the baseline penumbral area on 24-hour follow-up magnetic resonance imaging. Consistently, Min Lou and associates also found that the volume of infarct growth at 24 hours beyond baseline penumbral area (extra-infarct) was independently related to unEND. Besides, “Reperfusion injury,” defined as “a biochemical cascade causing a deterioration of ischemic brain tissue that parallels

TABLE 4  Multivariable analysis of the associations between BP fluctuation and the development of unEND

| SBP parameters | Unadjusted Model OR (95% CI) | Adjusted Model* OR (95% CI) | DBP parameters | Unadjusted Model OR (95% CI) | Adjusted Model* OR (95% CI) |
|----------------|-----------------------------|-----------------------------|----------------|-----------------------------|-----------------------------|
| SBPmean        |                             |                             | DBPmean        |                             |                             |
| Q1             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q1             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| Q2             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q2             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| Q3             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q3             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| Q4             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q4             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| SBPsd          |                             |                             | DBPsd          |                             |                             |
| Q1             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q1             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| Q2             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q2             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| Q3             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q3             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| Q4             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q4             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| SBPCV          |                             |                             | DBPCV          |                             |                             |
| Q1             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q1             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| Q2             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q2             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| Q3             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q3             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |
| Q4             | 1.000 (0.317-3.151)         | 1.000 (0.381-4.980)         | Q4             | 1.000 (0.388-5.065)         | 1.000 (0.737-5.147)         |

Abbreviations: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation; Q1, the first quartile; Q2, the second quartile; Q3, the third quartile; Q4, the fourth quartile; OR, odds ratios; CI, confidence interval.

*Adjusted variables were age, diabetes mellitus, baseline NIHSS, and the prestroke modified Rankin Scale score ≥ 2.
and antagonizes the beneficial effect of recanalization, and "collateral failure," defined as "insufficient endurance" of collateral circulation to maintain cerebral perfusion pressure, have been proposed as another two possible mechanisms of unEND. In brief, pathophysiology of unEND is yet incompletely understood and need to be further studied.

Because of the unclear pathophysiology of unEND, identifying early predictors of unEND is of considerable importance. In addition, these clinical predictors could help to screen patients who need more strict surveillance and to carry out, as early as possible, measures to prevent or halt deterioration, if available. Autonomic dysfunction in acute ischemic stroke has been extensively investigated. During the acute phase of ischemic stroke, the human brain has a decreased ability to auto regulate. BP is generally very dynamic and experiences important changes. Therefore, cerebral blood flow becomes passively dependent on the systemic arterial pressure and is more likely to be affected. Even minor fluctuations in BP may lead to important changes in cerebral perfusion via collaterals, such as under- or over-perfusion of the delicate ischemic neurons, which might lead to edema, hemorrhagic transformation, and infarct extension. Recently, blood pressure was a well-explored subject during the acute stage in cerebral hemorrhage. However, some other studies suggested that the parameters of BP variability were significantly related to clinical outcomes in both ischemic and hemorrhagic stroke. Of which, a recent study indicated that higher BP variability in the first 24 hours of admission was associated with unfavorable in-hospital outcome among intracerebral hemorrhage patients. The main strengths of the study were the use of a novel BP variability index called functional successive variation and assessing BP variability as a continuous covariate rather than applying a threshold or discretizing by tertiles, quartiles, or quintiles. All in all, further prospective studies with large samples are warranted to illustrate the association between BP variability and functional outcome among patients.

Given the absence of collateral vessels in the perforator territory of middle cerebral artery, acute ischemic stroke in this area was more sensitive to fluctuating hemodynamics and therefore more susceptible to clinical and biochemical factors associated with hemodynamics, such as blood pressure and emotional fluctuation. According to the results of this study, clinician should be concerned more about the impact of elevated BP levels after IVT in acute small subcortical infarcts as a risk factor for unEND.

Several caveats of this study should be noted. First, while the data was prospective collected, the present study was a single-hospital-based study and was limited by the small sample size. The findings needed to be further confirmed in multicenter prospective studies with large samples. Second, there was no data on successful recanalization during the first 24 hours after IVT are available, a parameter which can strongly affect the outcomes described. Finally, we cannot fully exclude the possibility that elevated BP levels may have been the result of unEND, rather than the cause of unEND, because a deteriorating or fluctuating clinical course may lead to BP changes. More prospective trials are needed to obtain more reliable results.

In conclusion, our study found that BP excursions above guide-line thresholds during the first 24 hours following intravenous thrombolysis treatment for acute small subcortical infarcts are common and independently associated with unEND. But none of the parameters of BP variability predicted unEND in multivariate analyses.

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CONFLICTS OF INTEREST
All the authors listed have approved the submitted manuscript and we declare that we have no conflict of interest.

AUTHOR CONTRIBUTIONS
Xiu’e Wei and Zuowei Duan wrote the first draft of the manuscript and provided statistical analysis. Yujia Zhai, Cuicui Zhang, and Jun Zhang were involved in data collection and literature review searches. Ting Hu, Tengfei Liu, Zhenqian Liu, and Jianguo Xie provided intellectual input in the area of data collection and analyses. Haiyan Liu and Liangqun Rong wrote the protocol and designed the study. All authors contributed and approved the final manuscript. All the authors listed have approved the submitted manuscript.

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