RESEARCH ARTICLE

Blood pressure variability estimated by ARV is a predictor of poor short-term outcomes in a prospective cohort of minor ischemic stroke

Zefeng Tan, Heng Meng, Dawei Dong, Ying Zhao, Anding Xu*

Department of Neurology, the First Affiliated Hospital, Jinan University, Guangzhou, Guangdong, China

* tlil@jnu.edu.cn

Abstract

Prior studies have shown that patients with minor ischemic stroke have substantial disability rates at hospital discharge. We sought to determine whether blood pressure variability (BPV) estimated by average real variability (ARV) is one of the predictors of poor outcome at 90 days. Four hundred fifty-one consecutive patients with ischemic stroke treated within 7 days after onset were enrolled prospectively. Baseline magnetic resonance imaging (MRI) was performed on all subjects. Blood pressure was measured for all recruited patients every 2 hours in the first 24 hours after admission, followed by measurements collected every 4 hours from day 2 to day 7 after admission. ARV was used to estimate BPV. A total of 192 patients with minor ischemic stroke were enrolled, and 11 of them (5.7%) had poor outcomes. Univariate regression analysis showed that early neurological deterioration ($X^2 = 21.44$, P = 0.000), severe symptomatic large artery stenosis or occlusion ($X^2 = 9.260$, P = 0.000), large artery atherosclerotic stroke ($X^2 = 7.14$, P = 0.002), total cholesterol (TC), and D2-7 SBP-ARV (t = 5.449, P = 0.001) of the poor outcome group were significantly higher than those of the good outcome group. Multivariate logistic regression analysis showed that early neurological deterioration (OR 4.369, 95% CI 3.54, 15.65; P = 0.001), severe symptomatic large artery stenosis or occlusion (OR 5.56, 95% CI 3.56, 13.65; P = 0.000), large artery atherosclerotic stroke (OR 3.56, 95% CI 1.45, 7.48; P = 0.004), and D2-7 SBP-ARV (OR 3.96, 95% CI 1.90, 20.18, P = 0.008) were significantly related to poor outcomes. In conclusion, approximately 5.7% of minor ischemic stroke patients had poor outcomes. D2-7 SBP-ARV, early neurologic deterioration, severe symptomatic artery stenosis or occlusion, and large atherosclerotic stroke were the independent risk factors of poor short-term outcomes.

Introduction

Minor ischemic stroke by definition represents the strokes that only cause minor symptoms or only result in minor neurologic defects, although the definition varies [1]. In real clinical practice, we have found that so-called minor ischemic strokes may be misidentified as such due to minor symptoms. Some clinical studies have recognized that ischemic stroke patients with fast

recovery or minor symptoms eventually developed morbidity and mortality [2–4]. Most recent studies of minor stroke have shown that 15% of minor stroke patients (National Institutes of Health Stroke Scale (NIHSS) of 0–3 within 72 hours) had a poor clinical prognosis [5].

Recent studies [6–9] have shown that BPV is one of the main predictors of any prognosis. However, the predictive value of BPV during the acute phase of minor ischemic stroke is uncertain. A recent systematic review of seven studies on the effect of BPV on functional outcome (death or disability) suggested that systolic BPV was significantly associated with a poor functional outcome (pooled odds ratio per 10-mm Hg increment, 1.2; 95% CI (1.1–1.3)) [10]. However, the review recommended future prospective studies to investigate best practices to measure and define BPV in acute stroke as well as to determine its prognostic significance [10]. Various indexes, such as standard deviation (SD), coefficient of variation (CV), the SD over 24 hours weighted for the time interval between consecutive readings (SD24), the average of the daytime and nighttime SDs weighted for the duration of the daytime and nighttime intervals (SDdn), variation independent of the mean (VIM), weighted standard deviation (wSD), and ARV, have been used to evaluate BPV by different researchers, but uncertainty remains about which index should be used to gauge the value of BPV as a risk factor.

The aim of this prospective study was to assess the predictive value of BPV estimated by ARV and the short-term functional outcome in acute minor ischemic stroke patients.

Materials and methods

We prospectively evaluated consecutive patients with acute ischemic stroke. The study was approved by the ethics committee of the Jinan University. All participants and/or caregivers gave their informed written consent according to the Declaration of Helsinki. All the patients were admitted to the neurological intensive care unit (NICU) in the first 24 hours after admission. After 24 hours observation in the NICU, patients were transferred out of the NICU according to the decisions of clinical doctors. Cerebral computerized tomography (CT) or MRI and magnetic resonance angiography (MRA) were performed and described routinely within 24 hours after admission. Minor ischemic stroke was defined as an NIHSS score < 4.

Inclusion criteria: Patients were chosen if (1) their cases conformed to the diagnostic criteria of the 2005 China cerebrovascular disease prevention and treatment guidelines for ischemic stroke; (2) the time of stroke onset was not more than 7 days prior to inclusion; and (3) their NIHSS score at admission was less than 4.

Exclusion criteria: Patients were excluded if they (1) were below 18 years of age; (2) had inadequate BP measurements; (3) had other serious or life-threatening diseases before stroke onset; (3) received thrombolytic therapy; or (4) had a previous stroke (modified Rankin Scale score, MRS >2). The research protocol was approved by the medical ethical committee of the First Affiliated Hospital, Jinan University for clinical research, and all the data were analyzed anonymously.

Measurement of blood pressure

The casual supine blood pressure (BP) was measured in the non-paralyzed arm using a standard electronic sphygmomanometer (OMROM-HEM-7200) upon admission. In the neurological intensive care unit (NICU), BP was measured at 2-hour intervals during the first 24 hours by using a noninvasive BP monitoring device (BeneView T5) and then every 4 hours, up until 7 days after admission, by using a standard electronic sphygmomanometer (OMROM-HEM-7200) by a trained nurse, with 1-hour error in the daytime and 2-hour error in the nighttime. All BP records were entered manually into the electronic medical record (EMR) system. The BP profiles during the first 24 hours and days 2–7 (D2-7) were described using the

following parameters for both systolic blood pressure (SBP) and diastolic blood pressure (DBP): standard deviation (SD) and coefficient of variation (CV). In addition, we used average real variability (ARV) [11] to represent BPV. The ARV averages the absolute differences of consecutive measurements and accounts for the order in which the blood pressure measurements are obtained. ARV was calculated by the following formula:

$$ARV = \frac{1}{N-1} \sum\nolimits_{k=1}^{n-1} \times |BP_{K+1} - BP_K|,$$

where k ranges from 1 to n-1, and n is the number of blood pressure readings.

Stroke risk factors

Patients with a clinical diagnosis of acute stroke were recruited from admissions to the First Affiliated Hospital of Jinan University. Each subject was assessed and examined according to the Oxfordshire Community Stroke Project (OCSP) classification [12]. Data of functional outcomes at 90 days and initial NIHSS scores were collected along with other relative stroke risk factors, including age, gender, history of hypertension (BP ≥ 140/90 mm Hg according to the World Health Organization-International Society of Hypertension guidelines[13] or presently under treatment with antihypertensive drugs) history of diabetes mellitus (fasting plasma glucose level ≥ 7.0 mmol/l, plasma glucose ≥ 11.1 mmol/l two hours after a 75 g oral glucose load as in a glucose tolerance test, symptoms of hyperglycemia and casual plasma glucose ≥ 11.1 mmol/l, glycated hemoglobin (Hb A1C) ≥ 6.5%[14,15], or under hypoglycemic treatment), history of hyperlipidemia (total cholesterol concentration > 6.22 mmol/L (240 mg/dL), triglycerides>2.26 mmol/L, HDL-cholesterol< 1.14 mmol/ the day after admission or already under lipid lowering therapy for hyperlipidemia), history of symptomatic ischemic heart disease (proven myocardial infarction, history of angina, existence of multiple lesions on thallium heart isotope screen or evidence of coronary disease on coronary angiography), atrial fibrillation (documented during hospitalization or history of atrial fibrillation), current cigarette smoking, alcohol abuse (>50 g per week) and previous stroke. In all subjects, the diagnosis of severe symptomatic intracranial artery stenosis or occlusion was confirmed by MRI angiography (MRA). MRA was performed using a standard protocol of three-dimensional time-of-flight sequences. Symptomatic large artery stenosis was defined as a reduction in luminal diameter of at least 50% in the intracranial arteries and the extracranial carotid artery using the methods described by the Warfarin-Aspirin for Symptomatic Intracranial Disease Study [16] and the North American Symptomatic Carotid Endarterectomy Trial method [17], respectively. The extracranial vertebral artery was not included in the data analysis since MRA cannot be used to clearly differentiate a normal variant of congenital hypoplasia from an acquired stenosis.

Assessment of outcome

The neurological severity on admission and at 7 days (or at discharge if earlier) was assessed by the NIHSS score by trained stroke neurologists. Early neurological deterioration was defined as an increase of ≥ 3 scores in the NIHSS Scale during the first 7 days after admission. Functional outcome was assessed by the mRS score at 90±7 days after the treatment and was dichotomized into good outcome (mRS 0 to 1) or poor outcome (mRS 2 to 6, death was graded 6). On admission (1st day) and on the 90th day, modified ranking scale was evaluated.

Statistical analysis

All analyses were performed using SPSS for Windows, release 19.0 (SPSS Inc., Chicago, IL, USA), and a P value of <0.05 was considered as statistically significant. Quantitative variables were summarized as the mean±SD, categorical variables as frequency distribution. The values are presented as the mean±SD, median (interquartile range [IQR] for continuous variable, or as the number (%) of subjects for categorical variables. Comparisons of baseline characteristics and BPV parameters between patients of good outcome and poor outcome were conducted with Pearson χ^2 test, Mann–Whitney U test, or Student t test as described. We analyzed the association between the clinical outcomes and relevant covariates with logistic regression analysis adjusting age, gender, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease, previous stroke, current or previous smoking, moderate or heavy alcohol, dual antiplatelet and statin therapy after admission, severe symptomatic artery stenosis, NIHSS at admission and relative blood pressure variables include SD, CV, and ARV of first 24 hours and D2-7. For ARV analysis, patients were divided into low ($\leq$ median) and high ($>$median) groups using the median value of systolic and diastolic ARV during the first 24 hours and over the subsequent 2–7 days. The patient proportion with the poor outcome was calculated, and its correlation with ARV was assessed using a Pearson χ^2 test. All parameters with statistical significance ($p<0.05$) in the univariate analysis were introduced into a multivariate logistic regression model to explore predictors for poor outcome. Due to the possible collinearity of tested variables, a stepwise logistic regression model was used.

Results

Of 451 patients (seen in Tables A-F in S1 File), 208 presented with minor strokes. The 90-day outcome analysis was limited to 192 patients after excluding those with missing blood pressure data (n = 13) or recombinant tissue-type plasminogen activator treatment (n = 3). The final analysis included 192 patients. Their age ranged from 33–93, and 24.2% of them were female. The median score of baseline NIHSS was 1 (1–3). At 90 days, 181 patients (94.3%) had good outcomes, and 11 patients (5.7%) had poor outcomes. In total, 18 cases of early neurological deterioration were found (12 and 6 patients in the good outcome and poor outcome group, respectively). Fifty-four cases (28%) were found to have severe symptomatic artery stenosis. Each enrolled patient was monitored for at least 46 time points (10 times in the first 24 hours and 36 times in the next 7 days). The systolic blood pressure in participants in both the good outcome and poor outcome groups fell from days 1 to 7, with the steepest decrease in the first 1 to 6 hours after enrollment (Fig 1). However, we detected no significant differences between the systolic blood pressure and the clinical outcome in either group. Comparisons of baseline characteristics between the two groups are reported in Table 1. Poor outcome results were significantly associated with higher D2-7 SBP-ARV (p = 0.001), early neurological deterioration (6.6% vs 54.5%; p = 0.00), higher TC (3.76±1.45 vs 5.04±1.36; p = 0.004), large artery atherosclerotic stroke (29.2% vs 72.7%; p = 0.002), and severe symptomatic artery stenosis or occlusion (25.4% vs 72.7%; p = 0.000). For the univariate analysis of systolic or diastolic ARV, patients were divided into groups with low and high ARV. A significant association was demonstrated between high D2-7 SBP-ARV and poor outcome (P = 0.005) (Table 2). After adjusting for the known baseline predictors, D2-7 SBP-ARV, symptomatic artery stenosis, major atherosclerosis, and early neurology deterioration were associated with good outcomes at day 90 (Table 3).

Discussion

One of the advantages of this study is that it focuses on the influence of read-to-read BPV rather than visit-to-visit BPV. Previous studies have already reported that the assessment of
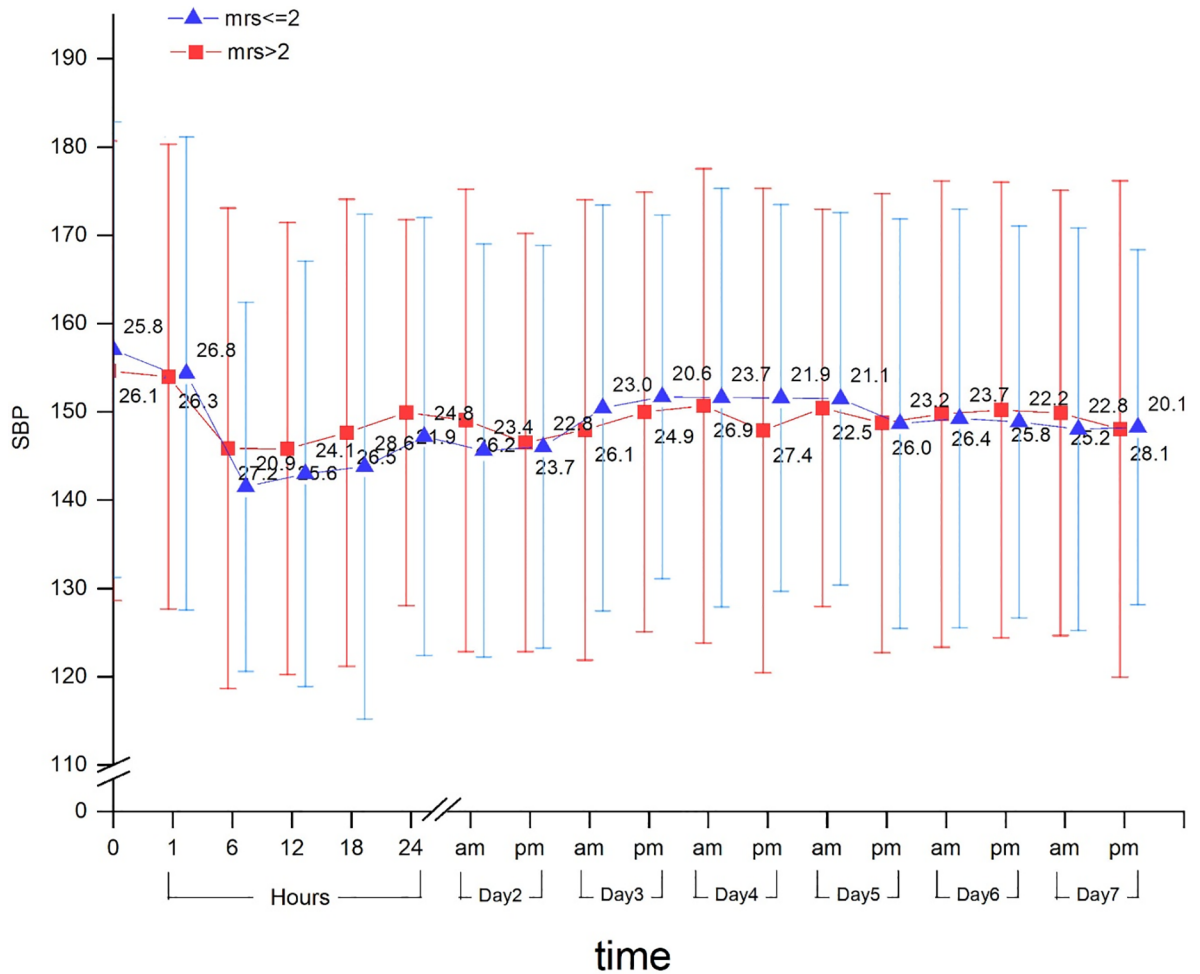
Fig 1. Within-group mean systolic blood pressure and standard deviation of systolic blood pressure over time. Note, the axes are broken.

https://doi.org/10.1371/journal.pone.0202317.g001

visit-to-visit BPV is a reliable predictor of stroke recurrence [18,19] and of the extent of target organ damage [11,20–23]. Meanwhile, the effect of read-to-read BP variability during the acute phase of stroke has been investigated in a limited number of studies [24–26]. This study is one of the few studies that shows an association between short-term SBP-ARV and clinical functional outcomes. In our study, D2-7 SBP-ARV (OR 3.96, 95% CI 1.90–20.18, P = 0.008) significantly associated with the 3-month functional outcome even when analyzed independently from DBP ARV. While a direct relationship between sub-acute phase BPV and outcome in a large population of stroke patients has been described [6], we still lack evidence from large scale prospective studies.

Second, the relationship between short-term BPV and acute minor ischemic stroke is unclear. Previous large scale retrospective studies mainly focused on cohorts of hypertension or secondary stroke prevention, not minor ischemic stroke patients, and BPV was determined to be a strong predictor of future stroke events [6,7,11,19,27–30]. Other research has also shown that acute phase BPV after stroke was significantly related to the stroke in progression [31–34]. The progression of stroke directly caused poor short-term outcomes. A registry study [34] found that higher post-stroke BP levels (the average values during the 48 hours after onset) were significantly associated with a lower probability of good neurological recovery,

Table 1. Comparisons of baseline characteristics according to a 3-month functional outcome based on mRS score.

Characteristics	Good outcome	Poor outcome	P
Age, year ± SD	67.3± 9.8	69.9± 8.2	0.205
Female, n (%)	47 (25.9)	4 (36.4)	0.448
Baseline pressure (mmHg, $\bar{x} \pm s$)			
SBP(mmHg)	156.2±25.8	155.42±27.51	0.873
DBP(mmHg)	88.24±15.74	88.52±24.26	0.931
Entry NIHSS (median)	2	2	0.222
Early neurological deterioration, n (%)	12 (6.6)	6 (54.5)	0.00
Smoking, n (%)	85 (47.0)	6 (54.5)	0.624
Alcohol, n (%)	11 (6.0)	1 (9.1)	0.688
History of stroke, n (%)	10 (5.5)	2 (18.1)	0.092
Coronary heart disease, n (%)	22 (12.1)	3 (27.2)	0.148
TC	3.76±1.45	5.04±1.36	0.004
Atrial fibrillation, n (%)	27 (14.9)	2 (18.1)	0.769
Diabetic mellitus, n (%)	48 (26.5)	3 (27.3)	0.956
Hypertension, n (%)	105 (58.0)	8 (72.7)	0.336
Large artery atherosclerotic stroke, n (%)	53 (29.2)	8 (72.7)	0.002
Small vessel disease, n (%)	89 (49.1)	3 (27.2)	0.158
Embolism, n (%)	10 (5.5)	1 (9.1)	0.360
Unclassified, n (%)	20 (11)	1 (9.1)	0.839
Dual antiplatelet, n (%)	126 (69.6)	10 (90.9)	0.131
Statin therapy, n (%)	180 (99.4)	8 (72.7)	1.697
Severe symptomatic artery stenosis or occlusion, n (%)	46 (25.4)	8 (72.7)	0.000
24-h SBP-SD (mmHg, $\bar{x} \pm s$)	13.27±5.27	12.93±5.49	0.669
24-h SBP-CV	0.09±0.04	0.09±0.04	0.772
24-h SBP-ARV (mmHg, $\bar{x} \pm s$)	9.53±2.13	11.02±5.73	0.051
24-h DBP-SD (mmHg, $\bar{x} \pm s$)	10.88±5.14	11.69±5.49	0.3
24-h DBP-CV	0.17±0.07	0.2±0.09	0.14
24-h DBP-ARV (mmHg, $\bar{x} \pm s$)	7.43±3.44	9.85±3.78	0.454
D_{2-7} SBP-SD (mmHg, $\bar{x} \pm s$)	14.22±4.28	14.62±3.93	0.535
D_{2-7} SBP-CV	0.1±0.03	0.1±0.02	0.457
D_{2-7} SBP-ARV (mmHg, $\bar{x} \pm s$)	11.98±3.73	16.21±3.67	0.001
D_{2-7} DBP-SD (mmHg, $\bar{x} \pm s$)	9.17±2.86	9.46±2.71	0.497
D_{2-7} DBP-CV	0.11±0.03	0.12±0.03	0.598
D_{2-7}DBP-ARV (mmHg, $\bar{x} \pm s$)	6.56±3.14	8.34±5.60	0.256

https://doi.org/10.1371/journal.pone.0202317.t001

elevated risk of neurological deterioration and poor functional outcome. The Glycine Antagonist in Neuroprotection International Trial (GAIN) [32] retrospectively analyzed data in 1445 cases of ischemic stroke patients and showed that variables describing the course of BP over the first 2.5 days have a marked and independent relationship with 1- and 3-month outcomes.

There can only be speculation about the mechanisms underlying this finding. The high BPV may be associated with large vessel atherosclerosis or decreased baroreflex sensitivity in carotid bifurcation [35]. In normal conditions, systolic and diastolic blood pressures change in parallel while responding to physiological stimuli, such as exercise or arousal. In subjects with stiff arteries, when systolic blood pressure increases, often diastolic blood pressure increases less or even falls [36,37], giving rise to larger variability. On the other hand, during the acute phase of stroke, cerebral auto-regulation is impaired and blood flow becomes completely dependent on systemic BP. For this reason, fluctuations in BP may be detrimental for ischemic

Table 2. Univariate analysis of patients with high and low systolic and diastolic ARV between good and poor outcomes groups.

	Good outcomes (n = 181)	Poor outcomes (n = 11)	P
24-h SBP-ARV			0.756
Low (≤11.0)	90 (49.7)	6 (54.3)	
High (>11.0)	91 (50.3)	5 (45.7)	
24-h DBP-ARV			0.097
Low (≤7.8)	96 (52.8)	3 (27.2)	
High (>7.8)	85 (47.2)	8 (72.8)	
D_{2-7} SBP-ARV			0.046
Low (≤11.8)	105 (58.0)	3 (27.2)	
High (>11.8)	76 (42.0)	8 (72.8)	
D_{2-7} DBP-ARV			0.222
Low (≥7.8)	100 (50.8)	4 (36.4)	
High (>7.8)	81 (49.2)	7 (63.6)	

https://doi.org/10.1371/journal.pone.0202317.t002

territories, particularly in the presence of an anatomic or functional compromise of small cerebral vessels [24,38].

As measures of short-term reading-to-reading blood pressure variability, we used the SD, CV and ARV. Various parameters can capture short-term blood pressure variability over 24 hours, but most studies only considered the SD of systolic, diastolic, or both blood pressures. [39–41] Currently, no specific parameter has been selected as the optimum choice to estimate short term BPV in acute stroke. The variability is commonly quantified as SD. This variability index has a notorious shortcoming: it only reflects the dispersion of BP measurements around a single value (the mean) not accounting for the order in which the BP measurements were obtained. SD and CV ignore the order of blood pressure data; as a result, two subjects with different BP measurement sets may have the same SD or CV. An explanation for apparently contradictory results in previous studies may be the selection of the index [standard deviation (SD)] used for quantifying variability[42–43]. ARV was a better predictor than SD24 and SDdn, probably because subjects with different blood pressure profiles might have similar SDs but a different ARV. Thus, ARV might be a more specific measure of blood pressure variability than SD[44]. A proper selection of the variability index is critical to assessing the value of BPV as a risk factor and could explain apparently contradictory results previously reported; a time series variability index such as ARV should be used.[45] ARV, which essentially averages the absolute differences of consecutive measurements, is sensitive to the individual BP measurement order, contrary to the SD. ARV index is a more reliable representation of time

Table 3. Final stepwise logistic regression model to predict poor outcomes.

Variable	P	Adjusted OR (95% CI)
D_{2-7} SBP-ARV	0.008	3.96 (1.90, 20.18)
Symptomatic artery stenosis	0.000	5.56 (3.56,13.65)
Major atherosclerosis	0.004	3.56 (1.45,7.48)
Early neurology deterioration	0.001	4.369 (3.54,15.65)

SBP, systolic blood pressure; ARV, average real variability (Final stepwise logistic regression model to predict poor outcome at 90 days, included variables: D2-7 SBP-ARV, Symptomatic artery stenosis, Major atherosclerosis, Early neurology deterioration and TC).

https://doi.org/10.1371/journal.pone.0202317.t003

series variability than SD and is even more sensitive to the relative high sampling frequency of blood pressure monitoring as in this study[45].

In addition, 208 of 451 patients (46.1%) presented with minor ischemic stroke (NIHSS<4) in this cohort of ischemic stroke. This result is similar to the rate in the Chinese national stroke registry research (30%) [46]. At day 90, 5.7% of them had a poor outcome, which is significantly lower than reported data in China [47]. The possible explanation is that in clinical practice of our center, up to 70% of minor ischemic stroke patients receive dual antiplatelet therapy. The CHANCE (Clopidogrel and Aspirin versus Aspirin Alone for the Treatment of High-risk Patients with Acute Non-disabling Cerebrovascular Event) [48]study has shown that the addition of clopidogrel to aspirin reduced the relative risk of recurrent stroke at 90 days by 32% in Chinese patients with acute minor ischemic stroke or TIA. Furthermore, almost 99% of patients in this study had been prescribed statin therapy. Additionally, compared with data from other stroke registries, we found a trend of a gradual decrease of poor outcomes over time (The Harvard Cooperative Stroke Registry (1978) 20%[49], Lausanne Stroke Registry (1988) 34%[50], the China National Stroke Registry (2008) 14.5%[47], and the Austrian Stroke Unit Registry (2010) 4.5%[51]). The recognition and application of recent guidelines have remarkably improved the outcomes of patients.

There are also some limitations in this study. First, the baseline NIHSS scores were acquired within 7 days of stroke, which is longer than in other studies. For this reason, our cohort may represent a more stable minor ischemic stroke group. Moreover, there was no specific analysis of the different items of the NIHSS score. Furthermore, this is a small sample study conducted in a single-center, and our findings carry a risk of causality error.

Conclusion

This study is one of the few prospective studies that uses ARV as a predictor to determine functional outcomes. Future large scale prospective studies on the relationship between ARV and minor ischemic strokes are warranted.

Supporting information

S1 File. Supporting tables. Table A. Frequency data of 474 cases of ischemic stroke patients Table B. Data of age, NIHSS (24hours after admission) and biomarkers. Table C. Data of time from onset to admission. Table D. Data of first Blood pressure after admission. Table E. Data of Blood pressure variability (24hours after admission). Table F. Data of Blood pressure variability (D2 to D7 after admission).
(DOCX)

Acknowledgments

Author Contributions

Conceptualization: Zefeng Tan, Ying Zhao, Anding Xu.

Data curation: Heng Meng, Dawei Dong, Ying Zhao, Anding Xu.

Formal analysis: Zefeng Tan, Anding Xu.

Funding acquisition: Zefeng Tan, Heng Meng, Anding Xu.

Investigation: Zefeng Tan, Heng Meng, Dawei Dong, Ying Zhao, Anding Xu.

Methodology: Zefeng Tan, Ying Zhao, Anding Xu.

Project administration: Anding Xu.

Resources: Dawei Dong, Ying Zhao, Anding Xu.

Software: Dawei Dong, Ying Zhao.

Supervision: Zefeng Tan, Anding Xu.

Validation: Zefeng Tan, Anding Xu.

Visualization: Zefeng Tan, Anding Xu.

Writing – original draft: Zefeng Tan.

Writing – review & editing: Zefeng Tan, Heng Meng, Anding Xu.

References

1. Fischer U, Baumgartner A, Arnold M, Nedeltchev K, Gralla J, De Marchis GM, et al. (2010) What is a minor stroke. Stroke 41: 661–666. https://doi.org/10.1161/STROKEAHA.109.572883 PMID: 20185781

2. Smith EE, Abdullah AR, Petkovska I, Rosenthal E, Koroshetz WJ, Schwamm LH (2005) Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. Stroke 36: 2497–2499. https://doi.org/10.1161/01.STR.0000185798.78817.f3 PMID: 16210552

3. Fink JN, Selim MH, Kumar S, Schlaug G (2001) Why are stroke patients excluded from tPA therapy? An analysis of patient eligibility. Neurology 57: 1739–1740. PMID: 11706134

4. Smith EE, Fonarow GC, Reeves MJ, Cox M, Olson DM, Hernandez AF, et al. (2011) Outcomes in mild or rapidly improving stroke not treated with intravenous recombinant tissue-type plasminogen activator: findings from Get With The Guidelines-Stroke. Stroke 42: 3110–3115. https://doi.org/10.1161/STROKEAHA.111.613208 PMID: 21903949

5. Sato S, Uehara T, Ohara T, Suzuki R, Toyoda K, Minematsu K (2014) Factors associated with unfavorable outcome in minor ischemic stroke. Neurology 83: 174–181. https://doi.org/10.1212/WNL.0000000000000572 PMID: 24907232

6. Kang J, Ko Y, Park JH, Kim WJ, Jang MS, Yang MH, et al. (2012) Effect of blood pressure on 3-month functional outcome in the subacute stage of ischemic stroke. Neurology 79: 2018–2024. https://doi.org/10.1212/WNL.0b013e3182749eb8 PMID: 23054228

7. Yong M, Diener HC, Kaste M, Mau J (2005) Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. Stroke 36: 2619–2625. https://doi.org/10.1161/01.STR.0000189998.74892.24 PMID: 16254220

8. Yong M, Kaste M (2008) Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. Stroke 39: 366–372. https://doi.org/10.1161/STROKEAHA.107.492330 PMID: 18096843

9. Endo K, Kario K, Koga M, Nakagawara J, Shiokawa Y, Yamagami H, et al. (2013) Impact of early blood pressure variability on stroke outcomes after thrombolysis: the SAMURAI rt-PA Registry. Stroke 44: 816–818. https://doi.org/10.1161/STROKEAHA.112.681007 PMID: 23329210

10. Manning LS, Rothwell PM, Potter JF, Robinson TG (2015) Prognostic Significance of Short-Term Blood Pressure Variability in Acute Stroke: Systematic Review. Stroke 46: 2482–2490. https://doi.org/10.1161/STROKEAHA.115.010075 PMID: 26243226.

11. Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T (2005) A reliable index for the prognostic significance of blood pressure variability. J Hypertens 23: 505–511. PMID: 15716690

12. Bamford JM, Sandercock PAG, Dennis MS, Burn J, Wardlow CP. Classification and natural history of clinically identifiable subtypes of clinical infarction. Lancet. 1991; 337:1521–1526. PMID: 1675378

13. (1999) 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens 17: 151–183. PMID: 10067786

14. (2011) Standards of medical care in diabetes—2011. Diabetes Care 34 Suppl 1: S11–61. https://doi.org/10.2337/dc11-S011 PMID: 21193625

15. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15: 539–553. https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S PMID: 9686693

16. Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. AJNR Am J Neuroradiol 2000; 21:643–646. PMID: 10782772

17. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991; 325:445–453. https://doi.org/10.1056/NEJM199108153250701 PMID: 1852179

18. Rothwell PM (2010) Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet 375: 938–948. https://doi.org/10.1016/S0140-6736(10)60309-1 PMID: 20226991

19. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al. (2010) Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 375: 895–905. https://doi.org/10.1016/S0140-6736(10)60308-X PMID: 20226988

20. Manios E, Stamatelopoulos K, Tsivgoulis G, Barlas G, Koroboki E, Tsagalis G, et al. (2011) Time rate of blood pressure variation: a new factor associated with coronary atherosclerosis. J Hypertens 29: 1109–1114. https://doi.org/10.1097/HJH.0b013e3283454ff4 PMID: 21430560

21. Stamatelopoulos KS, Manios E, Barlas G, Koroboki E, Zacharoulis A, Tsivgoulis G, et al. (2010) Time rate of blood pressure variation is superior to central hemodynamics as an associate of carotid intima-media thickness. J Hypertens 28: 51–58. https://doi.org/10.1097/HJH.0b013e328331b6c8 PMID: 19952783

22. Zakopoulos NA, Tsivgoulis G, Barlas G, Spengos K, Manios E, Ikonomidis I, et al. (2006) Impact of the time rate of blood pressure variation on left ventricular mass. J Hypertens 24: 2071–2077. https://doi.org/10.1097/01.hjh.0000244957.47114.88 PMID: 16957568

23. Zakopoulos NA, Tsivgoulis G, Barlas G, Papamichael C, Spengos K, Manios E, et al. (2005) Time rate of blood pressure variation is associated with increased common carotid artery intima-media thickness. Hypertension 45: 505–512. https://doi.org/10.1161/01.HYP.0000158306.87582.43 PMID: 15753234

24. Delgado-Mederos R, Ribo M, Rovira A, Rubiera M, Munuera J, Santamarina E, et al. (2008) Prognostic significance of blood pressure variability after thrombolysis in acute stroke. Neurology 71: 552–558. https://doi.org/10.1212/01.wnl.0000318294.36223.69 PMID: 18550860

25. Sare GM, Ali M, Shuaib A, Bath PM (2009) Relationship between hyperacute blood pressure and outcome after ischemic stroke: data from the VISTA collaboration. Stroke 40: 2098–2103. https://doi.org/10.1161/STROKEAHA.108.539155 PMID: 19359649

26. Stead LG, Gilmore RM, Vedula KC, Weaver AL, Decker WW, Brown RD (2006) Impact of acute blood pressure variability on ischemic stroke outcome. Neurology 66: 1878–1881. https://doi.org/10.1212/01.wnl.0000219628.78513.b5 PMID: 16801654

27. Ohkubo T (2007) Prognostic significance of variability in ambulatory and home blood pressure from the Ohasama study. J Epidemiol 17: 109–113. PMID: 17641445

28. Dolan E, O'Brien E (2010) Blood pressure variability: clarity for clinical practice. Hypertension 56: 179–181. https://doi.org/10.1161/HYPERTENSIONAHA.110.154708 PMID: 20606104

29. Bilo G, Giglio A, Styczkiewicz K, Caldara G, Maronati A, Kawecka-Jaszcz K, et al. (2007) A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. J Hypertens 25: 2058–2066. https://doi.org/10.1097/HJH.0b013e32829c6a60 PMID: 17885548

30. Pierdomenico SD, Di NM, Esposito AL, Di MR, Ballone E, Lapenna D, et al. (2009) Prognostic value of different indices of blood pressure variability in hypertensive patients. Am J Hypertens 22: 842–847. https://doi.org/10.1038/ajh.2009.103 PMID: 19498342

31. Tomii Y, Toyoda K, Suzuki R, Naganuma M, Fujinami J, Yokota C, et al. (2011) Effects of 24-hour blood pressure and heart rate recorded with ambulatory blood pressure monitoring on recovery from acute ischemic stroke. Stroke 42: 3511–3517. https://doi.org/10.1161/STROKEAHA.111.628586 PMID: 21960578

32. Aslanyan S, Fazekas F, Weir CJ, Horner S, Lees KR (2003) Effect of blood pressure during the acute period of ischemic stroke on stroke outcome: a tertiary analysis of the GAIN International Trial. Stroke 34: 2420–2425. https://doi.org/10.1161/01.STR.0000091233.04524.0C PMID: 14500934

33. Castillo J, Leira R, García MM, Serena J, Blanco M, Dávalos A (2004) Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke 35: 520–526. https://doi.org/10.1161/01.STR.0000109769.22917.B0 PMID: 14726553

34. Ishitsuka K, Kamouchi M, Hata J, Fukuda K, Matsuo R, Kuroda J, et al. (2014) High blood pressure after acute ischemic stroke is associated with poor clinical outcomes: Fukuoka Stroke Registry. Hypertension 63: 54–60. https://doi.org/10.1161/HYPERTENSIONAHA.113.02189 PMID: 24126175

35. Schilaci Giuseppe,GiacomoPucci and Benjamin Gavish, Ambulatory Pulse Pressure Does it:improve cardiovascular risk stratification? Hypertension. 2014; 63: 217–219.

36. Li Y, Wang JG, Dolan E, Gao PJ, Guo HF, Nawrot T, et al. (2006) Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. Hypertension 47: 359–364. https://doi.org/10.1161/01.HYP.0000200695.34024.4c PMID: 16432048

37. Macwilliam JA, Melvin GS (1914) SYSTOLIC AND DIASTOLIC BLOOD PRESSURE ESTIMATION, WITH SPECIAL REFERENCE TO THE AUDITORY METHOD. Br Med J 1: 693–697. PMID: 20767054

38. Saeed NP, Panerai RB, Horsfield MA, Robinson TG (2013) Does stroke subtype and measurement technique influence estimation of cerebral autoregulation in acute ischaemic stroke. Cerebrovasc Dis 35: 257–261. https://doi.org/10.1159/000347075 PMID: 23548789

39. Verdecchia P, Angeli F, Gattobigio R, Rapicetta C, Reboldi G. Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. Am J Hypertens. 2007; 20:154–161. https://doi.org/10.1016/j.amjhyper.2006.07.017 PMID: 17261460

40. Pierdomenico SD, Lapenna D, Di Tommaso R, Di Carlo S, Esposito AL,DiMascio R, Ballone E, Cuccurullo F, Mezzetti A. Blood pressure variability and cardiovascular risk in treated hypertensive patients. Am J Hypertens. 2006; 19:991–997. https://doi.org/10.1016/j.amjhyper.2006.03.009 PMID: 17027816

41. Kikuya M, Hozawa A, Ohkubo T, Tsuji I, Michimata M, Matsubara M, Ota M, Nagai K, Araki T, Satoh H, Ito S, Hisamichi S, Imai Y. Prognostic significance of blood pressure and heart rate variabilities: the Ohasama Study. Hypertension. 2000; 36:901–906.) PMID: 11082164

42. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation: a critical appraisal. Hypertension 1995; 25:1276–1286. PMID: 7768574

43. Mancia G, Parati G, Di Rienzo M, Zanchetti A. Blood pressure variability. In: Zanchetti A, Mancia G (editors): Handbook of hypertension, Vol.17: pathophysiology of hypertension. Amsterdam: Elsevier Science BV; 1997, 117–169.

44. Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, et al. (2010) Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. Hypertension 55: 1049–1057. https://doi.org/10.1161/HYPERTENSIONAHA.109.140798 PMID: 20212270

45. Mena L, Pintos S, Queipo NV, Aizpu´rua JA, Maestre G, Sulbara´n T. A reliable index for the prognostic significance of blood pressure variability.JHypertens. 2003; 23:505–511.

46. Zhao D, Liu J, Wang W, Zeng Z, Cheng J, Liu J, et al. (2008) Epidemiological transition of stroke in China: twenty-one-year observational study from the Sino-MONICA-Beijing Project. Stroke 39: 1668–1674. https://doi.org/10.1161/STROKEAHA.107.502807 PMID: 18309149

47. Wu L, Wang A, Wang X, Zhao X, Wang C, Liu L, et al. (2015) Factors for short-term outcomes in patients with a minor stroke: results from China National Stroke Registry. BMC Neurol 15: 253. https://doi.org/10.1186/s12883-015-0505-z PMID: 26645312

48. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. (2013) Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 369: 11–19. https://doi.org/10.1056/NEJMoa1215340 PMID: 23803136

49. Mohr JP, Caplan LR, Melski JW, Goldstein RJ, Duncan GW, Kistler JP, et al. (1978) The Harvard Cooperative Stroke Registry: a prospective registry. Neurology 28: 754–762. PMID: 567291

50. Yamamoto H, Bogousslavsky J, van Melle G (1998) Different predictors of neurological worsening in different causes of stroke. Arch Neurol 55: 481–486. PMID: 9561975

51. Ferrari J, Knoflach M, Kiechl S, Willeit J, Schnabl S, Seyfang L, et al. (2010) Early clinical worsening in patients with TIA or minor stroke: the Austrian Stroke Unit Registry. Neurology 74: 136–141. https://doi.org/10.1212/WNL.0b013e3181c9188b PMID: 20065248