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Morning hypertension is a risk factor of macrovascular events following cerebral infarction

A retrospective study

Qinhua Wu, MS, Jianfeng Qu, MS, Yong Yin, BS, Aihong Wang, BS, Wei Cheng, MS, Ruikang Duan, MS, Bin Zhang, MD*

Abstract

This study aimed to investigate risk factors (such as morning hypertension, drug compliance, and biochemical parameters) of macrovascular events after cerebral infarction.

This was a retrospective study of patients with cerebral infarction admitted between May 2015 and April 2016 at the Fengxian Branch, 6th People's Hospital of Shanghai. They were divided into the macrovascular events and control groups according to the diagnosis of macrovascular events following cerebral infarction.

Among the 702 patients included for analysis, 122 patients were with macrovascular events and 580 were without macrovascular events (controls). Morning hypertension ($P = .01$), dyslipidemia ($P = .007$), atrial fibrillation ($P = .039$), carotid artery plaque ($P = .014$), inflammatory infection ($P = .005$), high homocysteine ($P = .032$), antithrombotic compliance ($P < .001$), statins compliance ($P < .001$), morning diastolic blood pressure ($P < .001$), morning systolic blood pressure ($P < .001$), and morning heart rate (morHR) ($P = .033$) were associated with macrovascular events. Multivariable analysis showed that morning hypertension ($P = .021$, odds ratio [OR] = 1.753, 95% confidence interval [CI] [1.088, 2.826]), dyslipidemia ($P = .021$, OR = 1.708, 95% CI [1.085, 2.687]), and inflammatory infection ($P = .031$, OR = 2.263, 95% CI [1.078, 4.752]) were independent risk factors for macrovascular events, while antithrombotic compliance ($P < .001$, OR = 0.488, 95% CI [0.336, 0.709]), statin compliance ($P = .02$, OR = 0.64, 95% CI [0.44, 0.931]), and morHR ($P = .027$, OR = 0.977, 95% CI [0.958, 0.997]) were independent protective factors against macrovascular events. Atrial fibrillation showed a tendency to be associated with macrovascular events ($P = .077$, OR = 1.531, 95% CI [0.955, 2.454]).

Morning hypertension, dyslipidemia, and inflammatory infection may increase the risk of macrovascular events following cerebral infarction. Improving morning blood pressure management and drug compliance (antithrombotic drugs and statins) may reduce the risk of macrovascular events following cerebral infarction.

Abbreviations: ABPM = ambulatory blood pressure monitoring, BMI = body mass index, CI = confidence interval, CT = computed tomography, HCY = homocysteine, LDL-C = low-density lipoprotein cholesterol, MRI = magnetic resonance imaging, OR = odds ratio.

Keywords: cerebral infarction, macrovascular event, morning hypertension, recurrence, risk factor

1. Introduction

Stroke is a common and frequently occurring disease with high morbidity and mortality. In China, stroke has become the first cause of disability and death.[1] After a first stoke, patients have a high risk of recurrence and vascular death.[2] Hopefully, with the improvement of medical technologies, the incidence, morbidity, and mortality of stroke are declining in many developed countries, but they are still rising in developing countries such as China, continuously increasing the economic and social burdens of the disease.[3,4]

A study on the best management and risk factors for stroke has found that a low rate of stroke recurrence during hospitalization may be related to optimal management.[5] Among the known risk factors, morning hypertension is considered as one of the important factors associated with malignant cardio-cerebrovascular events.[6] In China, morning blood pressure control in hypertensive patients is not optimal, with a failure rate of 61.8%.[7] Importantly, the relationship between morning hypertension and recurrence of ischemic stroke has been rarely studied. In addition, diabetes, dyslipidemia, smoking, and carotid plaque formation may also be important risk factors for recurrent stroke,[8] and their impact on the relationship between morning hypertension and stroke is poorly known.

Therefore, in this study, patients with stroke were enrolled to observe the incidence of macrovascular events after stroke. The aim was to explore the relationships between risk factors of macrovascular events such as morning hypertension and drug

Editor: Xiaoxing Xiong.

This study was funded by the Technology Development Fund Project of Science and Technology Commission in Fengxian District, Shanghai (No. 20151204).

The authors have no conflicts of interest to disclose.

Department of Neurology, Fengxian Branch, Shanghai Jiaotong University Affiliated 6th People's Hospital, Shanghai, China.

* Correspondence: Bin Zhang, Department of Neurology, Fengxian Branch, Shanghai Jiaotong University Affiliated 6th People's Hospital, Shanghai, China (e-mail: zhangbin08070@126.com).

Medicine (2018) 97:34(e12013)

Received: 4 April 2018 / Accepted: 30 July 2018

http://dx.doi.org/10.1097/MD.0000000000012013

compliance, thereby to evaluate the risk of macrovascular events after stroke and provide some evidence to optimize the secondary prevention of stroke.

2. Materials and methods

2.1. Subjects

This was a retrospective study of patients with cerebral infarction who were hospitalized between May 2015 and April 2016 at the Department of Internal Neurology of the Fengxian Branch, 6th People's Hospital of Shanghai Affiliated to Shanghai Jiaotong University School of Medicine. The inclusion criteria were diagnosis of cerebral infarction[9]; first lifetime onset of acute cerebral infarction symptoms (duration $\leq$1 week); and imaging suggested acute cerebral infarction. The exclusion criteria were severe cardio-respiratory disorders and any other life-threatening diseases; or incomplete data. This study was approved by the ethics committee of Fengxian Branch, 6th People's Hospital of Shanghai Affiliated to Shanghai Jiaotong University School of Medicine. Informed consent was provided by each patient.

2.2. Data collection

The following data were collected from the medical charts: age, gender, body mass index (BMI), history of smoking, history of hypertension, history of coronary heart disease, family history of premature cardio-cerebrovascular disease, history of atrial fibrillation, diabetes, hyperlipidemia, history of oral contraceptives, and reproductive history. All patients underwent complete cranial computed tomography (CT) scan and/or magnetic resonance imaging (MRI), biochemistry examination (including blood glucose, blood lipids, blood electrolytes, and liver and kidney function), electrocardiogram, myocardial ischemia markers (troponin, creatine kinase isoenzyme, and myoglobin), and complete blood count (including platelet count and coagulation mechanism). Some patients underwent a pregnancy test, a full set of immunity tests (antinuclear antibody profile, antineutrophil antibody profile), thyroid function, infectious indicators (including hepatitis A, hepatitis B, hepatitis C, C-reactive protein, anti-HIV antibody, rapid plasma reagin circle test, and specific *Spirochaeta pallida* antibody), multimodal MRI (DWI, MRA, FLAIR/T2), transcranial Doppler, carotid ultrasound, digital subtraction angiography, Holter monitoring, and echocardiography.

Morning blood pressure (systolic and diastolic blood pressure; morning systolic blood pressure [morSBP] and morning diastolic blood pressure [morDBP], respectively), nocturnal blood pressure (systolic and diastolic), morning heart rate (morHR), nocturnal heart rate, blood glucose, blood lipids, smoking, combination of atrial fibrillation, carotid soft plaque, inflammatory infection, high homocysteine (HCY), antithrombotic compliance, and statin compliance were extracted from the medical charts.

Smoking was referred to patients still smoking after the first onset of cerebral infarction. Atrial fibrillation was based on the electrocardiogram and 24-hour dynamic electrocardiogram. Carotid soft plaques referred to low-echo unstable plaques on B-mode ultrasound (Logiq, GE Healthcare, Waukesha, WI). Inflammatory infections included syphilis, AIDS, and chronic infections. High HCY referred to blood HCY $>$15 μmol/L.

2.3. Grouping

The case group was made of the patients who experienced a macrovascular event during the 1-year period following discharge. The control group was made of the patients who did not experience a macrovascular event during the 1-year period following discharge.

2.4. Blood pressure management

Morning blood pressure was managed according to the Chinese guidelines.[9] Blood pressure was measured at home, within 1 hour after waking up in the morning, before administration of drugs, and before breakfast. Morning blood pressure could also be measured using 24-hour ambulatory blood pressure monitoring (ABPM) (2 hours after waking up) or measured between 6:00 and 10:00 in clinic. Nocturnal blood pressure referred to blood pressure taken before sleep (22:00–6:00). Hypertensive patients were required to measure their blood pressure once a week, while patients without hypertension were required to measure it once a month. Patients were diagnosed with hypertension when: blood pressure $\geq$ 140/90 mm Hg at the clinic; family history of blood pressure; and 24-hour ABPM $\geq$ 135/85 mm Hg. Morning and nocturnal heart rates were recorded at the same time. According to the Guidelines for secondary prevention of ischemic stroke and transient ischemic attack,[10] glycosylated hemoglobin $<$ 7% was used as the standard for diabetic blood glucose control. Low-density lipoprotein cholesterol (LDL-C) $<$ 1.8 mmol/L was the target for dyslipidemia. In terms of antithrombotic compliance, patients with noncardiac embolism were given antiplatelet drugs, while patients with cardiac embolism were given anticoagulant drugs.

The criteria for stroke recurrence were reoccurrence of stroke-related neurological impairment; exacerbated symptoms and signs for more than 1 month after onset, and were excluded to suffer from progressive stroke; and new lesions on cranial CT or MRI. Macrovascular events referred to the recurrence of cerebral infarction, cerebral hemorrhage, myocardial infarction, and all-cause death.

2.5. Statistical analysis

All data were entered in a database and analyzed using SPSS 19.0 (IBM, Armonk, NY). In the present study, all continuous data were non-normally distributed; they were presented as median (interquartile range) and nonparametric analyses were used. Categorical data were presented as frequencies (%) and analyzed using the Fisher exact test. Variables were included in a logistic regression using the enter method, and those with a P value $<$ .05 in univariable logistic regression analyses were included in a multivariable logistic regression analysis. All statistical tests were 2-sided, and P values $<$ .05 were considered statistically significant.

3. Results

3.1. Baseline data

A total of 770 patients with acute cerebral infarction were identified; 68 patients were excluded due to severe cardiopulmonary insufficiency, death during hospitalization, or self-discharge. Finally, 702 cases were included for analysis (Fig. 1).

3.2. Macrovascular events

Among the 702 patients, 122 cases suffered from macrovascular events within 1 year, for a total recurrence rate of 17.4%. Baseline age, gender, and BMI did not show significant differences between the macrovascular event and control groups

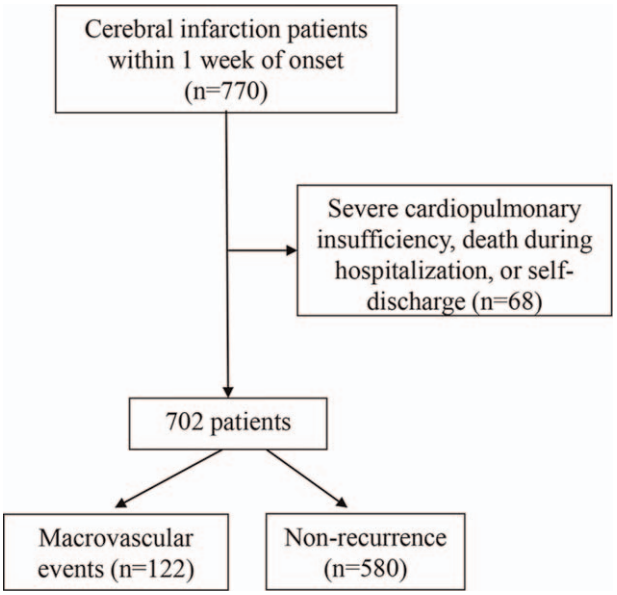

Figure 1. Study flowchart.

(all $P > .05$). There were significant differences in morDBP, morSBP, blood lipids, morning hypertension, atrial fibrillation, carotid artery plaque, antithrombotic compliance, and statins compliance between the 2 groups (all $P < .05$). Meanwhile, there were no differences between the 2 groups regarding family history, alcohol drinking, poor diet, smoking, nocturnal diastolic blood pressure, and nocturnal systolic blood pressure (Table 1).

3.3. Univariable analysis of macrovascular events-related risk factors

All the collected indicators were analyzed using univariable logistic regression. The results showed that morning hypertension ($P = .01$, odds ratio [OR] = 1.821, 95% confidence interval [CI] [1.155, 2.871]), dyslipidemia ($P = .007$, OR = 1.769, 95% CI [1.171, 2.675]), atrial fibrillation ($P = .039$, OR = 1.592, 95% CI [1.024, 2.476]), carotid artery plaque ($P = .014$, OR = 1.651, 95% CI [1.107, 2.462]), inflammatory infection ($P = .005$, OR = 2.655, 95% CI [1.348, 4.003]), high HCY ($P = .032$, OR = 1.595, 95% CI [1.040, 2.445]), antithrombotic compliance ($P < .001$, OR = 0.403, 95% CI [0.271, 0.599]), statins compliance ($P < .001$, OR = 0.412, 95% CI [0.277, 0.612]), morDBP ($P < .001$, OR = 1.032, 95% CI [1.018, 1.046]), morSBP ($P < .001$, OR = 1.043, 95% CI [1.020, 1.066]), and morHR ($P = .033$, OR = 0.979, 95% CI [0.961, 0.998]) were associated with macrovascular events (Table 2).

3.4. Multivariable analysis of macrovascular events-related risk factors

Variables with a P value $< .05$ in univariable analyses were included in the logistic multivariable analysis. Morning hypertension (categorical variable, yes/no) was defined according to the morDBP and morSBP; therefore, morDBP and morSBP were not included in the multivariable analysis. The multivariable analysis showed that morning hypertension ($P = .021$, OR = 1.753, 95% CI [1.088, 2.826]), dyslipidemia ($P = .021$, OR = 1.708, 95% CI [1.085, 2.687]), and inflammatory infection ($P = .031$, OR = 2.263, 95% CI [1.078, 4.752]) were independent risk factors for macrovascular events, while antithrombotic compliance ($P < .001$, OR = 0.488, 95% CI [0.336, 0.709]), statin compliance

Table 1

Characteristics of the patients.

Variables	Values	With macrovascular events (N = 122)	Without macrovascular events (N = 580)	All (N = 702)	P
Age		69 (60–78)	68 (60–77)	68 (60–77)	.406
Gender	Female	62 (50.8%)	250 (43.1%)	312 (44.4%)	.119
	Male	60 (49.2%)	330 (56.9%)	390 (55.6%)	
Body mass index		23.2 (22–25.8)	23.4 (22–25)	23.4 (22–25)	. 278
morDBP, mm Hg		150 (140–160)	148 (132–157)	150 (135–160)	<.001*
morSBP, mm Hg		90 (80–98)	86 (80–90)	89 (80–90)	<.001*
Nocturnal DBP, mm Hg		135 (131.5–142)	135 (130–142)	135 (130–142)	.981
Nocturnal SBP, mm Hg		78 (67–82)	78 (67–85)	78 (67–85)	.446
morHR		78 (67–85)	78 (70–86)	78 (70–86)	.044*
Nocturnal HR		77 (67–80)	76 (67–80)	76 (67–80)	.950
Morning hypertension	Yes	94 (77.1%)	376 (64.8%)	470 (67.0%)	.009*
Diabetes	Yes	52 (42.6%)	202 (34.8%)	254 (36.2%)	.103
Dyslipidemia	Yes	45 (36.9%)	144 (24.8%)	189 (26.9%)	.006*
Smoking	Yes	43 (35.3%)	178 (30.7%)	221 (31.5%)	.325
Atrial fibrillation	Yes	35 (28.7%)	177 (20.2%)	152 (21.7%)	.038*
Carotid plaques	Yes	52 (42.6%)	180 (31.0%)	232 (33.1%)	.013*
Inflammatory infection	Yes	14 (11.5%)	27 (4.7%)	41 (5.8%)	.004*
High HCY levels	Yes	39 (32.0%)	132 (22.8%)	171 (24.4%)	.031*
Antithrombotic compliance	Yes	55 (45.1%)	389 (67.1%)	444 (63.3%)	<.001*
Statin compliance	Yes	54 (44.3%)	382 (65.9%)	436 (62.1%)	<.001*
Family history	Yes	6 (4.9%)	25 (4.3%)	31 (4.4%)	.766
Alcohol drinking	Yes	36 (29.5%)	172 (29.7%)	208 (29.6%)	.974
Poor diet	Yes	7 (5.7%)	20 (3.5%)	27 (3.9%)	.296

Continuous data are presented as median (interquartile range).

HCY = homocysteine, morDBP = morning diastolic blood pressure, morHR = morning heart rate, morSBP = morning systolic blood pressure, nocturnal DBP = nocturnal diastolic blood pressure, nocturnal HR = nocturnal heart rate, nocturnal SBP = nocturnal systolic blood pressure.

* $P < .05$.

Table 2

Univariable logistic regression with macrovascular events as the endpoint.

Variables	OR	OR 95% CI lower limit	HR 95% CI upper limit	*P*
Gender	0.733	0.496	1.084	.120
Morning hypertension	1.821	1.155	2.871	.010*
Diabetes	1.39	0.934	2.068	.104
Dyslipidemia	1.769	1.171	2.675	.007*
Smoking	1.229	0.815	1.855	.325
Atrial fibrillation	1.592	1.024	2.476	.039*
Carotid plaques	1.651	1.107	2.462	.014*
Inflammatory infection	2.655	1.348	4.003	.005*
High HCY levels	1.595	1.04	2.445	.032*
Antithrombotic compliance	0.403	0.271	0.599	<.001*
Statin compliance	0.412	0.277	0.612	<.001*
Family history	1.148	0.461	2.862	.767
Drinking	0.993	0.647	1.523	.974
Poor diet	1.704	0.704	4.125	.237
Age	1.006	0.99	1.023	.467
BMI	1.057	0.974	1.149	.185
morDBP	1.032	1.018	1.046	<.001*
morSBP	1.043	1.02	1.066	<.001*
nocDBP	0.999	0.98	1.019	.959
nocSBP	0.993	0.975	1.012	.482
morHR	0.979	0.961	0.998	.033*
nocHR	0.998	0.979	1.018	.868

BMI = body mass index, CI = confidence interval, HCY = homocysteine, HR = hazard ratio, morDBP = morning diastolic blood pressure, morHR = morning heart rate, morSBP = morning systolic blood pressure, nocDBP = nocturnal diastolic blood pressure, nocHR = nocturnal heart rate, nocSBP = nocturnal systolic blood pressure, OR = odd ratio.
* $P < .05$.

($P = .02$, OR = 0.64, 95% CI [0.44, 0.931]), and morHR ($P = .027$, OR = 0.977, 95% CI [0.958, 0.997]) were independent protective factors against macrovascular events (Table 3).

4. Discussion

The relationship between morning hypertension and macrovascular events after ischemic stroke has been rarely studied. The present study showed that morning hypertension, dyslipidemia, and inflammatory infection may increase the risk of macrovascular events following cerebral infarction. Therefore, improving morning blood pressure management and drug compliance may reduce the risk of macrovascular events following cerebral infarction.

Table 3

Multivariable logistic regression with macrovascular events as the endpoint.

Variables	OR	OR 95% CI lower limit	HR 95% CI upper limit	*P*
Morning hypertension	1.753	1.088	2.826	.021*
Dyslipidemia	1.708	1.085	2.687	.021*
Atrial fibrillation	1.531	0.955	2.454	.077
Carotid plaques	1.465	0.95	2.259	.084
Inflammatory infection	2.263	1.078	4.752	.031*
High HCY levels	1.453	0.916	2.305	.113
Antithrombotic compliance	0.403	0.265	0.613	<.001*
Statin compliance	0.452	0.298	0.684	<.001*
morHR	0.977	0.958	0.997	.027*

CI = confidence interval, HCY = homocysteine, HR = hazard ratio, morHR = morning heart rate, OR = odd ratio.
* $P < .05$.

Cerebral infarction imposes a heavy burden on patients, families, and society. After the first stroke, there is a greater risk of recurrence of cardio-cerebrovascular events within 1 year. The recurrence rate of stroke has been reported to be higher in China than in Western countries.[11,12] A study in France showed a 1-year rate of cardiovascular death, myocardial infarction, or stroke of 4.2%.[13] Another study from the United Kingdom showed a 1-year recurrence risk of 11.1%.[14] In the United States, the 1-year recurrence rate of stroke was 9.4%.[15] Recently, a study in Sweden reported a 1-year recurrence rate of 5.3%.[16] In the present study, the 1-year recurrence rate was 17.4%. The discrepancies may be due to a number of factors such as lifestyle habits, economic status, and healthcare access. In addition, the rapid westernization of the life habits in China (i.e., diet rich in saturated fats and carbohydrates and higher stress) probably led to the rapid increase in stroke risk observed in the recent years.[1,3,4] Other possible reasons could be health knowledge, treatment compliance, and the preference for traditional Chinese medicine.[17,18] This highlights the need for health education.

Hypertension is an important risk factor for cerebrovascular diseases. Currently, the management of blood pressure has gradually shifted from the conventional idea of managing the "quantity" of lowering blood pressure to managing the "quality" of lowering blood pressure.[19] A meta-analysis showed that morning hypertension in the elderly in primary stroke prevention increases the risk of first stroke.[20] The present study revealed that morning hypertension was closely related to the recurrence of cerebral infarction, which is supported by recently published studies.[21–23] Physiologically, SBP and DBP usually increase slightly during awakening. If the blood pressure increases excessively in morning, it could have a greater impact on the vasculature.[24] Indeed, some studies suggested that morning hypertension is associated with the carotid intima-media thickness.[24] For patients with morning hypertension alone, some authors suggested that a good lifestyle can better regulate blood pressure, thereby reducing the risk of stroke recurrence.[25] Adjusting the medication timing, taking long-acting preparations, and using drugs that are proven to benefit the heart and brain can decrease cardio-cerebrovascular events and improve the quality of life of hypertensive patients.

Dyslipidemia is associated with the recurrence of cerebral infarction.[26] In the present study, dyslipidemia was independently associated with major macrovascular events after stroke. In addition, poor compliance with statins (which exert lipid-lowering and pleiotropic effects) was also independently associated with major macrovascular events after stroke. Indeed, LDL-C levels should be closely monitored and managed[27] and the present study highlights the need for blood lipid control after stroke. Carotid atherosclerotic plaque is closely associated with elevated LDL-C and Lp(a) levels and is a risk factor for recurrence of cerebral infarction.[11,28,29] Unstable plaque is rich in lipids, has a thin fibrous cap, and poor structural integrity, is easy to rupture, and is a predictor of recurrence of cerebral infarction.[11,28,29] Conducting regular examination and carotid ultrasound to timely discover and intervene on unstable plaque may reduce the recurrence of cerebral infarction.

The relationship between the use of antiplatelet drugs and statins and the recurrence of cerebral infarction has attracted the attention of many authors.[30,31] Compliance to guidelines and treatments has been shown to be relatively low in China.[17,18]

Antiplatelet drugs can decrease platelet aggregation and reduce blood viscosity, alleviating the symptoms of intracranial ischemia. A large-scale study showed that statins had beneficial effects for the secondary prevention of ischemic cerebrovascular diseases.[32] Some studies suggested that attention should be paid to controlling LDL-C and target blood pressure in patients with intracranial arteriosclerosis, so as to reduce the recurrence of stroke and vascular events,[33] which could not only reduce blood LDL-C levels, but also could reduce carotid intima-media thickness through anti-inflammation and antiatherosclerosis effects, thereby preventing recurrence of stroke. The present study showed that antithrombotic drugs and statins might reduce the recurrence of cerebral infarction.

Active inflammatory disorders and infections are well known to be associated with vascular events.[34–36] Since atherosclerosis has an important inflammatory/immune component, any increase in the systemic immune status might affect the development and instability of the plaques.[37–39] Accordingly, the present study showed that inflammatory infections were independently associated with the risk of major macrovascular event after stroke, but it should be noted that because of the small number of patients with individual diseases, they were all grouped together for analysis and it is probable that patients with systemic autoimmune diseases (e.g., lupus erythematosus) show different stroke recurrence patterns than patients with acute or chronic bacterial or viral infections. This will have to be explored further. Statins possess pleiotropic effects that include some anti-inflammatory effects,[40,41] but these effects in themselves are too weak to counteract the impacts of infection on inflammation and the immune system.

It is noteworthy to highlight that some factors were associated with major cerebrovascular events in the univariable analyses, but not in the multivariable analysis. Those factors should not be discarded as being insignificant, but should be considered as not statistically significant when considering their interaction with the other variables and in this specific study population. Among them, atrial fibrillation is a well-known factor for stroke and recurrent stroke.[42–45] In addition, some types of atrial fibrillation are vagally mediated and uncontrolled blood pressure is a risk factor for atrial fibrillation.[42–46] High catecholamines levels are associated with atrial fibrillation since they play important roles in the sympathetic activity and they show circadian variations.[47] Unfortunately, catecholamines could not be assessed in the present study. Additional studies are necessary to explore the roles of those factors in stroke recurrence.

This study is not without limitations. First, this was a retrospective study, and thus the screening of patients might be biased. In addition, only a small number of patients were included. Finally, no actual nutritional and lifestyle data from our study population. Thus, results of this study are subject to validation by multicenter prospective clinical studies.

In conclusion, the recurrence of stroke is multifactorial, and morning hypertension is an independent risk factor for 1-year stroke recurrence. Morning blood pressure management should be emphasized in clinical practice. By combining other risk factors to control and standardize secondary prevention, we could reduce the recurrence rate of macrovascular events after cerebral infarction and improve the survivorship of the patients.

4.1. Ethical approval

This study was approved by the ethics committee of Fengxian Branch, 6th People's Hospital of Shanghai Affiliated to Shanghai Jiaotong University School of Medicine. Informed consent was provided by each patient.

Author contributions

Conceptualization: Qinhua Wu, Bin Zhang.
Data curation: Qinhua Wu, Jianfeng Qu, Yong Yin, Wei Cheng, Ruikang Duan.
Formal analysis: Qinhua Wu, Jianfeng Qu, Yong Yin, Wei Cheng, Ruikang Duan, Bin Zhang.
Funding acquisition: Bin Zhang.
Investigation: Aihong Wang.
Methodology: Aihong Wang.
Project administration: Bin Zhang.
Supervision: Aihong Wang.
Writing – original draft: Qinhua Wu.
Writing – review and editing: Jianfeng Qu, Yong Yin, Wei Cheng, Ruikang Duan, Bin Zhang.

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