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Time point of nocturnal trough systolic blood pressure as an independent predictor of cardiovascular events

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Abstract

Nocturnal trough systolic blood pressure (NTSBP) and Time Point of Nocturnal Trough Systolic Blood Pressure (T-NTSBP) were important parameters of nocturnal blood pressure, the predictive values of which are unclear for stroke outcome. This study aimed to examine the relationship between NTSBP/T-NTSBP and stroke outcome. The authors used data from a nationwide ambulatory blood pressure monitoring cohort study conducted in China, which recruited 2348 ischemic stroke and transient ischemic attack (TIA) patients. NTSBP was defined as the lowest SBP during nighttime (22:00–6:00), and T-NTSBP was defined as the corresponding time point of NTSBP. The associations between NTSBP/T-NTSBP and stroke outcome (stroke recurrence and combined vascular event [CVE]) at 90 days or 1 year were analyzed using cox regression models. According to NTSBP classified by quartile, hazard ratio (HR) with 95% confidence interval (CI) for NTSBP quartile 4 (>129 mm Hg) was 2.727 (1.148–6.478) for CVE at 90-day, compared with quartile 1 (≤102 mm Hg). However, an attenuated association between NTSBP and CVE was observed at 1 year. In addition, we observed the group of T-NTSBP at 4:00–6:00 had a lowest CVE incidence at 90 days among four groups (22:00–23:59, 00:00–1:59 2:00–3:59, 4:00–6:00). After multivariable adjustment, T-NTSBP was significantly associated with CVE incidence at 90 days (T-NTSBP at the 4:00–6:00 versus the 22:00–23:59 group: HR, 0.433; 95%CI, 0.190–0.986), independent of NTSBP and average nocturnal SBP. Both of NTSBP and T-NTSBP were important predictors for short-term cardiovascular risk in ischemic stroke and TIA patients.

KEYWORDS
blood pressure, nocturnal trough systolic blood pressure, stroke outcome, time point of nocturnal trough systolic blood pressure

1 | INTRODUCTION

Ambulatory blood pressure monitoring (ABPM) has been recommended as gold standard for the diagnosis and management of hypertension.[1–3] A meta-analysis of nine cohorts with hypertension suggested high nocturnal systolic blood pressure is a stronger risk factor for cardiovascular events than daytime SBP.[4] Various epidemiological and clinical studies have shown that nocturnal blood pressure indexes, such as nocturnal hypertension, non-dipping pattern, blood pressure variability and blunted nocturnal BP fall, are better predictors for cardiovascular risk than daytime blood pressure.[5–14]

The circadian rhythm of blood pressure in stroke patients is different from healthy individuals. The dipper rhythm disappears and nocturnal average blood pressure is higher.[15,16] Previous studies showed these risk factors of ABPM were associated with adverse outcomes in stroke patients.[17,6] Moreover, the ability of nocturnal BP decline is reduced in stroke patients, leading to the emergence of reverse dipping and elevated nocturnal blood pressure.[19,20] The nocturnal trough systolic blood pressure (NTSBP) is an important indicator of the ability of nocturnal BP decline, but which has rarely been concerned in previous studies, especially stroke patients. In addition, the Time Point of Nocturnal Trough Systolic Blood Pressure (T-NTSBP) varies from person to person according to circadian clock and external factors. We hypothesize that the earlier T-NTSBP appear, the longer blood pressure climbed, which could lead to higher morning blood pressure surge. So far, there have been no studies on T-NTSBP /NTSBP and adverse outcomes. This is the first prospective study to assess the predictive ability of NTSBP and T-NTSBP for combined vascular events (CVE) and recurrent stroke in ischemic stroke and transient ischemic attack (TIA) patients.

2 | METHODS

2.1 | Study cohort

The recruitment of consecutive study patients from the Blood Pressure and Clinical Outcome in TIA or Ischemic Stroke (BOSS) study was conducted in 61 hospitals throughout China, aimed at assessing BP parameters and clinical outcomes in ischemic stroke and TIA patients. The design of the BOSS study has been described in detail elsewhere.[21] In brief, 2608 patients with acute ischemic stroke and TIA within 7 days of the index event over the age of 18 were enrolled between October 2012 and February 2014. Baseline ABPM data was collected, and follow-ups were conducted 90-days and 1-year later to assess CVE and stroke recurrence outcomes.

The protocol was approved the Institutional Review Board at Beijing Tian Tan Hospital, as well as the ethical committees at the 61 participating hospitals, in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients, or their designated relatives, who enrolled in the study.

2.2 | Ambulatory BP and classification

Within 3–10 days after the index event, 24-h ABPM was completed in order to avoid BP elevation during the stress period after stroke. This study did not use a uniform brand and model of automatic blood pressure monitors, but this study required that automatic blood pressure monitors must meet international standards and be clinically validated. Hence, the automatic blood pressure monitors used in participating hospitals are required to carry out quality audits. Automatic BP readings were obtained every 15 min during the daytime (from 6:00 to 21:59), and every 30 min during the nocturnal (from 22:00 to 6:00) over a period of 24 h.[2] If the recorded BP readings were less than 80% of expected measurements, ABPM was repeated.

Major ABPM parameters were calculated based on SBP in this study.[22] NTSBP was defined as the lowest SBP during nocturnal (22:00-6:00), and T-NTSBP was defined as the corresponding time point of NTSBP. In this study, patients were categorized into four groups according to the quartile of NTSBP and the T-NTSBP (22:00–23:59, 00:00–1:59, 2:00–3:59, 4:00–6:00).

Average morning BP was defined as the average BP from 6:00 to 8:00 a.m. Sleep-trough morning blood pressure surge (MBPS) was defined as the morning BP minus the lowest BP during nocturnal. Circadian rhythm was classified by nocturnal decline as follows: dipper hypertension (≥10% to < 20%), non-dipper hypertension (≥0% to < 10%), extreme dippers (≥20%), and reverse dippers (< 0%).

2.3 | Clinical outcomes

We collected follow-up data through face-to-face interview after 90 days, and by telephone interview after 1 year. For patients with nonfatal events, we scheduled face-to-face follow-ups or carried out home visits. Clinical outcomes included recurrent stroke and CVE at 90-days and 1 year after onset and excluded events during hospitalization in order to predict the occurrence of events prospectively, because ABPM was completed during hospitalization. The CVE were composed of ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death. Vascular death included fatal stroke, fatal myocardial infarction, and other cardiovascular death. Death certificates were obtained for deceased participants, and hospital data were abstracted for all CVE. Recurrent stroke was defined as a new neurological deficit or a deterioration of an existing deficit that fit the definitions for ischemic or hemorrhagic stroke.[23]

2.4 | Statistical analysis

Continuous variables are expressed as standard deviation and were compared using analysis of variance, while categorical variables were reported as frequency (percent) and were compared using chi-square test. The effects of T-NTSBP and NTSBP on clinical events were evaluated by multivariable cox regression models, C-statistics, NRI and

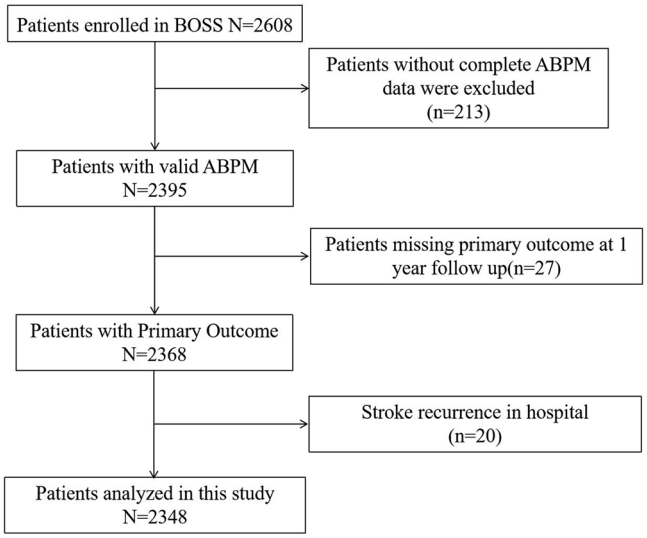

FIGURE 1 Decision making flow chart for study inclusion

IDI. The hazard ratio for the effects of T-NTSBP on clinical events was tested after controlling for the following variables: age, sex, smoking, drinking, medical history (atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia), secondary prevention drugs (antiplatelet, anti-hypertension, lipid-lowering, and anti-diabetic), NTSBP, and average nocturnal SBP. Covariates for the effects of NTSBP on clinical events were controlled as follows: age, sex, smoking, drinking, medical history (atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia), secondary prevention drugs (antiplatelet, anti-hypertension, lipid-lowering, and anti-diabetic). Data were analyzed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). All *p* values were two-tailed, and a significance level of 0.05 was used.

3 | RESULTS

3.1 | Patients characteristics by T-NTSBP

Figure 1 shows the decision-making process for study inclusion. Overall, 2608 patients were included in this study cohort, 213 patients with incomplete ABPM data were excluded, and 47 patients experienced stroke recurrence during the initial hospital stay and subsequently lost prior to follow-up. In total, 2348 patients remained available for analysis. Mean age was 62.40±10.95 years, and 67.84% was male. Mean baseline nocturnal SBP and NTSBP was 137.23±20.34 mm Hg and 115.98±20.08 mm Hg, respectively. Table 1 presents baseline demographic and clinical characteristics of participants in the four groups of T-NTSBP. Except for age, sex, sleep-trough MBPS, anti-hypertension drugs, and average morning BP, baseline data of each group showed no statistical difference.

3.2 | T-NTSBP and clinical outcomes

During 90-day follow-up, a total of 63 (2.68%) patients with CVE and 46 (1.96%) patients with recurrent stroke were identified. The lowest rates of CVE (1.58%) and recurrent stroke (1.39%) were in the 4:00–6:00 NTSBP group. Using 22:00–23:59 T-NTSBP as reference, the unadjusted hazard ratio for CVE was 0.881 (95% CI: 0.464–1.670) for 00:00–1:59 T-NTSBP, 0.728 (95% CI: 0.384–1.381) for 2:00–3:59 T-NTSBP, and 0.406 (95% CI: 0.180–0.918, $p < .05$) for 4:00–6:00 T-NTSBP. After adjusting for age, sex, smoking, drinking, medical history, secondary prevention, NTSBP, and average nocturnal SBP, the hazard ratios for CVE were calculated from NTSBP at 00:00–1:59, 2:00–3:59, and 4:00–6:00 compared to the 22:00–23:59. Hazard ratios were 0.864 (95% CI: 0.441–1.695), 0.746 (95% CI: 0.391–1.425), and 0.433 (95% CI: 0.190–0.986, $p < .05$) for CVE for the 00:00–1:59, 2:00–3:59, and 4:00–6:00 groups, respectively (Table 2). In unadjusted and adjusted models, the risks for stroke recurrence across all T-NTSBP groups were not significant.

At 1-year follow-up, 117 (4.98%) and 78 (3.32%) patients experienced CVE and stroke recurrence, respectively. The risks among T-NTSBP groups were not significant for CVE or stroke recurrence in unadjusted and adjusted models (Table 2).

3.3 | NTSBP and clinical outcomes

Results of unadjusted and adjusted associations of NTSBP with CVE and recurrent stroke stratified by quartile NTSBP are shown in Table 3. After adjustment for covariates including age, sex, smoking, drinking, medical history, and secondary prevention, the risk of CVE was increased at 90-day follow-up. The hazard ratio was 2.727 (95% CI: 1.148–6.478, $p < .05$) in the >129 mm Hg group, and at 1-year follow-up the hazard ratio was 1.844 (95% CI: 1.035–3.284) in the 102–115 mm Hg group, and 1.843 (95% CI: 1.026–3.311) in the 115–129 mm Hg group compared with quartiles 1 ($p < .05$). Recurrent stroke had no statistical significance at 90-day and 1-year follow-up.

3.4 | Incremental predictive value of T-NTSBP and NTSBP

We evaluated whether T-NTSBP and NTSBP would further increase the predictive value of conventional risk factors (Tables 4 and 5). For CVE within 90-day as the outcome of interest, the C statistic by the conventional model did not significantly improve with the addition of T-NTSBP (from 0.706 to 0.703, $p = .1342$) and NTSBP (from 0.706 to 0.704, $p = .1463$). However, the discriminatory power and risk reclassification appeared to be substantially better with the addition of T-NTSBP(integrated discrimination improvement 12.12%, $p = .0083$) and NTSBP (integrated discrimination improvement 8.56%, $p = .0941$).

4 | DISCUSSION

Our study showed the independent association of NTSBP and T-NTSBP with CVE at 90 days in ischemic stroke and TIA patients. However, an attenuated association between NTSBP and CVE was

TABLE 1 Baseline characteristics of the study population by T-NTSBP category

	T- NTSBP at 22:00–23:59	T-NTSBP at 00:00–1:59	T-NTSBP at 2:00–3:59	T-NTSBP at 4:00–6:00	*p**
Number of patients	611 (26.02%)	577 (24.57%)	655 (27.90%)	505 (21.51%)	
Age, years	64.10 ± 10.78	61.97 ± 11.29	61.35 ± 10.74	62.20 ± 10.84	**.0001**
>60year (*n*%)	378 (61.87%)	317 (54.94%)	339 (51.76%)	288 (57.03%)	**.0033**
≤60year (*n*%)	233 (38.13%)	260 (45.06%)	316 (48.24%)	217 (42.97%)	**.0033**
Male	406 (66.45%)	389 (67.42%)	452 (69.01%)	346 (68.51%)	**.7760**
Smoking	263 (43.04%)	252 (43.67%)	281 (42.90%)	219 (43.37%)	**.9933**
Drinking	217 (35.52%)	230 (39.86%)	249 (38.02%)	183 (36.24%)	**.4211**
Hypertension	442 (72.46%)	408 (70.96%)	463 (70.69%)	345 (68.45%)	**.5401**
Diabetes mellitus	144 (23.65%)	122 (21.25%)	135 (20.61%)	103 (20.44%)	**.5080**
Hyperlipidemia	72 (11.80%)	54 (9.44%)	64 (9.77%)	48 (9.52%)	**.4826**
Atrial fibrillation	18 (2.95%)	19 (3.31%)	10 (1.53%)	8 (1.59%)	**.0903**
TOAST type					**.1486**
Large - artery atherosclerosis	313 (57.12%)	281 (55.86%)	342 (59.69%)	276 (62.30%)	
Cardio-embolism	18 (3.28%)	20 (3.98%)	8 (1.40%)	8 (1.81%)	
Small - vessel occlusion	198 (36.13%)	189 (37.57%)	204 (35.60%)	148 (33.41%)	
Other	19 (3.47%)	13 (2.58%)	19 (3.32%)	11 (2.48%)	
Discharge medications					
Antiplatelet	568 (92.96%)	540 (93.59%)	619 (94.50%)	475 (94.06%)	**.7071**
Anti-hypertension	415 (67.92%)	401 (69.50%)	454 (69.31%)	309 (61.19%)	**.0110**
Lowering-lipid	515 (84.29%)	482 (83.54%)	562 (85.80%)	421 (83.37%)	**.6360**
Antidiabetic	135 (22.09%)	125 (21.66%)	128 (19.54%)	99 (19.60%)	**.5828**
Average 24-h BP					
Systolic, mm Hg	141.71 ± 18.63	140.80 ± 17.81	142.12 ± 18.58	141.47 ± 17.39	**.7347**
Diastolic, mm Hg	83.43 ± 13.85	83.94 ± 12.48	84.71 ± 12.94	83.61 ± 12.35	**.0820**
Average nocturnal BP					
Systolic, mm Hg	137.80 ± 21.35	135.79 ± 19.76	137.31 ± 20.29	138.08 ± 19.77	**.2138**
Diastolic, mm Hg	79.88 ± 14.11	79.80 ± 12.91	80.68 ± 13.13	80.67 ± 13.31	**.3501**
Sleep-trough MBPS, mm Hg					
Systolic, mm Hg	29.03 ± 15.75	28.45 ± 15.48	28.47 ± 16.73	23.21 ± 14.92	**<.0001**
Diastolic, mm Hg	23.38 ± 11.95	23.70 ± 11.87	24.58 ± 11.63	19.43 ± 11.55	**<.0001**
Average morning BP					
Systolic, mm Hg	145.72 ± 21.07	143.43 ± 20.20	143.81 ± 21.22	138.87 ± 20.07	**<.0001**
Diastolic, mm Hg	87.57 ± 16.20	87.23 ± 14.52	87.31 ± 14.43	84.15 ± 13.85	**.0003**
Circadian rhythm (Systolic)					**.0678**
Dipper, *n* (%)	105 (17.21%)	124 (21.53%)	118 (18.04%)	76 (15.05%)	
Non-dippers, *n* (%)	315 (51.64%)	304 (52.78%)	355 (54.28%)	260 (51.49%)	
Extreme dippers, *n* (%)	10 (1.64%)	9 (1.56%)	12 (1.83%)	6 (1.19%)	
Reverse dippers, *n* (%)	180 (29.51%)	139 (24.13%)	169 (25.84%)	163 (32.28%)	
Nocturnal Trough systolic blood pressure (NTSBP), mm Hg	117.42 ± 21.22	115.28 ± 19.02	115.50 ± 20.28	115.68 ± 19.54	**.3586**

TABLE 2 Multivariable cox regression analyses about relationship of T-NTSBP and outcome at 90-day/1 year

		Corresponding Inflection Time of TSBP categories										
		T-NTSBP 22:00–23:59		T-NTSBP 00:00–1:59			T-NTSBP 2:00–3:59			T-NTSBP 4:00–6:00		
	Total	Events	Reference	Events	HR (95% CI)	*p* value	Events	HR (95% CI)	*p* value	Events	HR (95% CI)	*p* value
combined vascular events-90 day	**63 (2.68%)**	**21 (3.44%)**		**17 (2.95%)**			**17 (2.60%)**			**8 (1.58%)**		
Unadjusted			1 [Reference]		0.881 (0.464-1.670)	.6972		0.728 (0.384-1.381)	.3316		0.406 (0.180-0.918)	.0304
Adjusted			1 [Reference]		0.864 (0.441-1.695)	.6713		0.746 (0.391-1.425)	.3755		0.433 (0.190-0.986)	.0462
recurrent stroke-90 day	**46 (1.96%)**	**15 (2.45%)**		**10 (1.73%)**			**14 (2.14%)**			**7 (1.39%)**		
Unadjusted			1 [Reference]		0.696 (0.312-1.550)	.3746		0.925 (0.466-1.917)	.8333		0.564 (0.230-1.384)	.2110
Adjusted			1 [Reference]		0.777 (0.346-1.747)	.5420		0.981 (0.468-2.057)	.9601		0.595 (0.241-1.465)	.2587
combined vascular events-1 year	**117 (4.98%)**	**32 (5.24%)**		**26 (4.51%)**			**39 (5.95%)**			**20 (3.96%)**		
Unadjusted			1 [Reference]		0.876 (0.522-1.470)	.6157		1.103 (0.691-1.761)	.6813		0.690 (0.395-1.208)	.1943
Adjusted			1 [Reference]		0.854 (0.500-1.458)	.5639		1.132 (0.706-1.816)	.6064		0.707 (0.403-1.242)	.2281
recurrent stroke-1year	**78 (3.32%)**	**21 (3.44%)**		**12 (2.08%)**			**29 (4.43%)**			**16 (3.17%)**		
Unadjusted			1 [Reference]		0.593 (0.292-1.206)	.1489		1.273 (0.726-2.232)	.4004		0.918 (0.479-1.759)	.7955
Adjusted			1 [Reference]		0.619 (0.304-1.264)	.1879		1.345 (0.760-2.381)	.3084		0.956 (0.497-1.839)	.8925

TABLE 3 Multivariable cox regression analyses about relationship of NTSBP and outcome at 90-day/1 year

		Nocturnal trough systolic blood pressure categories										
		NTSBP (quartile 1≤102mm hg)		NTSBP (102mm hg<quartile2≤115mm hg)			NTSBP (115mm hg<quartile 3≤129mm hg)			NTSBP (quartile4>129mm hg)		
	Total	Events	Reference	Events	HR (95% CI)	*p* value	Events	HR (95% CI)	*p* value	Events	HR (95% CI)	*p* value
combined vascular events-90 day	63 (2.68%)	7 (1.17%)		17 (2.88%)			16 (2.83%)			23 (3.87%)		
Unadjusted			1 [Reference]		2.352 (0.975-5.676)	.0570		2.472 (1.017-6.009)	.0458		3.472 (1.490-8.094)	.0039
Adjusted			1 [Reference]		1.933 (0.787-4.749)	.1508		2.195 (0.898-5.367)	.0848		2.727 (1.148-6.478)	.0231
recurrent stroke 90-day	46 (1.96%)	7 (1.17%)		13 (2.20%)			9 (1.59%)			17 (2.86%)		
Unadjusted			1 [Reference]		1.771 (0.706-4.441)	.2230		1.398 (0.521-3.754)	.5063		2.335 (0.968-5.633)	.0592
Adjusted			1 [Reference]		1.549 (0.611-3.930)	.3567		1.223 (0.452-3.313)	.6920		1.735 (0.701-4.296)	.2335
combined vascular events-1 year	117 (4.98%)	18 (3.01%)		36 (6.10%)			31 (5.49%)			32 (5.38%)		
Unadjusted			1 [Reference]		1.982 (1.125-3.492)	.0178		1.851 (1.035-3.308)	.0378		1.858 (1.043-3.310)	.0356
Adjusted			1 [Reference]		1.844 (1.035-3.284)	.0378		1.843 (1.026-3.311)	.0409		1.721 (0.950-3.119)	.0733
recurrent stroke-1year	78 (3.32%)	12 (2.01%)		24 (4.07%)			19 (3.36%)			23 (3.87%)		
Unadjusted			1 [Reference]		1.933 (0.966-3.865)	.0625		1.695 (0.823-3.491)	.1527		1.760 (0.875-3.538)	.1126
Adjusted			1 [Reference]		1.748 (0.868-3.523)	.1181		1.658 (0.801-3.434)	.1734		1.614 (0.788-3.303)	.1906

TABLE 4 Reclassification and discrimination statistics for outcomes within 90 days and 1 year by T-NTSBP

	C statistic		IDI		NRI (categorical)[a]	
	Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value
Outcomes within 90 d						
combined vascular events						
Conventional model [b]	0.706 (0.647–0.718)		Reference		Reference	
Conventional model+ T-NTSBP	0.703 (0.655–0.730)	.1342	12.12 (1.18–16.34)	.0083	−0.36 (−13.52–17.45)	.9734
recurrent stroke						
Conventional model b	0.659 (0.647–0.671)		Reference		Reference	
Conventional model+ T-NTSBP	0.663 (0.655–0.701)	.9077	9.13 (1.18–16.33)	.0332	7.13 (−4.97–17.44)	.4677
Outcomes within 1 y						
combined vascular events						
Conventional model b	0.685 (0.647–0.718)		Reference		Reference	
Conventional model+ T-NTSBP	0.690 (0.655–0.730)	.5808	4.21 (1.18–16.34)	.3549	3.37 (−13.52–17.45)	.7500
recurrent stroke						
Conventional model b	0.661 (0.647–0.672)		Reference		Reference	
Conventional model+ T-NTSBP	0.666 (0.655–0.701)	.7482	15.45 (1.18–16.34)	.0006	10.20 (4.97–17.45)	.2447

Abbreviations: CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification index; T-NTSBP, Time Point of Nocturnal Trough Systolic Blood Pressure.

[a]Patients were divided into four risk categories by T-NTSBP(22:00–23:59, 00:00–1:59, 2:00–3:59, 4:00–6:00).

[b]Conventional model: age, sex, smoking, drinking, medical history (atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia), secondary prevention drugs (antiplatelet, anti-hypertension, lipid-lowering, and anti-diabetic), NTSBP, and average nocturnal SBP.

observed at 1 year. Moreover, NTSBP and T-NTSBP seemed likely not to be associated with stroke recurrence, regardless at 90 days or 1 year.

A wide array of evidence shows that nocturnal BP during sleep is closely associated with cardiovascular events and organ damage in both general and hypertensive patients.[3,10–13] A large ABPM study demonstrated that nocturnal BP is more closely associated with CVE (stroke, myocardial infarction and cardiovascular death) than daytime BP.[12] Nocturnal BP variability results in a risk of CVE independently of the average of nocturnal BP,[25] especially in a patient with a riser pattern (higher nocturnal BP than daytime BP).[26,27] MBPS is a normal physiological phenomenon of the circadian clock, but high MBPS may lead to target organ damage and is associated with stroke and other adverse CVE.[28,24] In our study, the group of T-NTSBP at 22:00–23:59 had higher sleep-trough MBPS and incidence of CVE compare with the group at 4:00–6:00.These measures should have also been able to predict cardiovascular outcomes. Therefore, we verified that NTSBP and T-NTSBP was associated with CVE at 90 days, independent of average nocturnal SBP in this study. The Spanish ABPM Registry study showed that nocturnal SBP is the most powerful prognostic factor of CVE, after adjustment for possible confounders.[5] Average nocturnal SBP and nocturnal blood pressure pattern are not different among the groups classified by T-NTSBP in our study. This result could indicate that the prediction value of the T-NTSBP for CVE was independent of the nocturnal mean BP.

The mechanism by which T-NTSBP correlates with CVE is unclear. Circadian rhythm of BP is closely related to the circadian variation of sympathetic activity.[29] Average morning BP and sleep-trough MBPS will increase along with sympathetic activity. Our results found that sleep-trough MBPS and average morning BP was higher in the group of T-NTSBP at 22:00–23:59 compared with 4:00–6:00. This result may suggest that the earlier NTSBP appeared, the longer the duration of sympathetic excitation, which could lead to higher MBPS. On the other hand, the latter NTSBP appeared, the lower MBPS. This may be why the group of T-NTSBP at 4:00–6:00 has the lowest incident rate of CVE.

This study has some limitations. First, this study cohort included predominantly ischemic stroke and TIA participants, who have high cardiovascular risk factors. Therefore, these results may not directly apply to other cohorts with different population demographics. Second, because of the observational study design of our study, it is difficult to establish a causal relationship between T-NTSBP and CVE. Although we accounted for several potential confounders, especially average nocturnal SBP and secondary prevention drugs, we performed multivariate analyses adjusted for the main variables associated with major risk factors for cardiovascular disease. Thus, we cannot exclude the possibility of unmeasured confounders playing a role in the observed associations. Third, some potentially important covariates were lacking, such as sleep quality, sleep diary, and obstructive sleep apnea during ABPM performance. Poor sleep quality and nocturnal hypoxia during ABPM may not only increase NTSBP, but also change T-NTSBP.

TABLE 5 Reclassification and discrimination statistics for outcomes within 90 days and 1 year by NTSBP

	C statistic		IDI		NRI (continuous)		NRI (categorical)[a]	
	Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value
Outcomes within 90 d								
combined vascular events								
Conventional model [b]	0.706 (0.647–0.718)		Reference		Reference		Reference	
Conventional model+ T-NTSBP	0.704 (0.655–0.730)	.1463	8.56 (1.12–16.34)	.0941	29.50 (−33.83–54.54)	.2656	−4.29 (−13.52–17.45)	.68.59
recurrent stroke								
Conventional model [b]	0.659 (0.647–0.718)		Reference		Reference		Reference	
Conventional model+ T-NTSBP	0.660 (0.655–0.730)	.9130	2.68 (1.17–16.34)	.5902	15.34 (−33.83–54.54)	.5722	9.63 (−13.52–17.45)	.2114
Outcomes within 1 y								
combined vascular events								
Conventional model [b]	0.685 (0.647–0.718)		Reference		Reference		Reference	
Conventional model+ T-NTSBP	0.685 (0.655–0.730)	.8028	0.34 (0.00–16.34)	.9497	23.07 (−33.83–54.54)	.3788	3.37 (−13.52–17.45)	.7431
recurrent stroke								
Conventional model [b]	0.661 (0.647–0.718)		Reference		Reference		Reference	
Conventional model+ T-NTSBP	0.659 (0.655–0.730)	.8589	0.54 (0.00–16.34)	.9229	27.81 (−33.83–54.54)	.2931	2.55 (−13.52–17.45)	.7978

Abbreviations: CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification index; NTSBP, Nocturnal Trough Systolic Blood Pressure.

[a]Patients were divided into four risk categories by NTSBP quartiles.

[b]Conventional model: age, sex, smoking, drinking, medical history (atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia), .secondary prevention drugs (antiplatelet, anti-hypertension, lipid-lowering, and anti-diabetic) and average nocturnal SBP.

Fourth, doubts regarding the reproducibility of T-NTSBP and NTSBP have been raised because these findings were based on a single 24-h ABPM. Fifth, we did not collect a monitoring diary, so we used the fixed time points of day and night. The patients were hospitalized, and thus the sleep time was standardized. Sixth, this study did not use a uniform brand and model of automatic blood pressure monitors, but this study required that automatic blood pressure monitors must meet international standards and be clinically effective. Finally, this is an exploratory study lacking evidence of repeated comparisons, so further research should be done to confirmed.

5 | CONCLUSIONS

Both of NTSBP and T-NTSBP were important predictors for short-term cardiovascular risk in ischemic stroke and TIA patients. In the era of ABPM-guided management of hypertension, NTSBP and T-NTSBP may be simple and convenient prognostic indicators for cardiovascular risk. NTSBP and T-NTSBP by ABPM need more attention in future clinical practice.

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CONFLICT OF INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this review paper.

AUTHOR CONTRIBUTIONS

Jing Zhu, Xiwa Hao and Hefei Tang contributed equally to this work. Study concept and design: Hefei Tang, Yongjun Wang. Acquisition, analysis, or interpretation of data: Jie Xu; Anxin Wang; Xiaoli Zhang.

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