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The cumulative blood pressure load and target organ damage in patients with essential hypertension

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Abstract

The area under the blood pressure curve is associated with target organ damage, but accurately estimating its value is challenging. This study aimed to improve the utility of the area under the blood pressure curve to predict hypertensive target organ damage. This retrospective cohort study comprised of 634 consecutive patients with essential hypertension for >1 year. Target organ damage was defined as the presence of left ventricular hypertrophy and/or carotid artery plaques. We evaluated the associations between the cumulative blood pressure load, which was derived from ambulatory blood pressure monitoring data, and target organ damage. The predictive value of the cumulative blood pressure load for target organ damage was assessed using receiver operating characteristic curves. Left ventricular hypertrophy and carotid artery plaques were present in 392 (61.8%) and 316 (49.8%) patients, respectively. Patients with left ventricular hypertrophy and/or carotid artery plaques had higher 24-hour blood pressure, nocturnal cumulative systolic blood pressure, and nocturnal cumulative pulse pressure load. The nocturnal cumulative systolic blood pressure load was an independent predictor of left ventricular hypertrophy (odds ratio = 1.002, 95% confidence interval: 1.001-1.004; P = .000) and carotid artery plaques (odds ratio = 1.003, 95% confidence interval: 1.002-1.007; P = .007). The nocturnal cumulative systolic blood pressure and cumulative pulse pressure load, relative to mean blood pressure, were superior in predicting hypertensive target organ damage. Hence, the cumulative blood pressure load is a better indicator of blood pressure consequences, and the nocturnal cumulative systolic blood pressure and cumulative pulse pressure loads could predict target organ damage.

1 | INTRODUCTION

Hypertension is highly prevalent and is the leading preventable cause of all-cause death in the world.[1,2] Ambulatory blood pressure monitoring (ABPM) provides more comprehensive data to assess blood pressure (BP) changes throughout the day/night and better predict all-cause and cardiovascular mortality than clinic blood pressure.[3,4]

Zhou and Li contributed equally to this work.

Determining BP levels is the gold standard method for screening and diagnosing hypertension, and for monitoring the treatment of hypertension. However, estimating the magnitude of BP fluctuation, which is critical, can be achieved by the assessment and quantification of the specific BP variation in each patient.[5] Previous studies have shown that abnormal BP fluctuations are closely related to target organ damage (TOD), cardiovascular and cerebrovascular events, and mortality.[5] Some studies showed that the decline in nocturnal BP loses its predictive power for hypertensive TOD and cardiovascular mortality following adjustments that accounted for the 24-hour BP.[6] BP variability is associated with increased cardiovascular events, mortality, and TOD,[5,7] but its prognostic significance remains controversial, due, in part, to current methodological problems associated with the monitoring of BP variability that include poor reproducibility, association with BP level, and collinearity.[8] Thus, these authors[8] do not recommend BP variability as a target for hypertension management. New methods to determine BP variability are needed.

The BP load quantifies BP fluctuations above normal levels. However, the BP load calculated by traditional methods does not meaningfully refine risk predictions based on the 24-hour BP level.[9] The BP load only measures the proportion of how frequently BP readings exceed a predetermined threshold without providing any quantitative information.[10] Assessments of the BP load should integrate both the magnitude and the rate of BP elevations. The area under the curve (AUC) expressed in units of mm Hg × h could provide quantitative information that describes both the durations and the extents by which the BP exceeds a set threshold.[11] The area under the BP curve (BPAUC), which has been claimed to have no limitations regarding the BP load or 24-hour BP,[12] can be used to predict all-cause and cardiovascular mortality, and fatal and nonfatal events. By contrast, others have claimed that "adding BP load, either as percentage or as area under the curve, to models already including BP level, only marginally refined prediction." Thus, the actual predictive value of BPAUC remains elusive, because of the strong correlation between the BP level and BPAUC.[9] However, previous methods of calculating the BPAUC failed to consider some patients with normal BP levels but with abnormal BP fluctuations. Therefore, limitations remain regarding the methodology underlying the calculation of the BPAUC.

To address the above limitations, we improved the method used to calculate the BPAUC. The aims of this retrospective study were as follows: to improve the method used to calculate the BPAUC; to evaluate the BPAUC obtained by automated analyses; to correlate the BPAUC with other ABPM data, specifically, mean BP, BP load, and BP variation; and to explore the predictive value of the BPAUC in TOD in essential hypertension.

2 | METHODS

2.1 | Study setting and design and participants

In this retrospective cohort study, we followed 1593 essential hypertension inpatients from our department between January 2015 and December 2018, and finally involved 634 individuals according to the following inclusion criteria. The inclusion criterion was a diagnosis of essential hypertension according to the 2018 Chinese Guidelines for the Management of Hypertension: clinic systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg tested at three seperate visits or currently taking antihypertensive medication, for >1 year. Patients with secondary hypertension, cardiomyopathy, and congenital heart disease, and those who could not undergo 24-hour ABPM were excluded from the study. We evaluated the patients' medical histories, anthropometric measurements, and laboratory test results. We gathered data on serum creatinine, sodium, potassium, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and triglyceride, as well as venous blood fasting glucose levels. The study design was approved by the Army's Medical Center Ethics Committee and conducted in accordance with the principles of the Helsinki Declaration.

2.2 | Ambulatory blood pressure monitoring

All patients underwent 24-hour ABPM using a TM-2430 monitor (A&D). The daytime period was defined as the interval from 06:00 AM to 10:00 PM, during which time the BPs were recorded once every 30 minutes. The nighttime period was defined as the interval between 10:00 PM and 06:00 AM, during which time the BPs were recorded once every 60 minutes. These time definitions were based on the patient's daily routine. Valid 24-hour ABPM recordings comprised those with >80% of the total data recorded, ≥24 daytime BP readings, and ≥7 nighttime BP readings. The diagnostic thresholds for hypertension based on ABPM were a daytime systolic BP (SBP)/diastolic BP (DBP) ≥135/85 mm Hg, a nighttime SBP/DBP ≥ 120/70 mm Hg, and a 24-hour mean SBP/DBP ≥ 130/80 mm Hg.[1,13] The BP load was defined as the percentages of the SBP values ≥135 mm Hg or DBP values ≥85 mm Hg during the day, SBP values ≥120 mm Hg or DBP values ≥70 mm Hg at night, or SBP values ≥130 mm Hg or DBP values ≥ 80 mm Hg over 24 hours.[14] BP variability was calculated as the mean of the differences in the absolute values between consecutive BP readings.[15]

2.3 | Analysis of ambulatory blood pressure monitoring data

The cumulative BP load (cBPL) was defined as the area between the fluctuating ambulatory BP curve and the time axis. Fitting the fluctuating BP curve by connecting adjacent data points with straight lines was used to measure the magnitudes and durations of 24-hour cumulative BP increases. To calculate the cBPL, we deconstructed the curve into many small trapezoids, determined their areas, and added the values together (Figure 1).

Given two adjacent BP readings, BP_i and BP_{i+1}, at the time indices, τ_i and τ_{i+1}, respectively, an area, S_i, is defined as per equation.

$$S_i = \frac{(BP_i + BP_{i+1})}{2} \times (\tau_{i+1} - \tau_i)$$

The number of BP recordings (N) acquired during 24-hour ABPM enabled us to compute N−1 S_i, and all S_i values were summed to determine the cBPL. During ABPM, the results included serial time points (t_0–t_{n-1}) and the corresponding BP values (BP_1–BP_n). Since the ABPM device was programmed to record the BP, the time was fixed, and the cBPL in mm Hg × h is calculated, as follows:

$$cBPL = \sum_{i=1}^{n-1} S_i = \frac{\Delta t}{2} \sum_{i=1}^{n-1} (BP_i + BP_{i+1})$$

The cumulative pulse pressure load (cPPL) was defined as the area between the SBP curve and the DBP curve, which reflected the magnitudes and durations of the fluctuations in the cardiac cycles (Figure 1).

2.4 | Echocardiography

Echocardiography was performed using a Vivid 9 ultrasound system (GE Healthcare) with a 2.5 MHz probe. The left ventricular mass (LVM) and left ventricular mass index (LVMI) were calculated as recommended.[16,17]

2.5 | Carotid ultrasonography

The carotid intima-media thickness (IMT) and the presence of plaques were determined using a Vivid-E9 color Doppler ultrasound system (GE Healthcare) and 7.5 MHz linear array probes. A carotid IMT > 0.9 mm was considered abnormal.[1]

2.6 | Definition

TOD was defined as the presence of left ventricular hypertrophy (LVH) and/or carotid and/or renal function impaired. Cardiac damage was defined as the presence of left ventricular hypertrophy (LVH) as an LVMI > 115 g/m^2 in men and >95 g/m^2 in women.[1,13,17] Vascular damage was defined as the presence of carotid artery plaques as an IMT ≥ 1.5 mm or a focal increase in the thickness of 0.5 mm or 50% of the surrounding carotid IMT value,[1,18] or IMT thickening as IMT > 0.9 mm. Renal function impaired was defined as eGFR < 60 mL/min per 1.73 m^2. The glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.[19]

2.7 | Statistical analyses

The statistical analyses were performed using IBM® SPSS® software, version 22 (IBM Corporation). The K-S normality test method was used to check whether the data conform to the normal distribution. The normally distributed continuous variables are presented as the means and standard deviations (SDs). The non-normally distributed continuous data are presented as the medians with their interquartile ranges, and the categorical variables are presented as numbers and percentages. The Student *t* test, Mann-Whitney test, and chi-square tests were used to compare differences between groups. Pearson's or Spearman's correlation coefficients were used to evaluate the relationships between the cBPL and other variables. A multivariable logistic regression model was used to assess the factors associated with LVH and carotid artery plaques. The models were adjusted for age, sex, body mass index (BMI), smoking, fasting

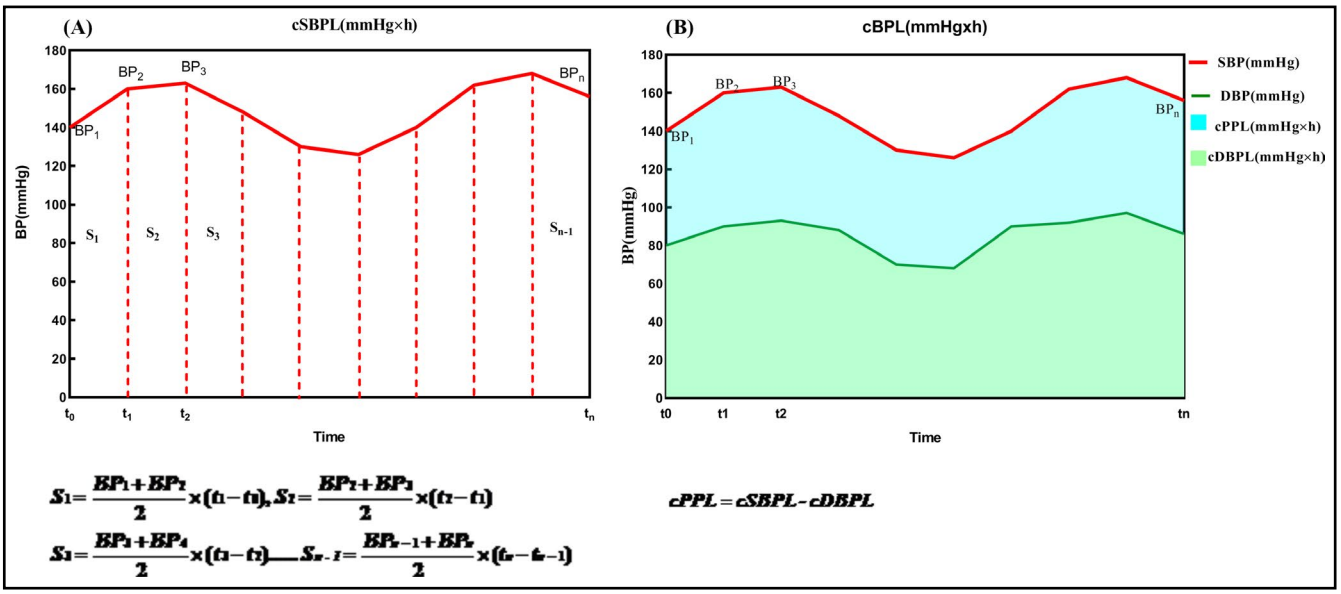

FIGURE 1 Blood pressure cumulative load example diagram. An example of a cumulative blood pressure load algorithm, t0 to tn are monitoring times, BP1 to BPn are systolic measured values at corresponding time points, and S1 to Sn-1 are the relevant trapezoidal areas. cSBPL, cumulative systolic blood pressure load; cDBPL, cumulative diastolic blood pressure load; cPPL, cumulative pulse pressure load

TABLE 1 General clinical characteristics of the patients

		LVH			Carotid plaque		
	Total (n = 634)	With LVH (n = 390)	Without LVH (n = 244)	*P* value	With carotid plaque (n = 316)	Without carotid plaque (n = 318)	*P* value
Male/Female	336/298	164/228	134/108		160/156	138/180	
Age (y)	61.6 ± 12.6	66.0 ± 11.9	61.9 ± 13.4	**<.001**	69.0 ± 11.5	59.7 ± 12.1	**<.001**
BMI (kg/m^2)	24.5 ± 3.4	25.0 ± 3.4	24.5 ± 3.5	.99	24.1 ± 3.5	25.0 ± 3.3	**.002**
Type 2 diabetes mellitus (%)	16	17	15	.67	17	16	.82
TIA/stroke (%)	12	12	11	.84	12	11	.82
CAD (%)	34	35	31	**<.001**	35	27	**.001**
History of smoking (%)	26	33	31	.07	40	23	.62
Laboratory parameters							
Cholesterol (mmol/L)	4.2 ± 1.0	4.1 ± 1.0	4.2 ± 1.0	.12	4.1 ± 1.0	4.2 ± 1.0	.16
Triglyceride (mmol/L)	4.8 ± 0.6	2.2 ± 0.9	1.7 ± 1.2	.17	1.6 ± 1.1	1.9 ± 1.4	.18
LDL-cholesterol (mmol/L)	3.7 ± 1.7	4.1 ± 2.1	3.2 ± 0.9	.55	3.0 ± 0.8	2.6 ± 0.7	.28
Glycemia (mmol/L)	5.1 ± 0.9	5.1 ± 1.0	5.0 ± 0.9	.37	5.1 ± 0.9	5.0 ± 0.9	.20
eGFR (mL/min/1.73 m^2)	110 ± 31	107 ± 31	114 ± 32	**.01**	117 ± 32	107 ± 31	**<.001**
Drugs (%)							
ACEIs	11.8	12.2	11.2	.33	10.7	13.0	.39
ARBs	24.3	26.4	28.9	.53	26.0	22.5	.31
β-blockers	12.3	12.5	12.0	.09	13.5	11.1	.39
CCBs	44.2	44.1	44.2	.53	49.2	45.6	.48
Diuretics	7.6	8.4	6.2	0.35	8.8	6.3	.29

Note: Data are shown as means ± standard deviation or percentage. The Student *t* test or chi-square test was used to assess between-group differences. Bold *P* values indicate significance.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CCBs, calcium channel blockers; eGFR, estimated glomerular filtration rateTIA, transient ischemic attack.

plasma glucose, TC, LDL-C, triglycerides, 24-hour SBP, hypertension duration, and antihypertensive. The areas under the receiver operating characteristic (ROC) curves were used to compare the predictive value of the cBPL and other ABPM parameters in relation to TOD. A value of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patients' characteristics

This study included 634 participants and 298 (47.0%) men, and their ages were between 38 years and 93 years (mean ± SD age: 64.5 ± 12.7 years). The mean duration of hypertension was 8.9 ± 8.4 years. Of the 634 participants, 168 patients (26.5%) had a history of smoking, 240 (33.8%) had coronary heart disease, 56 (8.8%) had type 2 diabetes, and 48 (7.6%) had cerebral infarctions. Three hundred and ninety-two patients (61.8%) had LVH, and 316 patients (49.8%) had carotid artery plaques. Among 634 patients, 192 patients (30.2%) received antihypertensive therapy, of which 11.8% of patients were taking ACEIs, 24.3% of patients were taking ARBs, 12.3% of patients were taking β-blockers, 44.2% of patients were taking CCBs, and 7.6% of patients were taking diuretics (Table 1).

Table 1 also shows the clinical characteristics of the patients with TOD who were grouped according to the presence of LVH or carotid artery plaques. The patients with TOD were older, and the patients with LVH or carotid artery plaques had a higher presence of coronary heart disease than the patients without carotid artery plaques ($P < .005$). eGFR was higher in those without LVH but lower in those with carotid plaques. The groups did not differ regarding the BMI; lipid profiles; glycemia; history of smoking, type 2 diabetes mellitus, or transient ischemic attacks/stroke; and antihypertensive medication.

3.2 | Associations between target organ damage and cumulative blood pressure load, and conventional ambulatory blood pressure parameters

Pearson's or Spearman's correlation coefficients were determined to assess the associations between the cBPL and conventional

ambulatory BP parameters, namely the mean BP, BP load, and BP variability. This analysis showed strong correlation between the cumulative SBP load (cSBPL) and 24-hour SBP (r = .748; P < .005; Figure 2A), as well as between SBP load (SBPL) and cSBPL (r = .72, P < .005; Figure 2B). There was also strong correlation between the cumulative DBP load (cDBPL) and 24-hour DBP (r = .732; P < .005; Figure 2D), as well as between DBP load (DBPL) and cDBPL (r = .686; P < .005; Figure 2E). In addition, strong correlations were evident between the cPPL and 24-hour SBP (r = .658; P < .005; Figure 2G), as well as between cPPL and SBPL (r = .637; P < .005; Figure 2H). The cSBPL and cDBPL weakly correlated with SBP variability (SBPV) and DBP variability (DBPV), respectively: cSBPL and SBPV (Figure 2C); cDBPL and DBPV (Figure 2F). There was a weak correlation between cPLL and SBPV (Figure 2I), and cPLL and DBPV (not shown).

Table 2 shows the comparisons of the cBPL parameters between the patients in whom TOD was present or absent. The SBP (daytime, nighttime, and 24-hour), pulse pressure (PP, daytime, nighttime, and 24-hour) and SBPL were slightly higher in the patients with LVH than in those without LVH group (P < .01). There were no significant differences between the patients with or without LVH regarding two of the 24-hour cBPL parameters (cSBPL and cDBPL) and cPPL. However, the nocturnal cSBPL and cPPL were significantly higher among the patients with LVH than those without LVH (P < .007 and P < .001, respectively). Except for the diurnal cSBPL, all the cBPL indices were significantly higher among the patients who had detectable carotid artery plaques than those who did not have carotid artery plaques (all P < .05). Besides, nighttime SBP and PP (daytime, nighttime, and 24-hour) were significantly higher among the patients who had detectable carotid artery plaques than those who did not have carotid artery plaques (all P < .01).

3.3 | Predictive value of the cumulative blood pressure load and conventional ambulatory blood pressure parameters for target organ damage

The multivariable logistic regression analyses (Table 3) showed that the nocturnal cSBPL, 24-hour cSBPL, nocturnal cPPL, and 24-cPPL and the conventional ABPM parameter 24-hour SBP and 24-hour PP were associated with LVH in the unadjusted model. After adjusting the model with other cardiovascular risk factors, only the nocturnal cSBPL and 24-hour PP were independently associated with LVH (P < .05). In the unadjusted model, nocturnal and 24-hour SBP, 24-hour PP, nocturnal and 24-hour cSPBL, and nocturnal and 24-hour cPPL were associated with the presence of carotid plaques. However, after adjusting the model, only the nocturnal cSBPL and nocturnal cPPL and 24-hour PP were associated with the presence of carotid artery plaques.

The ROC analyses evaluated the sensitivity and specificity of the cBPL in relation to predicting TOD (Table 4). Regarding the prediction of LVH, the AUC for the nocturnal cSBPL was 0.58 (sensitivity: 28%; specificity: 86%) and the AUC for the nocturnal cPPL was 0.58 (sensitivity: 60%; specificity: 55%). The AUC for 24-hour cSBPL was 0.58 (sensitivity: 38%; specificity: 72%), and the AUC for 24-hour cPPL was 0.56 (sensitivity: 44%; specificity: 69%). Regarding the prediction of carotid artery plaques, the AUC for nocturnal cSBPL was 0.56 (sensitivity 43%, specificity 68%) and the AUC for nocturnal cPPL was 0.62 (sensitivity 66%, specificity 54%). The AUC for 24-hour cSBPL was 0.57 (sensitivity: 69%; specificity: 44%), and the AUC for 24-hour cPPL was 0.62 (sensitivity: 73%; specificity: 47%).

To determine which ABPM parameters have the highest predictive value for hypertensive target organ damage, we performed a ROC curve comparison (Figure 3). Under LVH criteria, no differences were observed among nighttime SBP, mean SBP, SBPL, cSBPL, and

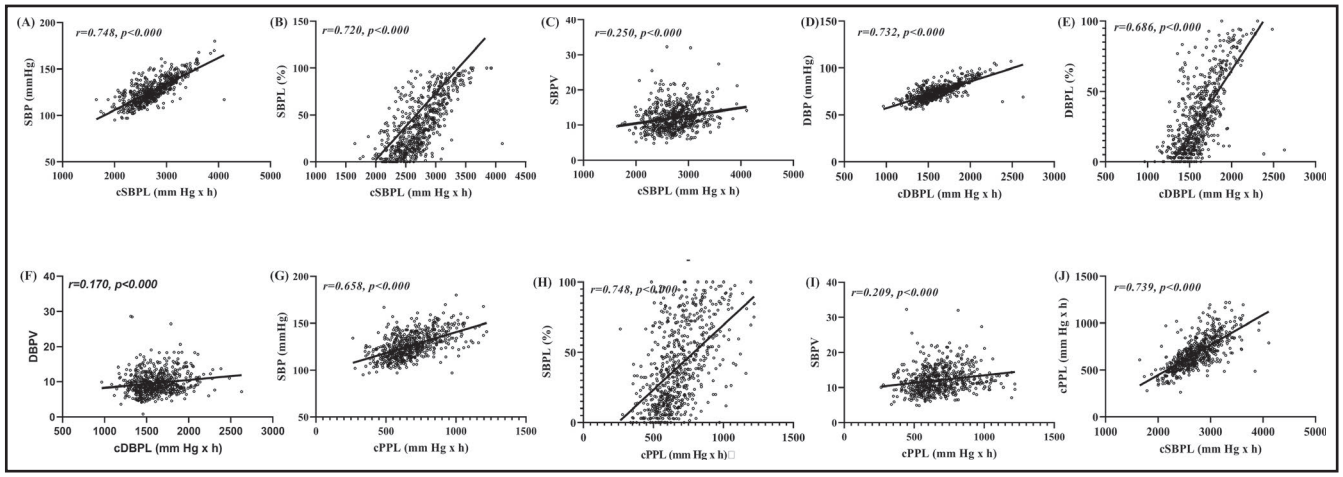

FIGURE 2 Correlation between cBPL and blood pressure load and mean blood pressure. cDBPL, cumulative diastolic blood pressure load; cPPL, cumulative pulse pressure load; DBP, diastolic blood pressure; DBPL, diastolic blood pressure load; cSBPL, cumulative systolic blood pressure load; SBP, systolic blood pressure; SBPL, systolic blood pressure load. Correlation with blood pressure load and mean blood pressure by Spearman's correlation coefficients. A, SBP and cSBPL correlation; B, SBPL and cSBPL correlation; C, SBPV and cSBPL correlation; D, DBP and cDBPL correlation; E, DBPL and cDBPL correlation; F, DBPV and cDBPL correlation; G, SBP and cPPL correlation; H, SBPL and cPPL correlation; I, SBPV and cPPL correlation; J, cSBPL and cPPL correlation

TABLE 2 Comparison of patients' ABPM data according to the presence or absence of LVH and carotid plaque

	LVH			Carotid plaque		
	With LVH (n = 390)	Without LVH (n = 244)	*P* value	With carotid plaque (n = 316)	Without carotid plaque (n = 318)	*P* value
Daytime SBP (mm Hg)	127 (119-137)	125 (117-133)	**.01**	127 (118-136)	125 (117-136)	.36
Daytime DBP (mm Hg)	75 (70-8)	75 (69-80)	.97	73 (69-80)	76 (70-82)	**.000**
Nighttime SBP (mm Hg)	123 (112-135)	119 (107-129)	**.000**	123 (112-134)	120 (107-131)	**.01**
Nighttime DBP (mm Hg)	70 (65-77)	69 (64-75)	.05	69 (65-75)	70 (65-7)	.08
24-h SBP (mm Hg)	126 (118-137)	123 (115-132)	**.010**	125 (118-136)	124 (115-134)	.33
24-h DBP (mm Hg)	74 (69-80)	74 (68-78)	.58	73 (67-78)	75 (70-80)	**.000**
Daytime PP (mm Hg)	52 (45-5)	48 (43-56)	**.000**	52 (46-61)	48 (44-56)	**.000**
Nighttime PP (mm Hg)	52 (43-60)	48 (40-57)	**.000**	53 (46-61)	47 (40-57)	**.000**
24-h PP (mm Hg)	52 (45-59)	47(43-55)	**.000**	53 (46-61)	48 (43-55)	**.000**
SBPL (%)	38 (16-48)	31 (13-54)	**.007**	37 (16-62)	33 (13-62)	**.000**
DBPL (%)	25 (10-48)	27 (10-47)	.59	21 (9-41)	33 (13-56)	.08
SBPV	11.5 (9.6-14.1)	11.7 (9.4-13.6)	.96	11.9 (9.7-14.1)	11.3 (9.3-13.8)	.05
DBPV	9.1 (7.6-11.2)	9.1 (7.6-10.7)	.72	9.2 (7.8-11.2)	8.8 (7.3-11.1)	.14
Daytime cSBPL(mm Hg × h)	1692 (1503-1870)	1689 (1502-1855)	.93	1708 (1508-1877)	1670 (1500-1836)	.12
Daytime cDBPL(mm Hg × h)	996 (982-1089)	1011 (904-1147)	.46	986 (890-1083)	1015 (909-1142)	**.01**
Nighttime cSBPL(mm Hg × h)	1043 (943-1157)	1005 (915-1099)	**.007**	1043 (956-1147)	1013 (913-1111)	**.008**
Nighttime cDBPL(mm Hg × h)	599 (552-660)	593 (546-643)	.28	593 (541-645)	602 (553-664)	**.04**
24-h cSBPL(mm Hg × h)	2723 (2485-2991)	2682 (2458-2927)	.28	2740 (2501-3012)	2647 (2447-2953)	**.01**
24-h cDBPL(mm Hg × h)	1594 (1454-1739)	1582 (1454-1762)	.80	1577 (1431-1718)	1604 (1478-1785)	**.01**
Daytime cPPL(mm Hg × h)	672 (569-794)	642 (565-758)	.06	691 (588-815)	617 (553-730)	**.000**
Nighttime cPPL(mm Hg × h)	425 (355-499)	396 (325-481)	**.001**	436 (364-513)	392 (327-475)	**.000**
24-h cPPL(mm Hg × h)	1091 (948-1283)	1035 (902-1220)	**.02**	1129 (982-1321)	1022 (894-1205)	**.000**

Note: Bold *P* values indicate significance.

Mann-Whitney test.

Abbreviations: cDBPL, cumulative diastolic blood pressure load; cPPL, cumulative pulse pressure load; cSBPL, cumulative systolic blood pressure load; DBP, diastolic blood pressure; DBPL, diastolic blood pressure load; DBPV, diastolic blood pressure variability; PP, pulse pressure; SBP, systolic blood pressure; SBPL, systolic blood pressure load; SBPV, systolic blood pressure variability.

cPPL. Under the carotid plaque standard, 24-hour cPPL had a higher predictive value than nighttime SBP (z = 2.72, P = .001). Nighttime cPPL had a higher predictive value than nighttime SBP (z = 3.31, P < .009).

4 | DISCUSSION

The present study indicates that the cBPL, which was derived from a computerized analysis of ABPM data using the new methods, was superior to conventional ambulatory BP parameters in predicting TOD, especially with carotid plaques. The cBPL was significantly associated with the average BP, BP load, and BP variability. The nocturnal cSBPL was greater in the patients with hypertension and TOD (LVH and carotid plaque) than those without TOD. Nocturnal cPPL was also greater in the patients with hypertension and carotid plaque than those without carotid plaque. These results suggest that the cSBPL and cPPL can specifically predict hypertensive TOD and that particular attention should be given to the magnitudes and durations of nocturnal BP fluctuations when managing patients with hypertension.

Currently, most of the major randomized controlled trials on hypertension used clinic or home BP readings. ABPM is often used as supplements to office BP readings. Recently, in addition to mean BP, the magnitude of BP fluctuation has gained more interest. Many traditional ABPM parameters are used to assess the BP fluctuations, but there are many limitations using the current methods. In general, the BP variability index, the predictive value of BP variability,

TABLE 3 Multiple logistic regression analyses for prediction of LVH and carotid plaque

Parameter	Unadjusted OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
LVH				
SBPL (%)	1.01 (1.004-1.016)	**.001**	0.996 (0.979-1.013)	.66
SBPV	1.024 (0.979-1.072)	.30	0.998 (0.950-1.048)	.93
Nighttime SBP (mm Hg)	1.007 (0.992-1.022)	.37	1.004 (0.989-1.019)	.62
24-h SBP (mm Hg)	1.024 (1.012-1.038)	**.000**	1.033 (0.991-1.077)	.12
Nighttime PP (mm Hg)	1.006 (0.991-1.002)	.41	1.005 (0.989-1.021)	.53
24-h PP (mm Hg)	1.046 (1.008-1.085)	**.01**	1.041 (1.001-1.081)	**.04**
Nighttime cSBPL (mm Hg × h)	1.002 (1.001-1.003)	**.001**	1.002 (1.001-1.004)	**.000**
24-h cSBPL (mm Hg × h)	1.001 (1.000-1.003)	**.02**	1.000 (0.999-1.001)	.51
Nighttime cPPL (mm Hg × h)	1.002 (1.001-1.004)	**.003**	1.000 (0.999-1.005)	.96
24-h cPPL (mm Hg × h)	1.001 (1.000-1.001)	**.02**	0.999 (0.997-1.001)	.37
Carotid plaque				
SBPL (%)	1.003 (0.997-1.008)	.34	0.986 (0.968-1.003)	.10
SBPV	1.033 (0.998-1.079)	.15	1.013 (0.963-1.065)	.61
Nighttime SBP (mm Hg)	1.015 (0.997-1.034)	**.009**	1.011 (0.992-1.029)	.26
24-h SBP (mm Hg)	1.049 (1.031-1.067)	**.000**	1.004 (0.963-1.047)	.85
Nighttime PP (mm Hg)	1.012 (0.996-1.029)	.15	1.010 (0.992-1.028)	.28
24-h PP (mm Hg)	1.058 (1.019-1.098)	**.003**	1.055 (1.010-1.101)	**.01**
Nighttime cSBPL (mm Hg × h)	1.002 (1.001-1.003)	**.004**	1.003 (1.002-1.005)	**.000**
24-h cSBPL (mm Hg × h)	1.001 (1.000-1.001)	**.01**	1.000 (0.999-1.001)	.66
Nighttime cPPL (mm Hg × h)	1.004 (1.002-1.005)	**.000**	1.002 (1.001-1.004)	**.004**
24-h cPPL (mm Hg × h)	1.002 (1.001-1.002)	**.000**	1.001 (0.998-1.003)	.53

Note: Bold *P* values indicate significance.

Multivariable model is adjusted for age, sex, body mass index, smoking, fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, triglycerides, 24-h systolic blood pressure, hypertension duration, and antihypertensive.

Abbreviations: CI, confidence interval; cPPL, cumulative pulse pressure load; cSBPL, cumulative systolic blood pressure load; LVH, left ventricular hypertrophy; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; SBPL, systolic blood pressure load; SBPV, systolic blood pressure variability.

which is based on SDs and coefficients of variation in 24-hour average ABPM data, does not consider the temporal order of the BP readings.[5] The time rate of BP variation measures the steepness and speed of BP changes, but does not reflect high-frequency short-term BP fluctuations.[20] The average real variability index, which focuses on changes that occur over short intervals, is a better estimator of 24-hour BP variability than other measures of dispersion.[7,15] However, the findings from studies of the International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome indicated that BP variability above the 24-hour BP level was of little independent prognostic significance.[6,7] BP load based on the proportion of BP readings above a set threshold or the integrated area under a BP curve above the same value was associated with TOD.[21-23] Li et al proposed that the nighttime BP load was a significant factor for predicting all-cause mortality, cardiovascular mortality, and renal and cardiovascular events.[24] The BP load expressed as a percentage only measures the frequency of blood pressure readings that exceed a predetermined threshold, without providing

TABLE 4 ROC of cBPL and conventional ABPM parameter in predicting TOD

	AUC	95% CI	Sensitivity (%)	Specificity (%)	Cut	*P* value
LVH diagnostic criterion						
Nighttime SBP (mm Hg)	0.58	0.54-0.62	67	47	>115	**.000**
24-h SBP (mm Hg)	0.58	0.53-0.62	60	49	>122	**.001**
SBPL (%)	0.57	0.53-0.62	46	68	>44	**.002**
SBPV	0.51	0.47-0.56	19	87	>15.3	.585
Nighttime cSBPL (mm Hg × h)	0.58	0.54-0.62	28	86	>1135	**.000**
Nighttime cPPL (mm Hg × h)	0.58	0.54-0.62	60	55	>4050	**.000**
24-h cSBPL (mm Hg × h)	0.58	0.50-0.59	38	72	>2866	**.027**
24-h cPPL (mm Hg × h)	0.56	0.52-0.61	44	69	>1138	**.008**
Carotid plaque diagnostic criterion						
Nighttime SBP (mm Hg)	0.55	0.51-0.59	88	23	>106	**.001**
24-h SBP (mm Hg)	0.54	0.49-0.58	67	41	>120	.117
SBPL (%)	0.53	0.48-0.57	65	44	>26	.250
SBPV	0.54	0.50-0.59	88	22	>8.9	.057
Daytime cPPL (mm Hg × h)	0.61	0.56-0.64	69	52	>620	**.000**
Nighttime cSBPL (mm Hg × h)	0.56	0.52-0.60	43	68	>1072	**.005**
Nighttime cPPL (mm Hg × h)	0.62	0.57-0.65	66	54	>400	**.000**
24-h cSBPL (mm Hg × h)	0.57	0.51-0.59	69	44	>2599	**.013**
24h cPPL (mm Hg × h)	0.62	0.58-0.66	73	47	>1000	**.001**

Note: Bold *P* values indicate significance.

Abbreviations: AUC, area under the curve; CI, confidence interval; cPPL, cumulative pulse pressure load; cSBPL, cumulative systolic blood pressure load; ROC, receiver operator characteristic; SBP, systolic blood pressure; SBPL, systolic blood pressure load; SBPV, systolic blood pressure variability.

any quantitative information. The BP load, expressed as the BPAUC, only included the data above the set thresholds, and data describing the prognostic role of abnormal BP fluctuations in patients with normal mean BP levels are lacking.[11,12,14] While the cBPL is a component of the BPAUC, it also includes the area between the fluctuating BP curve and the time axis. The calculation of the cBPL does not depend on the average BP, but rather reflects the extents and durations of the cumulative rises in BP, which comprises the SBP, DBP, and pulse pressure. The cBPL reflects the BP trend. Therefore, if BP data are not recorded during dynamic BP monitoring, the cBPL fills the gaps in the data that occur during periods when recordings are absent. Moreover, the method of fitting the fluctuating BP curve involves connecting adjacent data points with straight lines. By increasing the monitoring frequency, the cBPL can reflect BP fluctuations more accurately. Moreover, cBPLs calculated by our methods were superior in predicting TOD than mean BPs or traditional ABPM parameters used for BP variability prediction.

In our study, we found significant increases in the nocturnal cSBPL and cPPL among the patients with hypertensive TOD, but we did not find significant increases in the BP variability. Moreover, the nocturnal cSBPL and cPPL had relatively high predictive values for hypertensive TOD. Thus, the cBPL may play an important, useful, and wide-ranging role in the evaluation of ABPM data. The cBPL may be a useful criterion for analyzing ABPM data and may

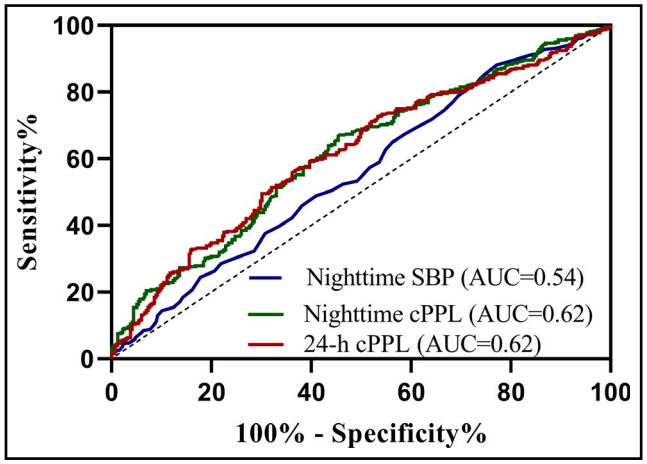

FIGURE 3 Comparison of ROC curves of 24-h PP, nighttime PP, and nighttime SBP in predicting carotid plaque. cPPL, cumulative pulse pressure load; SBP, systolic blood pressure

comprehensively reflect the characteristics of BP fluctuations. We suggest that the cBPL comprehensively represents the average BP level and its fluctuations, which may provide more useful information for assessing and managing patients with hypertension.

Our data demonstrated that the nocturnal cBPL is a better predictor of TOD. This finding concurs with those from previous studies of patients with hypertension who showed that a higher nocturnal BP level was associated with TOD and an independent predictor of cardiovascular disease and mortality.[25-28] Nocturnal hypertension leads to cardiovascular events, including stroke, acute heart failure, and coronary artery disease, and age-related TOD.[29] Therefore, managing nocturnal BP is essential to prevent cardiovascular events, especially as related to TOD.[30] In most countries, early morning drug administration is currently the drug treatment scheme of hypertension patients. This drug administration scheme takes into consideration the diurnal BP but may not treat nocturnal hypertension. Recently, many studies of chronotherapy have studied comorbid populations, including obstructive sleep apnea, chronic kidney disease, and diabetes. In our study, we found a significant increase in nocturnal cSBPL and cPPL in hypertensive patients with TOD. Therefore, the nocturnal administration of antihypertensive agents should be considered seriously for managing hypertension in the general population, and especially in patients with hypertension and certain comorbidities.[31-33]

The results of this retrospective cohort study should be interpreted in the context of its limitations. First, this was a single-center cohort study and all of the study participants were inpatients. Thus, some outpatients with hypertension who presented with TOD might have been excluded and may have biased the results. Second, the ABPM was set at 30-minutes intervals during the day and at 60-minutes intervals during the night in our study; these frequencies of BP monitoring would not be able to record relatively short-term BP fluctuations. Third, a small proportion of the patients in the study were on antihypertensive medications, and therefore, the effects of the drugs on the results cannot be ruled out. Finally, our study cohort comprised patients who had been hypertensive for >1 year. From our data, it is impossible to deduce the predictive value of the cBPL among people with normal blood pressure or patients with risk factors, including obesity, smoking, and hyperlipidemia.

4.1 | Perspectives

Our study provides the first data concerning the predictive value of cBPL and TOD in hypertension assessed by ABPM data analysis. The research shows that the cBPL can better reflect the characteristics of BP itself, and has a predictive value for TOD of hypertension. Additional studies are needed to investigate the clinical significance of cBPL in normotensive patients and patients with normal BP with high-risk factors, and prospectively evaluate the importance of cBPL on cardiovascular risk stratification.

5 | CONCLUSIONS

cBPL may be a better two-dimensional parameter of ABPM, which reflects blood pressure characteristics. Both the nocturnal cSBPL and cPPL are associated with TOD, which might be a predictor of TOD in patients with hypertension.

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CONFLICT OF INTERESTS

No potential conflicts of interest were disclosed.

AUTHOR'S CONTRIBUTIONS

CZ, BZ, and CL contributed to research idea and designed the study; BZ, CL, JS, YZ, and CW acquired the data; CZ, BZ, CL, JS, YZ, and CW analyzed and interpreted the data; BZ, CL, and CZ performed the statistical analysis; and CZ supervised the study and contributed to mentorship. Each author contributed to important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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