A Count-Based Binary Decision Method For Target Blood Pressure Achievement in Home Blood Pressure Monitoring Data Interpretation For Clinical Practices

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Research Article

Keywords: Count-based binary decision method, numbers of high blood pressure readings, home blood pressure monitoring, simulation, diagnostic performance

Posted Date: July 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-728435/v1

Version of Record: A version of this preprint was published at Scientific Reports on March 10th, 2022. See the published version at https://doi.org/10.1038/s41598-022-04913-9.

Abstract

Home blood pressure (HBP) is useful to decide whether blood pressure (BP) is controlled. However, applying HBP to daily clinical practices is still challenging without easy access to the average HBP. Therefore, we developed a simple method to make a binary decision for the control of HBP through high BP counts. We simulated 100 cases of HBP series for each combination of 3 numbers of BP readings (K = 16, 20, 24) and 4 levels of the standard deviations (SDs = 5, 10, 15, 20). A high BP was defined as an individual BP ≥ 135/85 mmHg, and an uncontrolled HBP was defined as a mean HBP ≥ 135/85 mmHg. Validation for the decision method was conducted using actual HBP data. The C-statistics and the accuracy of the high BP counts for the uncontrolled HBP were generally high (> 0.85) for all combinations of Ks and SDs but decreased as SDs increased but remained steady as Ks increased. In the validation, the C-statistic of the high BP count-to-total BP reading (C-T) ratio was 0.985, and a C-T ratio ≥ 0.5 showed a sensitivity of 0.957, a specificity of 0.907 and an accuracy of 0.927. The count-based decision method can provide an accurate quick assessment of the controlledness of HBP.

Introduction

Hypertension is one of the most important risk factors for cardiovascular events and deaths[1]. Home blood pressure (HBP) has been reported to be useful to detect hypertension and provide guidance on the treatment of hypertension[2]. As an alternative to ambulatory blood pressure monitoring (ABPM), HBP monitoring (HBPM) can be used for classifying hypertension phenotypes, including masked and white-coat (uncontrolled) hypertension; thus, it may have prognostic and therapeutic implications[3–5]. HBPM is also known to correlate better with target organ damage and cardiovascular outcomes than clinical BP[6,7]. Since clinical BP has been reported to be higher than home BP[8], guidelines recommend preferring home BP to clinical BP in diagnosing hypertension and guiding antihypertensive therapy when there is a discrepancy between HBP and clinical BP[9].

However, employing HBPM in daily practice may impose a substantial burden on physicians because the calculation of mean BP from HBP records could be cumbersome and time-consuming, especially when assistance or resources are insufficient in the clinic. It would be difficult for physicians to make a quick decision regarding whether target BP is achieved without ready-to-use analysis of the HBP records. This difficulty acts as a barrier to stop broadening the use of HBPM in daily practice[10,11]. Some HBPM devices provide built-in systems or solutions allowing storage and transfer of BP records through Bluetooth or wireless internet technology. However, these new electronic devices may not be familiar to elderly individuals, the most frequent type of hypertensive patient, and the majority of HBPM devices still do not include such systems or solutions.

HBPM is known to be effective in improving patient adherence, allowing patients to engage in self-management or self-monitoring of BP[12]. Because differences in perceiving BP levels between patients and physicians are evident, HBPM may play an important role in achieving a common understanding of the diagnosis and treatment of hypertension between patients and physicians[13]. Moreover, keeping a journal of patients' own HBP in a logbook would encourage them to take active roles in hypertension management and may have beneficial cognitive impact on their understanding of hypertension[13].

In this regard, despite technological improvements in HBPM devices, physicians still need simple and accurate methods to interpret HBPM results to broaden the use of HBPM in daily clinical practice. Therefore, we created a simple count-based method to make a quick binary decision regarding whether the BP was controlled using simulated BP series and validated the count-based method in a real-world HBPM dataset.

Results

Simulated BPs

We simulated 100 mean systolic BPs (SBPs) between 130 and 140 mmHg and paired 100 mean diastolic BPs (DBPs) using a random number generating function in the statistical software R. Then, around the mean SBPs and DBPs, we simulated HBPM series with 3 different numbers of BP readings (K = 16, 20 and 24) and 4 different standard deviation (SD) levels (SD = 5, 10, 15 and 20 mmHg) using another function generating random numbers with normal distributions. Because there are 12 possible combinations between Ks and SDs, 1200 cases of HBPM series were generated. The detailed methods for the simulation are described with R codes in the Methods section and Supplementary Data S1, and the entire simulated BP dataset is provided in Supplementary Data S2.

A high BP reading was defined as an individual SBP ≥ 135 mmHg and/or DBP ≥ 85 mmHg, and an uncontrolled BP was defined as a mean SBP ≥ 135 mmHg and/or DBP ≥ 85 mmHg. In the simulated BP cohort, the C-statistics of the high SBP and DBP counts in the receiver operating characteristic (ROC) curve analysis for uncontrolled SBP and DBP at all combinations of Ks and SDs were higher than 0.9 (Table 1), except that the C-statistic of the high SBP counts for uncontrolled SBP at K = 24 and SD = 20 mmHg was 0.868 (95% confidence interval [CI], 0.803–0.934). In general, C-statistics were higher when the SD levels were lower, while they appeared to be indifferent as the K values changed (Table 1). The best threshold of the high BP counts was ≥ 8 or 9 for a K of 16, ≥ 10 or 11 for a K of 20 and ≥ 11–13 for a K of 24, which were all near half of Ks (Supplementary Table S1). At the best thresholds, most sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs) and correct classification rates (CCRs) were higher than 0.8, although in general, the diagnostic performance indexes decreased as the SD level increased (Table 1 and Supplementary Table S1).

Table 1
C-statistics of the high BP counts for the uncontrolled BP

	SBP		DBP	
K	SD	C-statistics	SD	C-statistics
24	5	0.970 (0.945–0.996)	3.5	1.000 (1.000–1.000)
	10	0.933 (0.891–0.976)	7	0.983 (0.964-1.000)
	15	0.933 (0.887–0.979)	10.5	0.974 (0.950–0.998)
	20	0.868 (0.803–0.934)	14	0.966 (0.938–0.994)
20	5	0.984 (0.968-1.000)	3.5	0.996 (0.991-1.000)
	10	0.961 (0.932–0.991)	7	0.988 (0.971-1.000)
	15	0.933 (0.890–0.976)	10.5	0.986 (0.969-1.000)
	20	0.919 (0.869–0.968)	14	0.948 (0.911–0.985)
16	5	0.973 (0.945-1.000)	3.5	0.998 (0.993-1.000)
	10	0.944 (0.903–0.986)	7	0.978 (0.959–0.998)
	15	0.954 (0.922–0.988)	10.5	0.965 (0.938–0.992)
	20	0.920 (0.871–0.969)	14	0.911 (0.855–0.967)

K, the number of BP measurements; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure

When the threshold was set to 8, 10 and 12, half of *K*s, most diagnostic performance indexes remained similarly high as those at the best thresholds, except that the CCR for uncontrolled SBPs at a *K* of 24 and an SD of 20 mmHg was 0.76 (Table 2). Similar to the results with the best thresholds, the diagnostic performance indexes at half of *K*s decreased as SDs increased, while they appeared to be indifferent as *K*s changed.

Table 2
Diagnostic performance of the count-based decision method at the half of Ks for uncontrolled BP in the simulated cohort

	SBP							DBP					
K	SD	Uncontrolled SBP (N = 100)	Sensitivity	Specificity	PPV	NPV	CCR	SD	Uncontrolled DBP(N = 100)	Sensitivity	Specificity	PPV	NPV
24	5	50	0.907	0.895	0.867	0.927	0.90	3.5	54	1.000	1.000	1.000	1.000
threshold ≥ 12	10	50	0.880	0.800	0.815	0.870	0.84	7	56	1.000	0.867	0.902	1.000
	15	49	0.878	0.902	0.896	0.885	0.89	10.5	57	0.912	0.930	0.945	0.889
	20	48	0.854	0.673	0.707	0.833	0.76	14	53	0.962	0.766	0.823	0.947
20	5	44	0.980	0.882	0.889	0.978	0.93	3.5	51	0.980	0.959	0.962	0.979
threshold ≥ 10	10	54	0.918	0.902	0.900	0.920	0.91	7	47	0.957	0.906	0.900	0.960
	15	49	0.860	0.780	0.796	0.848	0.82	10.5	53	0.943	0.957	0.962	0.938
	20	50	0.907	0.719	0.709	0.911	0.80	14	54	0.889	0.848	0.873	0.867
16	5	48	0.958	0.904	0.902	0.959	0.93	3.5	51	0.980	0.939	0.943	0.979
threshold ≥ 8	10	50	0.918	0.902	0.900	0.920	0.88	7	53	0.962	0.830	0.864	0.951
	15	54	0.907	0.761	0.817	0.875	0.84	10.5	56	0.929	0.841	0.881	0.902
	20	51	0.863	0.816	0.830	0.851	0.84	14	53	0.943	0.766	0.820	0.923

K, The number of BP measurements; SBP, systolic blood pressure; DBP, diastolic blood pressure; PPV, positive predictive value; NPV, negative predictive value; correct classification rate

Uncontrolled SBP/DBP were defined as the mean SBP ≥ 135 mmHg or the mean DBP ≥ 85 mmHg

To compare the C-statistics and CCRs among the levels of *K*s and SDs, we generated 2,000 bootstrap samples of the 100 cases of HBPM for each combination of Ks and SDs, subsequently producing 24,000 bootstrap resampling data of the C-statistics and CCRs. The C-statistics and CCRs were compared using a mixed linear effect model in which the variations within a combination of *K*s and SDs were set to be the random effect and the variations among *K*s and SDs were set to be the fixed effect. Detailed methods for the bootstrap resampling and mixed linear effect models are described in the Methods

section and Supplementary data S1 (as R codes), and the entire bootstrap resampling data are provided in Supplementary Data S3. The mixed linear effect models using the bootstrap samples showed that the C-statistics of the high BP counts for uncontrolled SBPs and DBPs decreased as SDs increased, while they did not significantly differ among *K*s. The decreases in the C-statistics for uncontrolled DBPs were stiffer as *K*s decreased (Fig. 1). Similar to the C-statistics, CCRs for uncontrolled SBPs and DBPs decreased as SDs increased, while they did not change with *K*s. In general, C-statistics for uncontrolled DBPs were higher than the C-statistics for uncontrolled SBPs (median [interquartile range]: 0.982 [0.964–0.995] vs. 0.947 [0.922–0.969] for C-statistics, and 0.93 [0.88–0.97] vs. 0.87 [0.83–0.90] for CCRs; $p < 0.001$ for both in a Mann-Whitney test).

Linear regression models showed that the high SBP/DBP counts were linearly associated with mean SBP/DBP, while the association strengths decreased and widths of 95% prediction intervals of the linear models increased for both SBP and DBP as SDs increased (Fig. 2A for SBP; Fig. 2B for DBP). For an SD of 5 mmHg (3.5 mmHg for DBPs), high BP counts ≥ 15 (62.5%) and ≤ 9 (37.5%) of 24 BP readings predicted uncontrolled BP and controlled BP, respectively, at a 95% confidence level (Fig. 2). For the other SDs, high BP counts ≥ 16 (66.7%) and ≤ 8 (33.3%) of 24 BP readings predicted uncontrolled BP and controlled BP, respectively, with 95% confidence.

Validation

Validation for the count-based decision method was performed using HBPM data obtained from 412 patients on antihypertensive medications. The detailed methods for the data collection are described in the Methods section, and the HBPM dataset used for the validation is provided in Supplementary Data S4 and S5. In the validation cohort, the age was 58.4±12.1 years, and 217 patients (52.7%) were females. Body mass index (BMI) was 25.4±13.2 kg/$m^{2,}$ and diabetes was found in 47 patients (11.4%). The mean SBP was 128.2±14.8 mmHg (ranging between 89.1-182.8 mmHg), and the mean DBP was 79.9±9.7 mmHg (ranging between 52.0-125.4 mmHg). Uncontrolled BP (≥ 135/85 mmHg) was prevalent in 40.3% (n = 166), uncontrolled SBP in 27.9% (n = 115) and uncontrolled DBP in 29.1% (n = 140). The number of patients with mean SBPs ranging between 130–140 mmHg was 108 (26.2%), and the number of patients whose mean DBP ranged between 80–90 mmHg was 147 (35.7%).

Because, unlike the numbers of simulated BP readings with 3 fixed levels, the numbers of actual HBP readings varied widely from 8 to 70, we used the ratio between the high BP counts and the number of total BP readings or a high BP count-to-total BP reading (C-T) ratio to predict uncontrolled BP and to estimate mean SBPs/DBPs. A half count point (HCP) was defined as the smallest number of HBP readings at a C-T ratio ≥ 0.5. The overall C-statistic of the C-T ratios was 0.986 (95% CI, 0.975-997) for uncontrolled SBP and 0.974 (95% CI 0.961–0.987) for uncontrolled DBP. The CCR at the HCP was 0.954 for uncontrolled SBP and 0.925 for uncontrolled DBP. C-statistics of the C-T ratios were highest in the group with *K*s between 16–24, that with the lowest SDs (< 10 mmHg for uncontrolled SBP, < 7 mmHg for uncontrolled DBP) and that with the lowest BP differences (< 40 mmHg for uncontrolled SBP, < 30 mmHg for uncontrolled DBP) for both uncontrolled SBP and DBP (Table 3). CCRs were > 0.90 in all categories except in the group with *K*s ≥ 24 times, SD ≥ 10 mmHg and BP difference ≥ 45 mmHg for uncontrolled DBP (Table 3). In the groups with a mean SBP between 130–140 mmHg and those with a mean DBP between 80–90 mmHg, the C-statistics and all diagnostic performance indexes, including sensitivity, specificity, PPV, NPV and CCR, were lower than those in all patients but remained > 0.75.

Table 3
Diagnostic performances of the high BP counts for uncontrolled BP in the validation cohort

			N	Lack of control	Sensitivity	Specificity	PPV	NPV	CCR	C-statistics of C-T ratio*
SBP	Overall		412	115 (27.9%)	0.939	0.960	0.900	0.976	0.954	0.986 (0.939–0.997)
	*K*s	8 ~ 15	59	19 (32.2%)	0.947	0.950	0.900	0.974	0.949	0.978 (0.945-1.000)
		16 ~ 23	233	59 (25.3%)	0.967	0.954	0.879	0.988	0.957	0.997 (0.993-1.000)
		≥ 24	120	37 (30.8%)	0.892	0.976	0.943	0.953	0.950	0.963 (0.923-1.000)
	SDs of SBP	< 10 mmHg	200	36 (18.0%)	1.000	0.988	0.947	1.000	0.990	0.999 (0.997-1.000)
		10 ~ 14.9 mmHg	139	42 (30.2%)	0.881	0.918	0.822	0.947	0.906	0.960 (0.920–0.999)
		≥ 15 mmHg	73	37 (50.7%)	0.946	0.944	0.946	0.944	0.945	0.975 (0.941–0.999)
	Maximum ΔSBP	< 40 mmHg	200	33 (16.5%)	0.970	0.982	0.914	0.994	0.980	0.991 (0.974-1.000)
		40 ~ 59 mmHg	145	52 (35.9%)	0.942	0.925	0.875	0.966	0.931	0.979 (0.955-1.000)
		≥ 60 mmHg	67	30 (44.8%)	0.900	0.946	0.931	0.921	0.925	0.980 (0.950-1.000)
	Mean SBP	130–139 mmHg	1078	43 (39.8%)	0.860	0.831	0.771	0.900	0.843	0.892 (0.820–0.965)
DBP	Overall		412	120 (29.1%)	0.867	0.949	0.874	0.945	0.925	0.974 (0.961–0.987)
	*K*s	8 ~ 15	59	20 (33.9%)	0.950	0.897	0.826	0.972	0.915	0.967 (0.931-1.000)
		16 ~ 23	233	64 (27.5%)	0.922	0.953	0.881	0.970	0.944	0.989 (0.980–0.998)
		≥ 24	120	36 (30.0%)	0.722	0.964	0.897	0.890	0.892	0.952 (0.918–0.986)
	SDs of DBP	< 7 mmHg	200	53 (22.7%)	0.868	0.978	0.920	0.962	0.953	0.985 (0.973–0.997)
		7 ~ 9.9 mmHg	139	30 (28.8%)	0.900	0.905	0.794	0.957	0.904	0.971 (0.941-1.000)
		≥ 10 mmHg	73	37 (49.3%)	0.838	0.895	0.886	0.850	0.867	0.942 (0.894–0.989)
	Maximum ΔDBP	< 30 mmHg	200	70 (25.6%)	0.871	0.966	0.897	0.956	0.941	0.982 (0.970–0.995)
		30 ~ 44 mmHg	145	19 (24.1%)	0.895	0.917	0.773	0.965	0.911	0.976 (0.949-1.000)
		≥ 45 mmHg	67	31 (51.7%)	0.839	0.897	0.897	0.839	0.867	0.937 (0.880–0.994)
	Mean DBP	80–89 mmHg	147	62 (42.2%)	0.790	0.824	0.766	0.843	0.810	0.858 (0.794–0.923)

K, the number of HBP measurements; ΔSBP/DBP, difference in SBP/DBP; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; C-T ratio, high BP count-to-total BP readings ratio; CCR, correct classification rate; PPV, positive predictive value; NPV, negative predictive value.

The high SBP/DBP were defined as SBP ≥ 135 mmHg or DBP ≥ 85 mmHg.

Both mean SBP and DBP were highly associated with the corresponding C-T ratios (Fig. 3 and Supplementary Figure S1). The association between mean SBP/DBP and the corresponding C-T ratios fit well in logit curves in the entire SBP and DBP ranges (Supplementary Figure S1). However, because the mean SDs of SBP and DBP were 11.8 mmHg and 8.0 mmHg, we produced linear models within a range of the mean SBPs (125–145 mmHg) and the mean DBP (75–95 mmHg), similar to those used in the simulated cohort, where the SDs of SBP and DBP were 10 mmHg and 7 mmHg, respectively. The linear models showed that a C-T ratio < 0.24 indicated controlled SBP, and a C-T ratio > 0.76 indicated uncontrolled SBP with ≥ 95% confidence and that a C-T ratio < 0.29 indicated controlled DBP and a C-T ratio > 0.73 indicated uncontrolled DBP with ≥ 95% confidence (Fig. 3, Table 4). The average widths of the 95% prediction intervals derived within the BP ranges were 10.5 mmHg for SBP and 8.3 mmHg for DBP.

Table 4
Estimated mean SBP/DBP according to the C-T ratio

		Mean SBP		Mean DBP	
Model summary	Rate	Estimates	95% Prediction interval	Estimates	95% Prediction interval
Logit model	0.2	126.5	117.3-135.6	79.7	72.9–86.6
Y = *C*+ *β**log(X/(1-X)) | 0 < X < 1	0.3	130.0	120.8-139.1	81.9	75.1–88.7
Entire SBP/DBP ranges	0.4	132.8	123.7-141.9	83.7	76.9–90.5
	0.5	135.4	126.3-144.6	85.3	78.5–92.2
	0.6	138.0	128.9-147.2	87.0	80.2–93.8
	0.7	140.9	131.7–150.0	88.8	81.9–95.6
	0.8	144.4	135.2-153.5	91.0	84.1–97.8
Linear model	0.2	128.9	123.7-134.2	79.8	75.6–84.0
Y = β*X + C	0.3	131.0	125.7-136.2	81.5	77.4–85.7
SBP 125–145 mmHg	0.4	133.0	127.8-138.3	83.2	79.1–87.4
DBP 75–95 mmHg	0.5	135.1	129.8-140.3	84.9	80.8–89.1
	0.6	137.1	131.9-142.4	86.6	82.5–90.8
	0.7	139.2	133.9-144.4	88.3	84.2–92.5
	0.8	141.2	135.9-146.5	90.0	85.8–94.2
C-T ratio, High BP count-to-total BP reading ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure					
The high SBP/DBP were defined as SBP ≥ 135 mmHg or DBP ≥ 85 mmHg.					

Discussion

In this study, we developed a binary decision method to determine whether BP was controlled using high BP counts in simulated BPs and validated the method using a real HBPM dataset from patients under antihypertensive medications. A high BP count ≥ half of *K*s was highly accurate in the diagnosis of uncontrolled BP. The accuracy of the high BP counts was highly dependent on the variations of BPs but was not affected by Ks within the simulated range, 16–24. The binary decision method using HCP also accurately diagnosed uncontrolled HBP in real patients with HBPM records. The high BP counts were highly correlated with the mean HBPs, and approximately > 80% and < 20% of the C-T ratios indicated the lack of control and control of HBP with > 95% confidence, respectively.

Although the use of HBPM in clinical practices was recommended in most guidelines, it remains challenging because many HBP devices were not validated, were expensive to low-income families and did not provide friendly interfaces where HBP readings can be kept and easily reviewed[9]. It is especially difficult for patients who are typically elderly to keep a logbook for HBP readings, which requires a real commitment and keenness[11]. To date, all guidelines recommend a mean value of HBP readings as a criterion for the control of BP, which may also hamper the wider use of HBPM because calculating mean HBPs is burdensome not only for patients but also for physicians unless clinics are sufficiently resourced. In this regard, an intuitive tool to quickly assess the control of BP is desired, and the current study is the first to propose the use of a count-based method to decide the control of HBP.

The validity of the count-based decision method was tested using real HBPM data. Because the accuracy of the count-based method depends on the distributions of the BPs, other real-world HBP readings with SDs similar to those in the validation dataset including the Asian BP at Home Study data[14] may show similarly high diagnostic performances for uncontrolled BP. Although the accuracy of the count-based decision method was blunted when the mean SBP/DBP was restricted to 130 ~ 140/80–90 mmHg, around the cutoff point for uncontrolled HBP, 135/85 mmHg, in which it would be most difficult for a physician to recognize the lack of control of BP at a glance to an HBP reading, the C-statistics remained > 0.85, and the other diagnostic performance indexes, including the CCR at the HCP, were substantially high.

In the results, we also showed that the C-T ratios were highly correlated with the mean SBP/DBP. Although the relationship between the C-T ratios and the mean BPs must resemble a logit curve, within the BP ranges of approximately 138/85 mmHg, the relationship was similarly well explained by a linear curve. The C-T ratios could be useful to quickly rule out or diagnose uncontrolled SBP/DBP, given that C-T ratios ≤ 0.2 and ≥ 0.8 indicated the control and lack of control of BPs, respectively, with > 95% confidence. The C-T ratio would be much easier to measure than the average SBP if a physician could count the last 10 to 20 SBP readings in a patient's HBP logbook.

There are several limitations in our study. First, because the simulated BPs were produced using a function generating random numbers with a normal distribution, the simulated BPs would not harbor any characteristics related to the diurnal circadian and weekly rhythm residing in a series of real HBP readings[15], which may explain the difference between the accuracy of the count-based decision method in the simulated cohort and that in the real HBP readings. Although SDs were similar, the skewness and kurtosis may be greater in real HBP readings because of these diurnal and weekly regularities, which may blunt the accuracy of the binary decision method. Second, we simulated BPs in *K*s between16 and 24. These *K* values are not only recommended in

many guidelines but also the most frequent *K* values in the real HBPM. The accuracy of the binary decision method appeared to be independent of *K* values within this range. However, guidelines recommend the numbers of measurements more broadly from 2 times a day for 3 days (6 times) to 3 times a day for 2 weeks (36 times)[3,16]. At higher *K* values, the accuracy of the count-based decision method could converge into one value, but the accuracy may vary more widely at lower *K* values. Third, the real HBP readings used in the validation were obtained from patients on antihypertensive medications. The prevalence of a mean BP ≥ 135/85 mmHg and the levels of interest and education regarding HBPM may be different in those who were not diagnosed with hypertension or were not taking any antihypertensive agents. Therefore, the accuracy of the binary decision method using the HCP should be cautiously interpreted in other situations where HBPM is recommended.

Although HBPM is effective in identifying white-coat phenomena, masked uncontrolled hypertension and nocturnal hypertension[3], the accuracy of HBPM in the diagnosis of hypertension remains insufficient to replace ambulatory BP monitoring with a sensitivity of 86% and a specificity of 62%[17,18]. Because the count-based binary decision method was developed using the HBPM series, it is desirable to evaluate its diagnostic accuracy for uncontrolled hypertension compared to the diagnostic accuracy of ambulatory BP monitoring.

In conclusion, the count-based binary decision method using HCP could provide a quick and accurate assessment of whether the target BP was achieved in a series of HBP readings. When the SDs of SBPs/DBPs are within a usual range, the C-T ratio could allow a physician to estimate the approximate of the mean HBPs and to rule out or to confirm the lack of control of BPs quickly. The C-T ratio could be helpful for physicians trying to use HBPM as their primary measure for target BP achievement to quickly assess the control of HBP.

Methods

Simulation

1) Simulation of mean BPs

Simulated BPs and the count-based decision method were generated using statistical software R (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and RStudio (RStudio Team, Rstudio, BPC, Boston, MA, US). We produced 100 random sample cases of mean SBP level between 130 ~ 140 mmHg and mean DBP between 80 ~ 90 mmHg using “runif”, a random number generating function as follows to generate individual BP samples around the mean SBPs and DBPs later, because it will be most difficult for physicians to decide whether HBP achieves the target BP level, 135/85 mmHg, when the mean BP levels were close to the target BP level.

```
set.seed (1234)

N<-100

M.sbp<-runif(n = N, min = 130, max = 140)

M.dbp<-runif(n = N, min = 80, max = 90)
```

2) Simulation of individual BPs according to the numbers of BP readings and SDs

Guidelines recommend obtaining HBPM for at least 5 to 7 days serially and excluding BP readings obtained on the first day of a series in mean BP calculation[3]. Consequently, at least 16 (5 days) to 24 (7 days) readings in a month are required to standardize HBPM. Therefore, we generated 16, 20, and 24 SBP and DBP readings per 1 mean SBP and DBP sample.

For a number of BP readings *K*, a set of 100 SBPs and DBPs was simulated using “rnorm”, a function generating random numbers with a normal distribution at 4 different SD levels, which were 5, 10, 15 and 20 mmHg for SBP and 3.5, 7.0, 10.5, and 14 mmHg for DBP (70% of the SDs for SBP). Here is an example of *K* = 16, as follows. All sets of simulated BPs are provided in Supplementary data S2.

```
N <-100

K <-16

SD <-c(5, 10, 15, 20)

sd_label <-c("SD = 5", "SD = 10", "SD = 15", "SD = 20")

mk<-matrix (NA, ncol = k, nrow = N)

sbp <-list(mk, mk, mk, mk)

dbp <- list(mk, mk, mk, mk)

names(sbp)<-sd_label; names(dbp)<-sd_label

dimnames <-list(paste0("Pt", 1:N), sd_label)

msd <-matrix(NA, ncol = NROW(SD), nrow = N, dimnames = dimnames)
```

```
meansbp <-msd; meandbp <-msd

shtn <- msd; dhtn <- msd

nsbp135 <-msd; ndbp85 <-msd

for (j in 1:NROW(SD)){

for (i in 1:N){

sbp [[j]][i,]<-rnorm(n = k, mean = M.sbp[i], sd = SD[j])

dbp [[j]][i,]<-rnorm(n = k, mean = M.dbp[i], sd = SD[j]*0.7)

nsbp135[i,j]<-NROW(which(sbp[[j]][i,] > = 135))

ndbp85[i,j]<-NROW(which(dbp[[j]][i,] > = 85))

}

meansbp[,j]<-apply(sbp[[j]], 1, mean)

meandbp[,j]<-apply(dbp[[j]], 1, mean)

shtn[,j]<-ifelse(meansbp[,j] > = 135, 1, 0)

dhtn[,j]<-ifelse(meandbp[,j] > = 85, 1, 0)

}
```

4) Definition of a high BP reading and uncontrolled BP

A high SBP/DBP reading was defined as an individual SBP ≥ 135 mmHg and/or DBP ≥ 85 mmHg, and a high SBP/DBP count was defined as the number of high SBP/DBP readings in an HBPM series. An uncontrolled SBP/DBP was defined as a mean SBP ≥ 135 mmHg and/or a mean DBP ≥ 85 mmHg. Diagnostic performances of the count-based decision for uncontrolled BP were assessed using ROC curves and C-statistics. The best threshold for the number of high BPs was decided at the maximum values of Youden's J-indexes. In addition to the diagnostic performances at the best thresholds, we investigated the diagnostic performances at intuitive fixed cutoff values. For physicians to use the cutoff values widely, the cutoff values were set to half of the *K* values, 8, 10 and 12.

5) Assessments and comparisons of the diagnostic performances for uncontrolled BPs

Sensitivity, specificity, PPV, NPV, CCR and C-statistic were assessed as diagnostic performance indexes of the high BP counts. Although Delong's method can be employed to generate CIs for C-statistics and to compare 2 C-statistics, there have been no stable methods to compare the other diagnostic performance indexes among 3 or more groups. Therefore, we employed bootstrap resampling methods to create individual samples and distributions for the diagnostic performance indexes. For each combination of the 3 *K*s (16, 20 and 24) and 4 SD (5, 10, 15 and 20 mmHg) levels, we created 2,000 bootstrap samples (subsequently, 24,000 bootstrap samples for 12 levels) from a set of 100 SBPs/DBPs using the "boot" function as follows:

```
#For K = 16

roc.sbp.k16 <-list(NA, NA, NA, NA)

bootraw.auc.sbp.k16 <-list(NA, NA, NA, NA)

boot.auc.sbp.k16 <-matrix(NA, nrow = 2000, ncol = 4)

#For ROC curve objects

for (i in 1:4) {

roc.sbp.k16[[i]]<-roc(shtn[,i] ~ nsbp135[,i], ci = T, auc = T)

}

#For Bootstrap resampling

fx<-function(data, indices, x, y){

d<-data[indices, ]

roc<-roc(d$y ~ d$x, auc = T); return(roc$auc)
```

}

for (j in 1:4){

x<- roc.sbp.k16[[j]]$original.predictor

y<- roc.sbp.k16[[j]]$original.response

m<-data.frame(x, y)

boot<-boot(m, x="x", y="y", R = 2000, statistic = fx)

boot.auc.sbp.k16[,j]<-boot$t

bootraw.auc.sbp.k16[[j]]<-boot

}

Therefore, 24,000 bootstrap variations of C-statistics and CCRs were created for both SBP and DBP (2,000 bootstrap variations for each possible combination of *K*s and SDs). With these bootstrap samples, we compared the C-statistics and CCRs among the numbers of measurements *K* and the SD levels and evaluated the interactions between *K* values and SD levels using mixed linear effect models. In the models, each combination of *K* values and SD levels was used as an identifier, and variations within the combination were considered random effects, and the variations among the *K* values and SD levels were considered fixed effects. All bootstrap variations of C-statistics and CCRs are provided in Supplementary Data S3.

7) Estimation of the mean SBPs and DBPs using the numbers of high BPs

Linear regression models were used to predict the mean SBPs and DBPs corresponding to the numbers of high SBPs and DBPs with 95% prediction intervals. A linear regression model was produced for each SD level at $K = 24$.

Validation

Validation for the count-based decision method for uncontrolled BP was performed using HBPM data retrospectively obtained from 424 patients who had visited the cardiology department for antihypertensive medications at Hanyang University Seoul Hospital from November 2017 to September 2018. The HBPM data collection and study protocol adhered to the Declaration of Helsinki. The use of these data was approved by the Institutional Review Board of Hanyang University Seoul Hospital, and informed consent was waived because the HBPM data were obtained from the electrical medical records produced in the past. HBPM data from 12 patients whose number of BP readings was < 8 were excluded. Patients were categorized into 3 groups according to *K*s (8 ~ 15 times, 16 ~ 23 times and ≥ 24 times), SDs (< 10 mmHg, 10-14.9 mmHg and ≥ 15 mmHg), SBP ranges (< 40 mmHg, 40–59 mmHg and ≥ 60 mmHg) and mean SBPs/DBPs.

Diagnostic performances of the count-based decision for uncontrolled BP were assessed using ROC curve analyses and the C-statistics according to the categories of patients. Because, unlike the numbers of simulated BP readings with 3 fixed levels, the numbers of actual HBP readings widely varied from 8 to 70, we used the ratio between the high BP counts and the number of total BP readings or a high BP count-to-total BP reading ratio (C-T ratio), instead of the simple high BP counts, to predict uncontrolled BP and to estimate mean SBPs/DBPs. Sensitivity, specificity, PPV, NPV and CCR were assessed at the smallest number of high BP counts when the C-T ratio was ≥ 0.5, or at a HCP, as follows:

 # When "V" *is a list of matrixes containing columns for home SBPs and DBPs*,

 # And "m" *is a dataframe containing columns for the mean SBPs and mean DBPs*,

for(i in 1:NROW(V)){

dt<-V[[i]]

m$n.sbp135[i]<-NROW(which(dt$sbp > = 135, 1, 0))

m$n.dbp85[i]<-NROW(which(dt$dbp > = 85, 1, 0))

}

m$nhalf<-ceiling(m$nmeasure/2)

m$rate.sbp135<-m$n.sbp135/m$nmeasure

m$rate.dbp85<-m$n.dbp85/m$nmeasure

*#*m$n.sbp135 > = nhalf or m$n.dbp85 > = nhalf *indicates the HCP*,

#"nmeasure" *indicates the number of entire BP readings*,

#"rate.sbp135" *and* "rate.dbp85" *indicate the systolic and diastolic C-T* ratios, respectively.

The mean HBPs were predicted with 95% prediction intervals using the C-T ratio. Unlike the simulated BP series, which were generated within the programmed range, the real HBP series had a wider distribution, ranging between 89–183 mmHg for the mean SBPs and 59–125 mmHg for the mean DBPs. Consequently, the fitting curve between the high BP counts and the mean BP was expected to resemble a logit curve ($y = C + b*\log(x/(1-x)) \mid 0 < x < 1$). However, because the fitting curve will be linear within the range applied to the simulated BPs, we fitted the C-T ratio to the mean BPs using a linear curve within the range of the simulated BPs with an SD most similar to the real SD of the mean BPs, as well as the logit curve.

Statistical analysis

All simulations and statistical analyses were performed using R-4.04 and RStudio-1.3. R codes required to simulate BPs and to conduct the statistical analyses are provided in supplementary data S1.

The sample size of 100 cases was determined empirically, given that a physician would prescribe 50 patients per session and 100 patients per day in primary care clinic settings. To assess the diagnostic performances of the count-based decision method for uncontrolled BP, ROC curve analysis with the "pROC" package was used. The 95% CIs of the C-statistics were estimated using 2 methods, Delong's method and the bootstrap resampling method. The comparisons of C-statistics and CCRs among *K*s and SDs were performed through mixed linear effect models on the 24,000 permuted results of the C-statistics and CCRs from the bootstrap resamples using the "lme4" package. A linear regression model in the "stats" package was used to fit the high BP counts and the mean BPs on both a linear curve and a logit curve.

C-statistics of < 0.70, 0.70–0.89 and > 0.90 were interpreted as poor, moderate and high in diagnostic accuracy, and a p-value < 0.05 was considered significant.

Declarations

Acknowledgements

This research was supported by a grant of Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI19C1055)

Author contributions

Y.L., J.S. and S.H.L. conceived the original idea, Y.L. and J.H.S. designed the study, Y.L. and J.S. analyzed the data and interpreted the results, J.S. drafted the original manuscript, B.S.K. produced the illustrations for data presentations, H.J.K., H.C.P., Y.H.L. and J.K.P. revised the manuscript critically, and all authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Competing interests

The authors declare no competing interests.

Data availability

All data generated or analyzed during this study are included in this published article and its Supplementary Information files. The raw datasets, including the simulated BPs, the bootstrap resampling results for C-statistics and CCRs, the real HBPs and the R script used to simulate and analyze the data, are all provided in Supplementary Data S1-S5.

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Figures

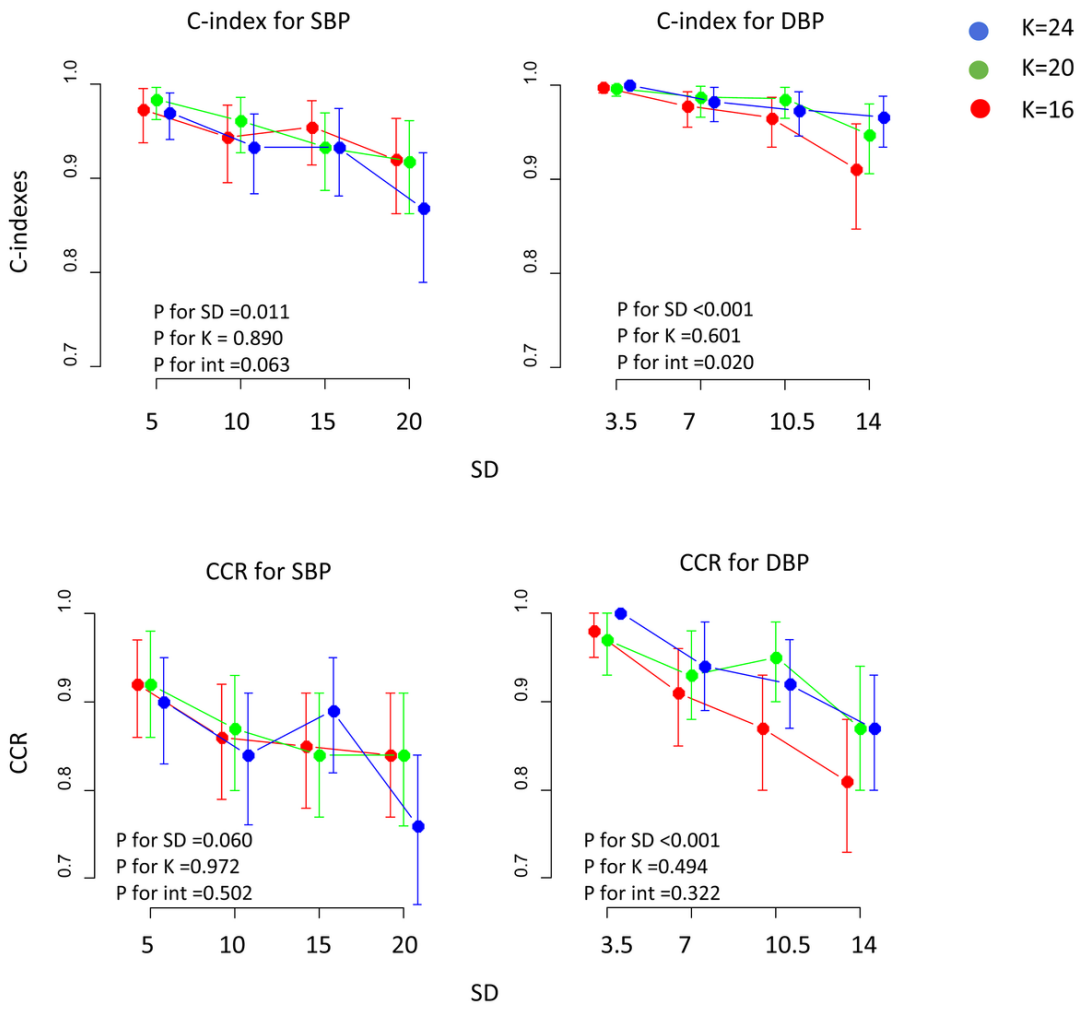

Figure 1

Diagnostic performances according to Ks and SDs in the simulated cohort. The C-statistics and CCR for both SBP and DBP gradually decreased as SDs increased. The influences of Ks on both the C-statistics and CCR were not statistically significant. Each CI was generated using a set of 2,000 bootstrap samples from the original simulated data, and the p-values were generated using mixed-linear effect models. SD, standard deviation; K, number of measurements; Int, interaction

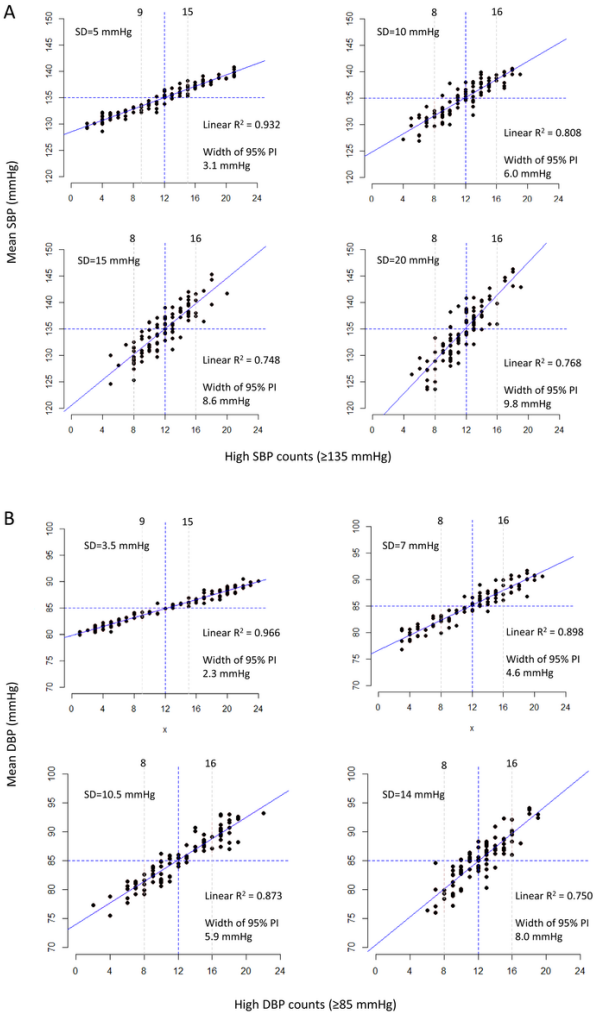

Figure 2

Relationship between the high BP counts and the mean SBP/DBP in the simulated cohort (when K=24). There were tight linear associations between the high BP counts and the mean SBP/DBP. As SDs increased, the strength of the association decreased, and the width of the 95% PIs increased. When the SD was 5, high BP counts ≤9 indicated controlled SBP/DBP, and high BP counts ≥15 indicated uncontrolled SBP/DBP with ≥95% confidence. When SD >5, high BP counts ≤8 indicated controlled SBP/DBP, and high BP counts ≥16 indicated uncontrolled SBP/DBP with ≥95% confidence. The blue solid lines indicate the linear regression fits between the high BP counts and mean SBP/DBP, and the red ribbons indicate the 95% PI of the mean SBP/DBP. High SBP/DBP was defined as an SBP ≥135 mmHg/DBP ≥85 mmHg. PI, prediction interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation

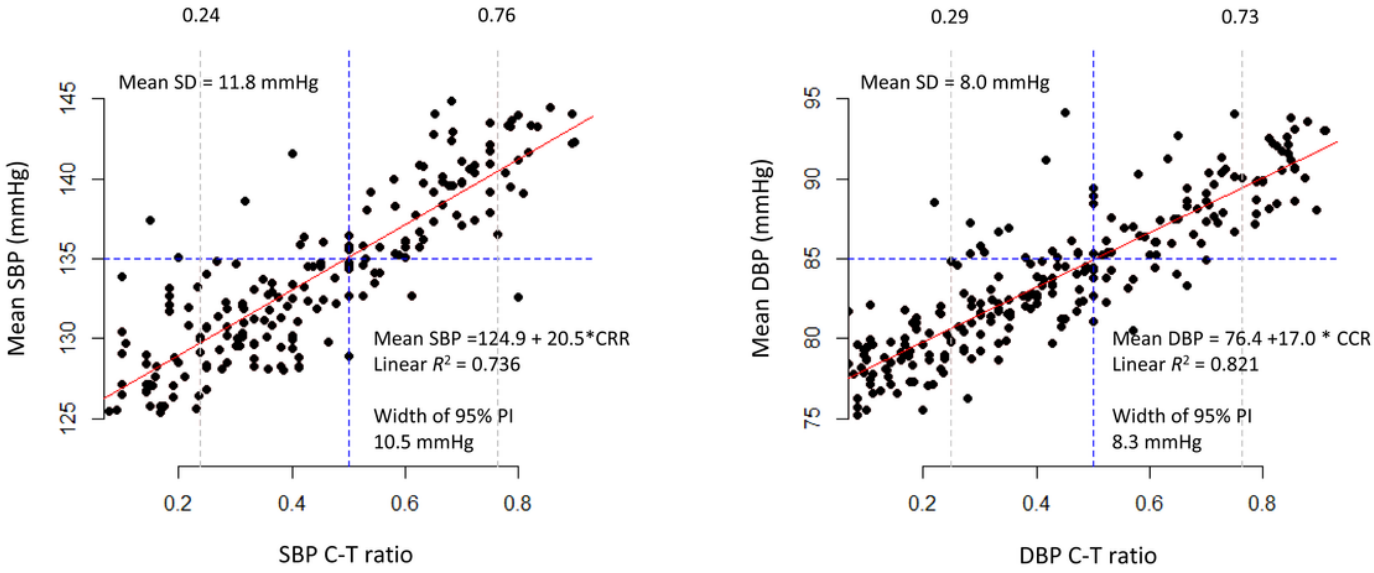

Figure 3

Relationship between the C-T ratio and the mean SBP/DBP in the validation cohort. There was a strong linear association between the C-T ratio and the mean SBP/DBP. Because the SDs of the mean SBP/DBP were 11.8 mmHg and 8.0 mmHg, respectively, the linear regression models between the C-T ratio and mean BP were produced within the mean SBP of 125-145 mmHg and the mean DBP of 75-95 mmHg, which are similar to those of the simulated SBPs with SD=10 mmHg and that of the simulated DBPs with SD =7 mmHg. High SBP/DBP was defined as SBP ≥135 mmHg/DBP ≥85 mmHg. C-T ratio, high BP count-to-total BP reading ratio; PIs, prediction intervals; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ShinSRSupplementarydata1.docx
- ShinSRSupplementarydata2BP.xlsx
- ShinSRSupplementarydata3Bootstrap.xlsx
- ShinSRSupplementarydata4realHBPM.xlsx
- ShinSRSupplementarydata5realHBPMrawdata.xlsx
- ShinSRSupplementaryFiguresandTables.docx
- ShinSRSupplementaryFileLegends.docx