ARTICLE

Cutoffs for white-coat and masked blood pressure effects: an ambulatory blood pressure monitoring study

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The values used to define white-coat and masked blood pressure (BP) effects are usually arbitrary. This study aimed at investigating the accuracy of various cutoffs based on the differences (ΔBP) between office BP (OBP) and 24h-ambulatory BP monitoring (ABPM) to identify white-coat (WCH) and masked (MH) hypertension, which are phenotypes coupled with adverse prognosis. This cross-sectional study included 11,350 [Derivation cohort; 45% men, mean age = 55.1 ± 14.1 years, OBP = 132.1 ± 17.6/83.9 ± 12.5 mmHg, 24 h-ABPM = 121.6 ± 11.4/76.1 ± 9.6 mmHg, 25% using antihypertensive medications (AH)] and 7220 (Validation cohort; 46% men, mean age = 58.6 ± 15.1 years, OBP = 136.8 ± 18.7/87.6 ± 13.0 mmHg, 24 h-ABPM = 125.5 ± 12.6/77.7 ± 10.3 mmHg; 32% using AH) unique individuals who underwent 24 h-ABPM. We compared the sensitivity, specificity, positive and negative predictive values and area under the curve (AUC) of diverse ΔBP cutoffs to detect WCH (ΔsystolicBP/ΔdiastolicBP = 28/17, 20/15, 20/10, 16/11, 15/9, 14/9 mmHg and ΔsystolicBP = 13 and 10 mmHg) and MH (ΔsystolicBP/ΔdiastolicBP = −14/−9, −5/−2, −3/−1, −1/−1, 0/0, 2/2 mmHg and ΔsystolicBP = −5 and −3mmHg). The 20/15 mmHg cutoff showed the best AUC (0.804, 95%CI = 0.794-0.814) to detect WCH, while the 2/2 mmHg cutoff showed the highest AUC (0.741, 95%CI = 0.728–0.754) to detect MH in the Derivation cohort. Both cutoffs also had the best accuracy to detect WCH (0.767, 95%CI = 0.754–0.780) and MH (0.767, 95%CI = 0.750–0.784) in the Validation cohort. In secondary analyses, these cutoffs had the best accuracy to detect individuals with higher and lower office-than-ABPM grades in both cohorts. In conclusion, the 20/15 and 2/2 mmHg ΔBP cutoffs had the best accuracy to detect hypertensive patients with WCH and MH, respectively, and can serve as indicators of marked white-coat and masked BP effects derived from 24 h-ABPM.

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INTRODUCTION

Hypertension stands as a primary contributor to cardiovascular morbidity and mortality among adults [1–3]. Traditionally, the diagnosis and control of hypertension have centered on office blood pressure (BP) assessments (OBP). Yet, this approach might not fully reflect the actual BP burden. As a result, contemporary hypertension guidelines advise the inclusion of out-of-office BP measurements, utilizing either ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM), when available [4–6].

OBP and out-of-office BP usually do not yield similar values and can lead to the identification of phenotypes coupled with adverse long-term prognosis, such as white-coat (high office and normal out-of-office BP) hypertension (WCH) and masked (normal office and high out-of-office BP) hypertension (MH) [7–9]. Conversely, the value of the difference between OBP and out-of-office BP (ΔBP), which, according to the direction, is described as a white-coat or masked effect, may also have clinical value and usually indicates a natural trait of the individual's BP behavior that might persist in subsequent BP evaluations [10–12]. Notably, the magnitude of ΔBP may be relevant to patients' management, because patients with significant white-coat or masked effects are recommended to undergo out-of-office BP measurements more frequently as an adjuvant strategy to increment BP management and monitor the therapeutic response [13, 14].

A consensus on the ΔBP values used to determine the presence of significant white-coat or masked effects in clinical practice is lacking, despite the existence of various proposed ΔBP cutoffs [13–20]. The absence of standardized definitions of white-coat and masked effects may result in excessive and costly out-of-office BP monitoring or in the exclusion of individuals that would benefit

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from more regular out-of-office evaluations [21]. Regarding ABPM values, individuals with systolic ΔBP (ΔSBP) ≥ 20 mmHg or diastolic ΔBP (ΔDBP) ≥ 10 mmHg have been empirically considered to have significant white-coat effect [13]. Although these ΔBP cutoffs have been endorsed by some current hypertension guidelines, including those from the National Institute for Health and Care Excellence (NICE) [14] and the American College of Cardiology/American Heart Association (ACC/AHA) [4], their clinical relevance is not established. One approach proposed to detect ΔBP thresholds reflecting significant white-coat or masked effects is the identification of ΔBP values with best accuracy to detect WCH and MH, respectively. This strategy was formerly used by a study evaluating a large sample of patients undergoing OBP and HBPM measurements, which reported that ΔSBP ≥ 15 mmHg and ΔDBP ≥ 9 mmHg mmHg had the best accuracy to detect WCH, while ΔSBP or ΔDBP ≤ − 1 mmHg had the best accuracy to detect MH, suggesting that these cutoffs could be used to identify significant white-coat and masked effects, respectively, derived from HBPM [20]. Therefore, as an approach to define the presence of significant white-coat or masked effects derived from ABPM, the present study aimed at investigating the accuracy of various ΔBP cutoffs to identify WCH and MH in two large and independent cohorts of individuals who underwent 24 h ABPM exams. Furthermore, we tested the performance of the studied ΔBP cutoffs to identify individuals with higher and lower office-than-ABPM BP grades.

METHODS

Design

This cross-sectional study retrospectively evaluated two independent (Derivation and Validation) cohorts of Brazilian adults who underwent 24 h-ABPM and were using or not antihypertensive medications. The Derivation cohort comprised a convenience sample of 11,350 consecutive individuals who underwent 24 h-ABPM measurements from 2015 to 2021 in two centers located in the cities of Recife and Goiânia, Brazil. The Validation cohort comprised a convenience sample of 7220 consecutive individuals who underwent 24 h-ABPM measurements from 2011 to 2021 in one center, located in the city of Criciúma, Brazil. The aforementioned time spans corresponded to the years when there were data derived from ABPM exams available for analysis in the study centers. Exclusion criteria included age<18 years old and the presence of less than 16 valid daytime readings or less than 8 valid nighttime readings in ABPM exams. The study protocol followed the ethical guidelines outlined in the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Oswaldo Cruz University Hospital/PROCAPE, São José Hospital, and Clinics Hospital of the Federal University of Goiás, which waived the need for informed consent.

BP measurements, hypertension phenotypes, and clinical variables

All participants underwent 24 h-ABPM evaluation using a DynaMapa device (Cardios, São Paulo, Brazil). The protocol for 24 h-ABPM used in the current analysis comprised two initial attended BP measures obtained with 1 min interval at the office, with the participant in the sitting position after resting for 5 min. The first sitting BP reading was not recorded, but the second sitting BP reading was systematically recorded by the DynaMapa device and was considered as the OBP measurement in the current analysis. 24 h-ABPM measurements comprised the average of 24 h readings obtained at 20 min and 15 min intervals at daytime in the Derivation and Validation cohorts, respectively, and at 30 min intervals at nighttime in both cohorts. Only participants with a minimum of 16 valid daytime readings and 8 valid nighttime readings were included in the analysis. The average number of valid total, daytime, and nighttime readings were 56 ± 8, 41 ± 8, and 15 ± 3 in the Derivation cohort and 66 ± 10, 52 ± 10, and 14 ± 4 in the Validation cohort, respectively. Data on sex, age, body mass index, and use of antihypertensive medications were also collected from all participants.

Hypertension at the office was defined as grade 1 if systolic BP (SBP) = 140–159 mmHg or diastolic BP (DBP) = 90–99 mmHg, grade ≥2 if SBP ≥ 160 mmHg or DBP ≥ 100 mmHg [5, 6], while hypertension at 24 h-ABPM was defined as grade 1 if SBP = 130–144 mmHg or DBP = 80–89 mmHg and grade 2 if SBP ≥ 145 mmHg or DBP ≥ 90 mmHg [4–6]. Hypertension phenotypes were defined as follows: normotension (office SBP < 140 mmHg and DBP < 90 mmHg and 24 h SBP < 130 mmHg and 24 h DBP < 80 mmHg), WCH (office SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and 24 h SBP < 130 mmHg and 24 h DBP < 80 mmHg), MH (office SBP < 140 mmHg and DBP < 90 mmHg and 24 h SBP ≥ 130 mmHg or 24 h DBP ≥ 80 mmHg) and sustained hypertension (SH) (office SBP ≥ 140 or DBP ≥ 90 mmHg and 24 h SBP ≥ 130 or 24 h DBP ≥ 80 mmHg) [5, 6]. Current guidelines have suggested that individuals with normotension, WCH, MH, and sustained hypertension should be labeled as having controlled hypertension, white-coat uncontrolled hypertension (WUCH), masked uncontrolled hypertension (MUCH), and sustained uncontrolled hypertension when using antihypertensive medications [5]. In the current manuscript, however, to simplify the presentation of the results, we opted to label the studied participants solely as having normotension, WCH, MH, and sustained hypertension, regardless of the use of antihypertensive medications.

BP cutoffs for white-coat and masked effect

We used ΔSBP and ΔDBP values to build cutoffs to identify white-coat and masked effects. Eight cutoffs for the white-coat effect were selected: (a) ΔSBP ≥ 28 mmHg or ΔDBP ≥ 17 mmHg [reflecting 2.0 standard deviations (SD) of ΔSBP or ΔDBP] [20]; b) ΔSBP ≥ 20 mmHg or ΔDBP ≥ 15 mmHg; (c) ΔSBP ≥ 20 mmHg or ΔDBP ≥ 10 mmHg [13, 15, 16]; (d) ΔSBP ≥ 16 mmHg or ΔDBP ≥ 11 mmHg (based on receiver operating characteristic (ROC) curve cutoff points for ΔSBP or ΔDBP that showed the best association with WCH in our Derivation cohort); (e) ΔSBP ≥ 15 mmHg or ΔDBP ≥ 9 mmHg [20]; (f) ΔSBP ≥ 14 mmHg or ΔDBP ≥ 9 mmHg (reflecting 1.0 SD of ΔSBP or ΔDBP) [20]; (g) ΔSBP ≥ 13 mmHg (reflecting the mean ΔSBP plus 0.2 SD of ΔSBP) [17]; and (h) ΔSBP ≥ 10 mmHg [19]. Eight cutoffs for the masked effect were selected: (a) ΔSBP ≤ − 14 mmHg or ΔDBP ≤ − 9 mmHg (reflecting −1.0 SD of ΔSBP or ΔDBP) [20]; (b) SBP ≤ − 5 mmHg or DBP ≤ − 2 mmHg (reflecting the mean ΔSBP minus 1.1 SD of ΔSBP or mean ΔDBP minus 1.1 SD of ΔDBP) [17]; c) ΔSBP ≤ − 5 mmHg (reflecting the mean ΔSBP minus 1.1 SD of ΔSBP) [17]; (d) ΔSBP ≤ − 3 mmHg or ΔDBP ≤ − 1 mmHg (reflecting the mean ΔSBP minus 1 SD of ΔSBP or the mean ΔDBP minus 1 SD of ΔDBP) [22]; (e) ΔSBP ≤ − 3 mmHg (reflecting the mean ΔSBP minus 1 SD of ΔSBP) [22]; (f) ΔSBP ≤ − 1 mmHg or ΔDBP ≤ − 1 mmHg [17, 18, 20, 22]; (g) ΔSBP = 0 mmHg or ΔDBP = 0 mmHg; and (h) ΔSBP ≥ 2 mmHg or ΔDBP ≥ 2 mmHg (based on the ROC curve cutoff points for ΔSBP or ΔDBP that showed the best association with MH in our Derivation cohort).

Statistical analysis

Continuous and categorical variables are expressed as the mean ± SD, and number of subjects and proportion, respectively. As a primary analysis, we evaluated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) derived from ROC curves with the studied cutoffs for detecting WCH or MH in the Derivation and Validation cohorts [20]. As a secondary analysis, we compared the performance of the cutoffs to detect: a) participants with significant decreases in BP grade at 24 h-ABPM compared to the office, i.e., the sum of patients with WCH and those with SH who had a higher hypertension grade at the office than at 24 h-ABPM in each cohort; and b) participants with significant increases in BP grade at 24 h-ABPM compared to the office, i.e., the sum of patients with MH and those with SH who had lower hypertension grade at the office than at 24 h-ABPM in each cohort [20]. We also repeated the primary and secondary analyses solely in the subsample of participants using antihypertensive medications from both cohorts (n = 5182) and in the subsample of participants not using antihypertensive medications from both cohorts (n = 13,388). In addition, we evaluated the AUC derived from the studied cutoffs for detecting WCH or MH in the Validation cohort solely including the individuals who performed ABPM from 2015 to 2021 (n = 6398). The Stata *roccomp* command was used to compare the AUCs derived from ROC analysis (https://www.stata.com/manuals/rroccomp.pdf). P values < 0.05 were considered statistically significant. The statistical analysis was performed using Stata software version 14.1 (Stata Corp LP, College Station, TX, USA).

RESULTS

The characteristics of the Derivation (n = 11,350) and Validation (n = 7220) cohorts are shown in Table 1. The cohorts had similar rates of men, but the Derivation cohort was younger, leaner, less likely to use antihypertensive medications, and had lower OBP and

Table 1. Characteristics of the cohorts.

Characteristics	Derivation cohort n = 11,350	Validation cohort n = 7220	P
Male sex, n (%)	5064 (45)	3352 (46)	0.016
Age, years	55.1 ± 14.1	58.6 ± 15.1	<0.001
Body mass index, kg/m^2	28.0 ± 4.7	28.5 ± 4.6	<0.001
Office SBP, mmHg	132.1 ± 17.6	136.8 ± 18.7	<0.001
Office DBP, mmHg	83.9 ± 12.5	87.6 ± 13.0	<0.001
24 h SBP, mmHg	121.6 ± 11.4	125.5 ± 12.6	<0.001
24 h DBP, mmHg	76.1 ± 9.6	77.7 ± 10.3	<0.001
ΔSBP, mmHg	10.5 ± 13.9	11.3 ± 14.1	<0.001
ΔDBP, mmHg	7.8 ± 8.6	9.9 ± 8.4	<0.001
Antihypertensive medications, n (%)	2841 (25)	2341 (32)	<0.001
ACEI or ARB	1533 (14)	1880 (26)	<0.001
Diuretic	460 (4)	602 (8)	<0.001
Calcium-channel blocker	459 (4)	422 (6)	<0.001
Beta-blocker	580 (5)	651 (9)	<0.001
Direct vasodilator	116 (1)	81 (1)	0.52
HT phenotypes, n (%)			<0.001
Normotension	5193 (46)	2477 (34)	
White-coat HT	1736 (15)	1148 (16)	
Masked HT	1123 (10)	655 (9)	
Sustained HT	3298 (29)	2940 (41)	
Office BP grades, n (%)			<0.001
Normal (<140/90 mmHg)	6316 (56)	3132 (43)	
Grade 1 HT (140–159/90–99 mmHg)	3475 (31)	2473 (34)	
≥Grade 2 HT (≥160–179/100–109 mmHg)	1559 (14)	1615 (22)	
Ambulatory BP grades, n (%)			<0.001
Normal (<130/80 mmHg)	6929 (61)	3625 (50)	
Grade 1 HT (130–144/80–89 mmHg)	3354 (30)	2541 (35)	
≥Grade 2 HT (≥145/90 mmHg)	1067 (9)	1054 (15)	

ACEI or ARB angiotensin converting enzyme inhibitor or angiotensin receptor blocker, *BP* blood pressure, *SBP* systolic BP, *DBP* diastolic BP, *HT* hypertension.

24 h-ABPM levels than the Validation cohort. The Derivation cohort also had lower values of ΔSBP (10.5 ± 13.9 vs. 11.3 ± 14.1 mmHg, p < 0.001) and ΔDBP (7.8 ± 8.6 vs. 9.9 ± 8.4 mmHg, p < 0.001) compared to the Validation cohort. The normotension, WCH, MH, and SH rates were 46%, 15%, 10 and 29% in the Derivation cohort and 34%, 16%, 9 and 41% in the Validation cohort, respectively.

White-coat effect

Supplemental Table 1 presents the prevalence of individuals of both cohorts with BP values greater or equal to the proposed ΔBP cutoffs for identifying the white-coat effect. Table 2 shows the sensitivity, specificity, PPV, NPV, and AUC of the ΔBP cutoffs for detecting WCH in the Derivation and Validation cohorts. The 20/15 mmHg cutoff resulted in the highest numerical AUC (0.804, 95%CI = 0.794–0.814) for the detection of WCH, followed by the 16/11 mmHg (AUC = 0.801, 95%CI = 0.795–0.807; p = 0.52 compared with the 20/15 mmHg cutoff) and 20/10 mmHg (AUC = 0.789, 95%CI = 0.781–0.797; p < 0.001 compared with the 20/15 mmHg cutoff) cutoffs in the Derivation cohort. Likewise, the 20/15 mmHg cutoff yielded the highest numerical AUC (0.767, 95% CI = 0.754–0.780) for the detection of WCH, followed by the 16/11 mmHg (AUC = 0.762, 95% CI = 0.754-0.771; p = 0.41 compared with the 20/15 mmHg cutoff) and 20/10 mmHg (AUC = 0.748, 95%CI = 0.739–0.757; p < 0.001 compared with the 20/15 mmHg cutoff) cutoffs in the Validation cohort. The sensitivity and specificity of the 20/15 mmHg cutoff were 80.6 (95% CI = 78.7–82.5) and 80.2 (95%CI = 79.4–81.0) in the Derivation cohort and 80.0 (95%CI = 77.5–82.2) and 73.5 (95% CI = 72.4–74.6) in the Validation cohort, respectively, while the sensitivity and specificity of the 16/11 mmHg cutoff were 97.1 (95%CI = 96.2–97.8) and 63.1 (95%CI = 62.2–64.1) in the Derivation cohort and 96.3 (95%CI = 95.1–97.4) and 56.1 (95% CI = 54.9–57.4) in the Validation cohort, respectively. Similar AUC findings were obtained when only including individuals of the Validation cohort who performed ABPM from 2015 to 2021 (Supplemental Table 2).

We then evaluated the ability of the ΔBP cutoffs to identify individuals with significant decreases in BP grades at 24 h-ABPM compared to the office, which corresponded to the sum of participants with WCH and those with SH who had a hypertension grade at the office higher than at 24 h-ABPM (Table 3). This analysis showed that the 20/15 mmHg cutoff yielded the highest AUC (0.839, 95%CI = 0.831–0.848; p-value at least ≤ 0.003 compared with all other cutoffs in the Derivation cohort; 0.828, 95%CI = 0.818–0.838; p < 0.001 compared with all other cutoffs in the Validation cohort) to identify individuals with significant decreases in BP grades at 24 h-ABPM compared to the office.

Results of analysis including solely individuals using antihypertensive medications of both cohorts showed that the 20/15 mmHg cutoff had the highest AUC to detect either WCH or individuals with significant decreases in BP grades at 24 h-ABPM compared to the office (Supplemental Tables 3 and 4). Conversely, further analysis including solely individuals not using antihypertensive medications of both cohorts demonstrated that the 20/15 mmHg cutoff had the highest AUC to detect individuals with significant decreases in BP grades at 24 h-ABPM compared to the office (p-value at least ≤ 0.011 compared with all other cutoffs), while the 20/15 and 16/11 mmHg cutoffs had similar AUC to detect WCH, with the former cutoff having lower sensitivity but greater specificity compared to the later one (Supplemental Tables 3 and 5).

Masked effect

Supplemental Table 6 presents the prevalence of individuals of both cohorts with BP values greater or equal to the proposed ΔBP cutoffs to masked effects. Table 4 shows the sensitivity, specificity, PPV, NPV, and AUC of the ΔBP cutoffs for detecting MH in the Derivation and Validation cohorts. The 2/2 mmHg cutoff resulted in the highest AUC (0.741, 95%CI = 0.728–0.754; p < 0.001 compared with all other cutoffs) to detect MH in the Derivation cohort, with a sensitivity and specificity of 78.9 (95% CI = 76.4–81.2) and 69.3 (95%CI = 68.4–70.2). Similarly, this cutoff yielded the highest AUC (0.767, 95%CI = 0.750–0.784; p < 0.001 compared with all other cutoffs) to detect MH in the Validation cohort, with a sensitivity and specificity of 77.6 (95% CI = 74.2–80.7) and 75.8 (95%CI = 74.8–76.8). The 2/2 mmHg cutoff also had the greatest accuracy to identify individuals with

Table 2. Performance of studied cutoffs derived from the difference between office and 24 h BP to detect white-coat hypertension[a] in the studied cohorts.

ΔBP cutoffs, mmHg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC (95% CI)	p-value**
Derivation cohort						
28/17	54.1 (51.8–56.5)	89.5 (88.9–90.2)	48.3 (46.1–50.6)	91.5 (91.0–92.1)	0.718 (0.706–0.731)	<0.001
20/15	80.6 (78.7–82.5)	80.2 (79.4–81.0)	42.3 (40.7–44.1)	95.8 (95.4–96.2)	0.804 (0.794–0.814)	–
20/10	93.5 (92.2–94.6)	64.3 (63.3–65.3)	32.1 (30.8–33.4)	98.2 (97.8–98.5)	0.789 (0.781–0.797)	<0.001
16/11	97.1 (96.2–97.8)	63.1 (62.2–64.1)	32.2 (31.0–33.5)	99.2 (98.9–99.4)	0.801 (0.795–0.807)	0.52
15/9	98.8 (98.2–99.3)	54.5 (53.5–55.5)	28.2 (27.0–29.3)	99.6 (99.4–99.8)	0.767 (0.761–0.772)	<0.001
14/9	99.4 (98.9–99.7)	52.9 (51.9–53.9)	27.6 (26.5–28.7)	99.8 (99.6–99.9)	0.761 (0.756–0.767)	<0.001
13 (SBP)	84.5 (82.7–86.2)	68.5 (67.6–69.5)	32.7 (31.3–34.0)	96.1 (95.6–96.5)	0.765 (0.755–0.775)	<0.001
10 (SBP)	90.1 (88.6–91.5)	57.8 (56.8–58.8)	27.8 (26.7–29.0)	97.0 (96.5–97.4)	0.740 (0.731–0.748)	<0.001
Validation cohort						
28/17	59.1 (56.2–61.9)	84.5 (83.6–85.4)	41.9 (39.5–44.3)	91.6 (90.9–92.3)	0.718 (0.703–0.733)	<0.001
20/15	80.0 (77.5–82.2)	73.5 (72.4–74.6)	36.3 (34.4–38.2)	95.1 (94.4–95.7)	0.767 (0.754–0.780)	–
20/10	95.1 (93.7–96.3)	54.5 (53.2–55.8)	28.3 (26.9–29.8)	98.3 (97.8–98.7)	0.748 (0.739–0.757)	0.001
16/11	96.3 (95.1–97.4)	56.1 (54.9–57.4)	29.3 (27.9–30.8)	98.8 (98.4–99.1)	0.762 (0.754–0.771)	0.41
15/9	98.5 (97.6–99.1)	45.9 (44.7–47.2)	25.6 (24.3–26.9)	99.4 (99.0–99.6)	0.722 (0.715–0.729)	<0.001
14/9	98.8 (98.0–99.3)	44.8 (43.5–46.0)	25.3 (24.0–26.6)	99.5 (99.1–99.7)	0.718 (0.711–0.725)	<0.001
13 (SBP)	80.7 (78.3–82.9)	66.0 (64.8–67.2)	31.0 (29.3–32.7)	94.8 (94.0–95.4)	0.733 (0.720–0.746)	<0.001
10 (SBP)	87.4 (85.3–89.2)	56.3 (55.0–57.5)	27.4 (26.0–28.9)	95.9 (95.2–96.6)	0.718 (0.707–0.730)	<0.001

ΔBP—difference between office and 24 h-BP.
AUC area under ROC curve, *PPV* positive predictive value, *NPV* negative predictive value, *BP* blood pressure, *SBP* systolic BP, *CI* confidence interval.
**p-value for the difference between AUC of studied BP cutoffs vs. AUC of 20/15 mmHg cutoff.
[a]Office SBP ≥ 140 or DBP ≥ 90 mmHg and 24 h SBP < 130 and DBP < 80 mmHg.

significant increases in BP grades at 24 h-ABPM compared to the office, which corresponded to the sum of participants with MH and those with SH who had a hypertension grade at the office lower than at 24 h-ABPM (AUC = 0.734, 95%CI = 0.722–0.746; $p < 0.001$ compared with all other cutoffs in the Derivation cohort; AUC = 0.765, 95%CI = 0.750-0.779; $p < 0.001$ compared with all other cutoffs in the Validation cohort) (Table 5).

Results of further analysis including solely individuals using antihypertensive medications (Supplemental Tables 3 and 7) or individuals not using antihypertensive medications (Supplemental Tables 3 and 8) of both cohorts or individuals of the Validation cohort who performed ABPM from 2015 to 2021 (Supplemental Table 9) showed that the 2/2 mmHg cutoff had the highest AUC to detect either MH or individuals with significant increases in BP grades at 24 h-ABPM compared to the office.

DISCUSSION

The present study investigated the best ΔBP cutoff values to detect WCH or MH and higher or lower OBP-than-ABPM grades in two large and independent cohorts. Our findings revealed two key outcomes. Firstly, the 20/15 mmHg cutoff had the best accuracy to identify WCH, particularly among individuals using antihypertensive medications, and to identify individuals with higher OBP-than-ABPM grades. Secondly, the 2/2 mmHg cutoff had the greatest accuracy to identify MH and individuals with lower OBP-than-ABPM grades. These findings suggest that the 20/15 mmHg and 2/2 mmHg cutoffs may serve as markers for significant white-coat and masked effects in individuals undergoing 24 h ABPM, respectively.

In the present report, the ΔBP cutoffs that had the best performance to identify WCH were considered markers of significant white-coat effect. We opted to use this endpoint because WCH is associated with adverse long-term prognosis and might lead to unnecessary antihypertensive treatment with potential adverse and debilitating effects, particularly among elderly individuals [7, 9, 23]. Our analysis showed that the 20/15 and 16/11 mmHg cutoffs yielded statistically similar AUCs to identify WCH in both studied cohorts, with the former cutoff exhibiting lower sensitivity but greater specificity than the latter. However, further analysis revealed that the 20/15 mmHg cutoff had significantly greatest accuracy to identify WCH in treated individuals of both cohorts and to detect higher office BP than 24 h-ABPM grades among all studied cutoffs in both cohorts regardless of antihypertensive medications use. Because office-induced increases in BP commonly persist in later measures [10, 12], these data suggest that the 20/15 mmHg cutoff might be more suitable to identify preferential candidates for more routine 24 h-ABPM aiming to define appropriate BP management strategies and therapy regimens.

The 20/10 mmHg cutoff has been commonly recommended to identify the presence of a significant white-coat effect by several hypertension guidelines [4, 14]. This empirical value was originally proposed in 1991 by Myers and Reeves [15] and was subsequently reported to represent approximately 2.0 standard deviations from the average of a series of ambulatory blood pressure measurements [13]. However, the clinical relevance of this cutoff was not defined. In a previous report evaluating 6049 treated and 5521 untreated individuals who underwent HBPM, the 15/9 mmHg cutoff had significantly superior ability to identify individuals with either WCH or greater OBP-than-HBPM grades compared to the 20/10 mmHg cutoff [20]. In the present report, we extended this analysis to a larger sample of individuals undergoing 24 h-ABPM and found that the 20/15 mmHg cutoff, but not the 20/10 mmHg cutoff, had the greatest accuracy to identify individuals with WCH and greater OBP-than-ABPM grades. In summary, this body of evidence contradicts the retention of the 20/10 mmHg cutoff

Table 3. Performance of studied cutoffs derived from the difference between office and 24 h BP to detect the sum of patients with white-coat hypertension[a] and those with sustained hypertension who had hypertension grade higher at the office than at 24 h ambulatory BP monitoring in the studied cohorts.

ΔBP cutoffs, mmHg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC (95% CI)	p-value**
Derivation cohort						
28/17	58.6 (56.6–60.6)	94.0 (93.5–94.5)	72.4 (70.3–74.4)	89.4 (88.8–90.0)	0.763 (0.753–0.773)	<0.001
20/15	82.6 (81.1–84.1)	85.2 (84.5–86.0)	60.1 (58.4–61.7)	94.8 (94.3–95.3)	0.839 (0.831–0.848)	–
20/10	95.0 (94.1–95.9)	69.0 (68.1–70.0)	45.2 (43.8–46.6)	98.1 (97.7–98.4)	0.820 (0.814–0.827)	<0.001
16/11	97.6 (96.9–98.2)	67.8 (66.8–68.7)	44.9 (43.5–46.2)	99.1 (98.8–99.3)	0.827 (0.821–0.833)	0.003
15/9	99.2 (98.7–99.5)	58.5 (57.5–59.5)	39.1 (37.9–40.3)	99.6 (99.4–99.8)	0.788 (0.783–0.794)	<0.001
14/9	99.5 (99.2–99.8)	56.9 (55.8–57.9)	38.3 (37.1–39.5)	99.8 (99.6–99.9)	0.782 (0.777–0.787)	<0.001
13 (SBP)	84.5 (83.0–85.9)	72.5 (71.5–73.4)	45.2 (43.7–46.7)	94.6 (94.0–95.1)	0.785 (0.776–0.794)	<0.001
10 (SBP)	90.1 (88.8–91.3)	61.4 (60.4–62.4)	38.5 (37.3–39.8)	95.8 (95.3–96.3)	0.758 (0.750–0.765)	<0.001
Validation cohort						
28/17	63.7 (61.5–65.9)	91.6 (90.8–92.3)	72.1 (69.8–74.3)	88.1 (87.3–89.0)	0.777 (0.765–0.788)	<0.001
20/15	84.0 (82.2–85.6)	81.6 (80.6–82.7)	60.8 (58.9–62.7)	93.7 (93.0–94.4)	0.828 (0.818–0.838)	–
20/10	96.8 (95.9–97.5)	61.4 (60.1–62.7)	46.0 (44.4–47.6)	98.2 (97.7–98.7)	0.791 (0.783–0.798)	<0.001
16/11	97.7 (96.9–98.3)	63.2 (61.9–64.5)	47.5 (45.8–49.1)	98.8 (98.3–99.1)	0.804 (0.797–0.812)	<0.001
15/9	99.1 (98.5–99.5)	51.8 (50.4–53.1)	41.1 (39.7–42.6)	99.4 (99.0–99.6)	0.754 (0.747–0.761)	<0.001
14/9	99.2 (98.7–99.6)	50.5 (49.1–51.8)	40.5 (39.1–42.0)	99.5 (99.1–99.7)	0.748 (0.742–0.755)	<0.001
13 (SBP)	81.1 (79.2–82.8)	72.1 (70.8–73.3)	49.7 (47.9–51.5)	91.8 (90.9–92.6)	0.766 (0.755–0.776)	<0.001
10 (SBP)	87.3 (85.7–88.8)	61.8 (60.5–63.1)	43.8 (42.1–45.4)	93.5 (92.6–94.3)	0.746 (0.736–0.756)	<0.001

ΔBP—difference between office and 24 h-BP.
AUC area under ROC curve, *PPV* positive predictive value, *NPV* negative predictive value, *BP* blood pressure, *SBP* systolic BP, *CI* confidence interval.
**p-value for the difference between AUC of studied BP cutoffs vs. AUC of 20/15 mmHg cutoff.
[a]Office SBP ≥ 140 or DBP ≥ 90 mmHg and 24 h SBP < 130 and DBP < 80 mmHg.

as an indicator of clinically relevant white-coat effects based on both 24 h ABPM and HBPM in clinical practice.

Previous studies suggested ΔBP cutoffs to define the presence of masked effect, but there is still no consensus on the optimal threshold to be used in clinical routine [17, 18, 20, 22]. The -1/-1mmHg cutoff, which considers all absolute SBP or DBP values lower at the office compared to the out-of-office environment, has been the most used threshold to define masked effect [17, 18, 22]. In this regard, the analysis of a large sample of treated and untreated alternative Brazilian individuals who underwent HBPM demonstrated that this cutoff had the best performance to identify individuals with MH, a phenotype recognizably associated with long-term adverse prognosis [8], as well as lower OBP-than-HBPM grades [20]. In contrast to these findings, we found herein that the 2/2 mmHg had a superior ability to detect individuals with MH and lower OBP-than-ABPM grades compared to the −1/−1mmHg cutoff. The reasons for the discrepancies between the studies are unclear but may involve differences in the clinical characteristics of the respective populations. Another explanation may be related to the fact that ABPM and HBPM are not similar measurements. Previous studies evaluating populations who underwent both ABPM and HBPM demonstrated that average 24 h-ABPM values are usually lower than average HBPM values, resulting in greater ΔBP values derived from 24 h-ABPM compared to HBPM [24, 25]. In agreement with this notion, our Derivation and Validation cohorts had ΔSBP and ΔDBP values that were in average 2–4 mmHg greater than those described in the aforementioned HBPM study [20]. This difference could contribute to explain the 3 mmHg difference between the −1/−1 and 2/2 mmHg cutoffs derived from HBPM and 24 h-ABPM, respectively, and reinforce the notion that the BP measurements derived from these techniques may not be interchangeable for estimating masked effects [26].

This study's strengths lie in its utilization of diverse multicenter cohorts with substantial sample sizes. However, this study has some limitations that should be addressed. Firstly, only one BP reading was used to define OBP, which is lower than the number of readings recommended by current hypertension guidelines and could potentially lead to a greater white-coat effect and prevalence of WCH [4–6]. However, it is noteworthy that in our protocol the OBP reading was systematically preceded by another OBP reading performed with the same device, but that was not recorded. Thus, it can be expected that this first unrecorded OBP reading might have played a role in attenuating the white-coat effect in our estimated OBP measure. Secondly, data on cardiovascular risk factors that could affect OBP and ABPM, such as smoking, diabetes status, and alcohol intake, were unavailable. Thirdly, the lack of information on follow-up and incident cardiovascular events does not allow us to evaluate the prognostic value of the studied cutoffs. Fourthly, given the long time span of data collection (from 2015 to 2021 in the Derivation cohort and from 2011 to 2021 in the Validation cohort), it cannot be discarded that potential temporal effects or changes in clinical practices over those years might have affected ABPM measurements and therefore the obtained results.

CONCLUSION

The current study showed that the 20/15 mmHg cutoff had the best accuracy to detect WCH and higher OBP-than-ABPM grades, whereas the 2/2 mmHg cutoff had the best accuracy to detect MH and lower OBP-than-ABPM grades in two large and independent cohorts. These cutoffs may indicate significant white-coat and masked effects and might be used to identify preferential candidates for regular 24 h-ABPM to determine appropriate BP management strategies and therapy regimens.

Table 4. Performance of studied cutoffs derived from the difference between office and 24 h BP to detect masked hypertension[a] in the studied cohorts.

ΔBP cutoffs, mmHg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC (95% CI)	p-value**
Derivation cohort						
−14/−9	17.1 (14.9–19.4)	97.0 (96.6–97.3)	38.3 (34.0–42.7)	91.4 (90.9–91.9)	0.570 (0.559–0.582)	<0.001
−5/−2	47.2 (44.2–50.2)	86.8 (86.1–87.4)	28.2 (26.2–30.3)	93.7 (93.2–94.2)	0.670 (0.655–0.685)	<0.001
−5 (SBP)	31.4 (28.7–34.2)	92.6 (92.0–93.1)	31.7 (29.0–34.5)	92.5 (91.9–93.0)	0.620 (0.606–0.634)	<0.001
−3/−1	55.8 (52.9–58.8)	82.9 (82.1–83.6)	26.4 (24.6–28.2)	94.5 (94.0–94.9)	0.694 (0.679–0.708)	<0.001
−3 (SBP)	38.6 (35.7–41.5)	89.8 (89.2–90.4)	29.3 (27.0–31.7)	93.0 (92.5–93.5)	0.642 (0.627–0.656)	<0.001
−1/−1	61.4 (58.4–64.2)	80.2 (79.4–81.0)	25.4 (23.7–27.1)	95.0 (94.5–95.4)	0.708 (0.693–0.722)	<0.001
0/0	66.4 (63.6–69.2)	76.9 (76.1–77.7)	24.0 (22.5–25.5)	95.4 (95.0–95.9)	0.717 (0.702–0.731)	<0.001
2/2	78.9 (76.4–81.2)	69.3 (68.4–70.2)	22.0 (20.8–23.3)	96.8 (96.3–97.2)	0.741 (0.728–0.754)	–
Validation cohort						
−14/−9	17.1 (14.3–20.2)	98.3 (98.0–98.6)	50.0 (43.3–56.7)	92.2 (91.6–92.9)	0.577 (0.562–0.591)	<0.001
−5/−2	44.7 (40.9–48.6)	90.9 (90.2–91.6)	32.9 (29.8–36.1)	94.3 (93.7–94.8)	0.678 (0.659–0.698)	<0.001
−5 (SBP)	35.4 (31.8–39.2)	93.6 (93.0–94.2)	35.6 (31.9–39.4)	93.6 (92.9–94.1)	0.645 (0.627–0.664)	<0.001
−3/−1	54.7 (50.8–58.5)	87.8 (87.0–88.6)	30.9 (28.2–33.6)	95.1 (94.5–95.6)	0.712 (0.693–0.732)	<0.001
−3 (SBP)	43.1 (39.2–46.9)	91.3 (90.6–91.9)	33.0 (29.8–36.2)	94.1 (93.5–94.7)	0.672 (0.652–0.691)	<0.001
−1/−1	61.4 (57.5–65.1)	84.7 (83.8–85.6)	28.6 (26.3–31.1)	95.6 (95.1–96.2)	0.730 (0.711–0.750)	<0.001
0/0	66.3 (62.5–69.9)	81.9 (81.0–82.9)	26.8 (24.7–29.0)	96.1 (95.5–96.5)	0.741 (0.722–0.760)	<0.001
2/2	77.6 (74.2–80.7)	75.8 (74.8–76.8)	24.2 (22.4–26.1)	97.1 (96.6–97.6)	0.767 (0.750–0.784)	–

ΔBP—difference between office and 24 h-BP.
AUC area under ROC curve, *PPV* positive predictive value, *NPV* negative predictive value, *BP* blood pressure, *SBP* systolic BP, *CI* confidence interval.
**p-value for the difference between AUC of studied BP cutoffs vs. AUC of 2/2 mmHg cutoff.
[a]Office SBP < 140 and DBP < 90 mmHg and 24 h SBP ≥ 130 or DBP ≥ 80 mmHg.

Table 5. Performance of studied cutoffs derived from the difference between office and 24 h BP to detect the sum of patients with masked hypertension[a] and those with sustained hypertension who had hypertension grade lower at the office than at 24 h ambulatory BP monitoring in the studied cohorts.

ΔBP cutoffs, mmHg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC (95% CI)	p-value**
Derivation cohort						
−14/−9	14.7 (13.0–16.7)	97.1 (96.8–97.4)	43.3 (38.9–47.8)	88.4 (87.8–89.0)	0.559 (0.550–0.569)	<0.001
−5/−2	43.3 (40.8–45.9)	87.4 (86.7–88.1)	33.9 (31.8–36.1)	91.2 (90.6–91.8)	0.654 (0.641–0.667)	<0.001
−5 (SBP)	28.0 (25.7–30.4)	92.9 (92.4–93.4)	37.0 (34.1–39.9)	89.6 (89.0–90.2)	0.604 (0.593–0.616)	<0.001
−3/−1	52.3 (49.7–54.9)	83.7 (83.0–84.4)	32.4 (30.5–34.3)	92.2 (91.6–92.7)	0.680 (0.667–0.693)	0.003
−3 (SBP)	34.9 (32.5–37.4)	90.2 (89.6–90.8)	34.8 (32.3–37.3)	90.3 (89.7–90.9)	0.626 (0.613–0.638)	<0.001
−1/−1	57.6 (55.0–60.1)	81.1 (80.3–81.9)	31.2 (29.5–33.0)	92.8 (92.2–93.3)	0.694 (0.680–0.707)	<0.001
0/0	63.3 (60.8–65.8)	78.0 (77.1–78.8)	30.0 (28.4–31.6)	93.4 (92.9–94.0)	0.706 (0.693–0.719)	<0.001
2/2	76.2 (73.9–78.3)	70.6 (69.7–71.5)	27.9 (26.5–29.3)	95.2 (94.7–95.7)	0.734 (0.722–0.746)	–
Validation cohort						
−14/−9	13.6 (11.4–16.0)	98.4 (98.1–98.7)	55.4 (48.6–62.0)	88.7 (88.0–89.5)	0.560 (0.549–0.571)	<0.001
−5/−2	42.7 (39.5–46.0)	92.1 (91.4–92.7)	43.8 (40.5–47.2)	91.7 (91.0–92.4)	0.674 (0.658–0.690)	<0.001
−5 (SBP)	33.6 (30.6–36.8)	94.5 (93.9–95.1)	47.1 (43.2–51.0)	90.8 (90.0–91.5)	0.641 (0.625–0.656)	<0.001
−3/−1	52.9 (49.6–56.2)	89.3 (88.5–90.0)	41.6 (38.8–44.5)	92.9 (92.2–93.5)	0.711 (0.694–0.727)	<0.001
−3 (SBP)	41.5 (38.3–44.8)	92.5 (91.8–93.1)	44.3 (41.0–47.7)	91.6 (90.9–92.3)	0.670 (0.654–0.686)	<0.001
−1/−1	60.0 (56.8–63.2)	86.4 (85.5–87.2)	39.0 (36.4–41.6)	93.7 (93.1–94.3)	0.732 (0.716–0.749)	<0.001
0/0	65.1 (61.9–68.2)	83.7 (82.8–84.7)	36.7 (34.3–39.1)	94.3 (93.7–94.9)	0.744 (0.728–0.760)	<0.001
2/2	75.2 (72.3–78.0)	77.7 (76.6–78.7)	32.8 (30.8–34.8)	95.6 (95.0–96.1)	0.765 (0.750–0.779)	–

ΔBP—difference between office and 24 h-BP.
AUC area under ROC curve, *PPV* positive predictive value, *NPV* negative predictive value, *BP* blood pressure, *SBP* systolic BP, *CI* confidence interval.
**p-value for the difference between AUC of studied BP cutoffs vs. AUC of 2/2 mmHg cutoff.
[a]Office SBP < 140 and DBP < 90 mmHg and 24 h SBP ≥ 130 or DBP ≥ 80 mmHg.

SUMMARY

What is known about topic

- Patients with large white-coat and masked blood pressure (BP) effects are recommended to undergo out-of-office BP measurements more frequently as an adjuvant strategy to increment BP management and monitor the therapeutic response.
- However, the values used to define white-coat and masked blood pressure effects are arbitrary and not consensual.

What this study adds

- This study investigated the accuracy of various cutoffs based on the differences (ΔBP) between office BP and 24h-ambulatory BP monitoring (ABPM) to identify white-coat (WCH) and masked (MH) hypertension as markers of white-coat and masked BP effects.
- Two large cohorts were evaluated: Derivation cohort (n = 11,350) and Validation cohort (n = 7220).
- The 20/15 mmHg cutoff showed the greatest accuracy to detect WCH, while the 2/2 mmHg cutoff showed the highest accuracy to detect MH in both cohorts. These cutoffs may serve as indicators of marked white-coat and masked BP effects derived from 24 h-ABPM.

DATA AVAILABILITY

Additional data are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

CSDP, ADMF, and WNJ contributed to the conception and design of the work. CSDP, ADMF, RB, AHBM, GMV, SS, GSAA, MAM-G, WSB, RDM, ECDB, AAB, CLDMF, TATG, FN, DMJ, ACS, and WNJ contributed to the acquisition, analysis, or interpretation of data for the work. CSDP, ADMF, and WNJ drafted the manuscript. AHBM, GMV, SS, GSAA, MAM-G, WSB, RDM, ECDB, AAB, CLDMF, TATG, FN, DMJ, and ACS critically revised the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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