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Office blood pressure threshold of 130/80 mmHg better predicts uncontrolled out-of-office blood pressure in apparent treatment-resistant hypertension

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Abstract

The objective of this study was to compare the diagnostic accuracy of office blood pressure (BP) threshold of 140/90 and 130/80 mmHg for correctly identifying uncontrolled out-of-office BP in apparent treatment-resistant hypertension (aTRH). We analyzed 468 subjects from a prospectively enrolled cohort of patients with resistant hypertension in South Korea (clinicaltrials.gov: NCT03540992). Resistant hypertension was defined as office BP ≥ 130/80 mmHg with three different classes of antihypertensive medications including thiazide-type/like diuretics, or treated hypertension with four or more different classes of antihypertensive medications. We

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conducted different types of BP measurements including office BP, automated office BP (AOBP), home BP, and ambulatory BP. We defined uncontrolled out-of-office BP as daytime BP ≥ 135/85 mmHg and/or home BP ≥ 135/85 mmHg. Among subjects with office BP < 140/90 mmHg and subjects with office BP < 130/80 mmHg, 66% and 55% had uncontrolled out-of-office BP, respectively. The prevalence of controlled and masked uncontrolled hypertension was lower, and the prevalence of white-coat and sustained uncontrolled hypertension was higher, with a threshold of 130/80 mmHg than of 140/90 mmHg, for both office BP and AOBP. The office BP threshold of 130/80 mmHg was better able to diagnose uncontrolled out-of-office BP than 140/90 mmHg, and the net reclassification improvement (NRI) was 0.255. The AOBP threshold of 130/80 mmHg also revealed better diagnostic accuracy than 140/90 mmHg, with NRI of 0.543. The office BP threshold of 130/80 mmHg showed better than 140/90 mmHg in terms of the correspondence to out-of-office BP in subjects with aTRH.

1 | INTRODUCTION

Resistant hypertension is defined as blood pressure (BP) above treatment goals despite the concurrent use of three or more antihypertensive drugs, including diuretics, and also includes cases of patients whose BP achieves target values on four or more antihypertensive drugs.[1] The prevalence of resistant hypertension is between 12% and 18% of the hypertensive population[1-3] and is associated with increased risk for end-stage renal disease, cardiovascular events, and mortality.[1,4] Therefore, correct identification and BP control in these high-risk subjects are imperative. However, office BP measurement has limitations for identifying true resistant hypertension because up to 37.5% of apparent treatment-resistant hypertension (aTRH) cases, based on office BP measurements, have white-coat uncontrolled hypertension.[5] Additionally, an office BP threshold that better predicts uncontrolled out-of-office BP is imperative, as ambulatory BP measurements are more significantly associated with cardiovascular events than are office BP measurements.[6]

Recently, the American College of Cardiology (ACC) and the American Heart Association (AHA) redefined most of the target blood pressures as below 130/80 mmHg as well as hypertension threshold as 130/80 mmHg.[7] Based on this new target BP, the 2018 scientific statement from the AHA lowered the BP threshold of resistant hypertension from above 140/90 mmHg, based on the 2008 AHA definition, to above 130/80 mmHg.[1,8] Theoretically, lowering the office BP target to 130/80 mmHg would lower the prevalence of masked uncontrolled hypertension while increasing white-coat uncontrolled hypertension, assuming that the diagnostic threshold for ambulatory BP monitoring (ABPM) remains the same.

The objective of this study was to compare the diagnostic accuracy of the 2018 and 2008 definitions of aTRH for correctly identifying controlled and uncontrolled out-of-office BP (ABPM and home BP measurements) and evaluate the change in the prevalence of masked uncontrolled hypertension according to threshold change in a prospective cohort of subjects with baseline aTRH.

2 | METHODS

2.1 | Study design and subjects

This prospective, multi-center, cohort study for patients with resistant hypertension was conducted in twelve tertiary hospitals in South Korea (clinicaltrials.gov: NCT03540992). The institutional review board of the Yonsei University Health System Clinical Trial Center approved the study (IRB No. 4-2017-1222), and all subjects provided written informed consent.

Subjects were eligible for enrollment if they were ≥20 years of age, had a diagnosis of resistant hypertension based on office systolic BP (SBP) ≥130 mmHg or office diastolic BP (DBP) ≥80 mmHg with three different classes of antihypertensive medications including thiazide-type/like diuretics, or treated hypertension with four or more different classes of antihypertensive medications regardless of the BP level. Those subjects with a desired life expectancy of under six months due to non-cardiovascular disease, and pregnant or nursing women, were excluded. We also excluded those subjects who had acute renal allograft rejection within the first 3 months of transplantation, those within the first 6 months of discharge from hospitalization for acute coronary syndrome or acute stroke, and those with systolic heart failure (left ventricular ejection fraction ≤40%). In this study, we included 468 subjects who had enrolled in the registry between February 2018 and April 2020. At the baseline, all subjects completed a standardized survey including collection of anthropometric data, past medical history, current medications, socioeconomic status, cognitive function, and medication adherence. All subjects had biochemical parameters measured, including lipid profile, serum creatinine

level, blood urea nitrogen level, electrolyte levels, fasting glucose levels, and urinary albumin/creatinine ratio.

2.2 | Measurements of BP

For all subjects, we performed and analyzed different types of BP measurements, including office BP, automated office BP (AOBP), home BP, and ambulatory BP measurement. Office BP was taken in the research examination room by a trained nurse. After 5 minutes of rest in a sitting position, single brachial BP measurement was performed on the dominant arm using a validated automated device (HEM 7080-IC; Omron). After a further 5 minutes of rest, either unattended or attended AOBP measurements were obtained using a validated automated device (HEM 7080-IC; Omron), according to the discretion of the investigators at each research center. For unattended AOBP measurements (four centers, *N* = 78), after positioning the subjects and setting the device, the trained nurse left the subject alone in the examination room. For attended AOBP measurements (six centers, *N* = 390), after positioning the subjects and setting the device, the trained nurse left the subject alone but did not leave the examination room. The average of three BP readings taken at 2-minute intervals after 5 minutes of rest was used in this study using the nocturnal automatic BP measurement mode.[9,10] Home BP was measured using the validated digital device (HEM-7130; Omron). Home BP was measured twice a day in the morning and the evening, at the same time and location, for seven consecutive days before the hospital visits. In principle, morning BP was measured twice before the subjects took antihypertensive medications within 2 hours of waking up, and evening BP was measured twice within 1 hour of bedtime. We used the average of these measurements for analysis. Twenty-four-hour ABPM was performed every 30 minutes with the sphygmomanometers recommended by the Dabl Educational Trust.[11] Among the total subjects, 400 were measured by TM-2430 (A&D Medical), 55 were measured by Mobil-O-Graph (IEM), and 13 were measured by Tonoport V (GE). Ambulatory BP readings were averaged for 24-hour, daytime, and nighttime periods.[12] Daytime and nighttime periods were defined according to the information provided by the patient.

Home BP ≥ 135/85 mmHg and ABPM daytime BP ≥ 135/85 mmHg were defined as uncontrolled home BP and uncontrolled daytime BP, respectively.[13] If home BP or daytime BP was ≥ 135/85 mmHg, it was defined as uncontrolled out-of-office BP.[14,15] Hypertension phenotypes were defined as controlled hypertension (office BP < target BP and out-of-office BP < target BP), white-coat uncontrolled hypertension (office BP ≥ target BP and out-of-office BP < target BP), masked uncontrolled hypertension (office BP < target BP and out-of-office BP ≥ target BP), and sustained uncontrolled hypertension (office BP ≥ target BP and out-of-office BP ≥ target BP).[16]

2.3 | Statistical analysis

Descriptive statistics included sample size (*N*), the arithmetic mean ± standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables, which were calculated for all baseline demographics. The patient group was divided into two according to whether out-of-office BP was controlled or uncontrolled.

To identify the office SBP/DBP or automated office SBP/DBP with the highest sensitivity and specificity that best matched uncontrolled out-of-office BP, we used the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. We calculated the sensitivity, specificity, and accuracy of each office BP threshold for uncontrolled out-of-office BP. In addition, we also used net reclassification of improvement (NRI) to quantify the discrimination improvement, a method previously described by Pencina et al.[17,18] An NRI greater than zero (NRI > 0) represents a relative increase in the predicted probabilities for subjects who have uncontrolled out-of-office BP and a decrease for subjects who do not. All statistical analyses were performed in R version 3.6.3 (http://www.r-project.org).

3 | RESULTS

3.1 | Baseline characteristics of study subjects

The mean age of the study subjects was 61 ± 13 years, and 58% of the subjects were male. The mean body mass index was 28.0 ± 4.1 kg/m^2, and the majority of subjects (77%) had body mass index >25 kg/m^2. The most common comorbid condition was dyslipidemia, followed by diabetes. Therefore, mean fasting blood glucose was above 100 mg/dl, although the mean LDL-cholesterol level was 89.6 ± 32.3 mg/dl because many subjects were taking statins. The prevalence of chronic kidney disease and stroke was higher in the uncontrolled out-of-office BP group than in the controlled out-of-office BP group (Table 1).

Table 2 shows blood pressure measurements, types of antihypertensive medications prescribed, and number of medications. All BP measurements, including office BP and AOBP, were higher in the uncontrolled out-of-office BP group than in the controlled out-of-office BP group. Among all study subjects, the prescription rates of thiazide-like diuretics, renin-angiotensin system blockers, and calcium channel blockers were all above 97%, with beta-blockers the next most prescribed. Mineralocorticoid antagonist (MRA) had only 17.9% utilization. The majority of the study subjects were taking more than four antihypertensive drugs. The rate of MRA use was lower in the uncontrolled out-of-office BP group than in the controlled out-of-office BP group. The number of prescribed antihypertensive medications did not differ between the groups.

TABLE 1 Baseline characteristics

Variables	Total (*N* = 468)	Controlled out-of-office BP (*N* = 111)	Uncontrolled out-of-office BP (*N* = 357)	*p* Value
Age, years	60.8 ± 12.9	61.1 ± 11.8	60.7 ± 13.2	.77
Male, *N* (%)	270 (57.7%)	62 (55.9%)	208 (58.3%)	.735
Height, cm	163.8 ± 9.7	163.1 ± 10.4	164.1 ± 9.5	.366
Weight, kg	75.7 ± 15.3	75.1 ± 17.2	75.9 ± 14.8	.693
Body mass index, kg/m^2	28.0 ± 4.1	28.0 ± 4.3	28.0 ± 4.1	.949
Current smoker, *N* (%)	72 (15.4%)	9 (8.1%)	63 (17.6%)	.022
Alcohol drinking, *N* (%)	283 (60.5%)	66 (59.5%)	217 (60.8%)	.89
Diabetes, *N* (%)	311 (66.5%)	75 (67.6%)	236 (66.1%)	.865
Dyslipidemia, *N* (%)	467 (99.8%)	111 (100.0%)	356 (99.7%)	1.00
Chronic kidney disease, *N* (%)	31 (6.6%)	2 (1.8%)	29 (8.1%)	.034
Heart failure, *N* (%)	42 (9.0%)	10 (9.0%)	32 (9.0%)	1.00
Myocardial infarction, *N* (%)	21 (4.5%)	6 (5.4%)	15 (4.2%)	.785
Angina, *N* (%)	102 (21.8%)	30 (27.0%)	72 (20.2%)	.162
Stroke, *N* (%)	45 (9.6%)	4 (3.6%)	41 (11.5%)	.023
Transient ischemic attack, *N* (%)	8 (1.7%)	1 (0.9%)	7 (2.0%)	.739
Blood urea nitrogen, mg/dl	18.5 ± 11.1	17.8 ± 5.1	18.8 ± 12.4	.222
Creatinine, mg/dl	0.9 ± 0.3	0.9 ± 0.2	1.0 ± 0.4	.001
Glucose, mg/dl	117.5 ± 31.2	118.5 ± 30.3	117.2 ± 31.5	.711
Total cholesterol, mg/dl	165.7 ± 34.6	164.0 ± 38.0	166.2 ± 33.5	.575
LDL-cholesterol, mg/dl	89.9 ± 32.3	88.7 ± 33.1	90.3 ± 32.1	.669
HDL-cholesterol, mg/dl	48.9 ± 11.5	49.2 ± 11.7	48.9 ± 11.4	.825
Triglyceride, mg/dl	141.0 (105.0-191.5)	142 (104.0-182.0)	141 (105.0-198.5)	.642
Na^+, mmol/L	141.1 ± 2.6	140.6 ± 2.5	141.3 ± 2.6	.018
K^+, mmol/L	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	.877
Urine albumin creatinine ratio	18.5 (8.9-76.5)	16.8 (8.1-42.2)	20.1 (9.2-83.5)	.094

Note: Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical variables are presented as number (%).

Abbreviations: BC, both controlled; BU, both uncontrolled; BP, blood pressure; DU, daytime uncontrolled; HU, home uncontrolled.

3.2 | Accuracy of the 140/90 and 130/80 mmHg in-office BP and AOBP for diagnosis of uncontrolled out-of-office BP in patients with resistant hypertension

We defined uncontrolled out-of-office BP as daytime BP ≥ 135/85 mmHg and/or one-week average home BP of ≥ 135/85 mmHg, and tried to assess the discriminative value of the different office BP levels and identify the most appropriate office BP threshold for diagnosis of uncontrolled out-of-office BP. In the ROC curve analysis (Figure 1), the office SBP and DBP with the highest sensitivity and specificity for identifying uncontrolled out-of-office BP was 137 and 79 mmHg, respectively (Figure 1A,B). The AUC of office SBP and office DBP was 0.697 (95% CI, 0.644-0.750) and 0.614 (95% CI, 0.557-0.614), respectively. The automated office SBP and DBP of 142 and 80 mmHg, respectively, showed the highest sensitivity and specificity for identifying uncontrolled out-of-office BP (Figure 1C,D). The AUC of automated office SBP and office DBP was 0.703 (95% CI, 0.651-0.756) and 0.636 (95% CI, 0.583-0.589), respectively. The AUC of office SBP and automated Office SBP were not different (p = .755), and so were the AUC of Office DBP and automated office DBP (p = .252). However, the AUC of SBP was significantly greater than that of DBP in both office BP (p = .002) and automated office BP (p = .018).

Table 3 compares the diagnostic accuracy for uncontrolled out-of-office BP using an office BP threshold of 140/90 and 130/80 mmHg. Scatter plots of office BP and automated office BP according to out-of-office BP status were shown in supplemental material (Figure S1). The threshold of 130/80 mmHg was better able to diagnose uncontrolled out-of-office BP than was a threshold

TABLE 2 Blood pressure measurement and use of antihypertensive medications

Variables	Total (*N* = 468)	Controlled out-of-office BP (*N* = 111)	Uncontrolled out-of-office BP (*N* = 357)	*p* Value
Office SBP	140.0 ± 18.2	130.6 ± 14.2	143.0 ± 18.3	<.001
Office DBP	80.0 ± 11.7	76.5 ± 10.1	81.1 ± 12.0	<.001
Automated office SBP	137.1 ± 16.4	128.0 ± 12.7	139.9 ± 16.5	<.001
Automated office DBP	78.0 ± 11.1	74.2 ± 7.9	79.2 ± 11.6	<.001
Home SBP	129.9 ± 12.5	120.1 ± 8.5	133.0 ± 11.9	<.001
Home DBP	78.9 ± 9.2	74.0 ± 6.1	80.4 ± 9.5	<.001
Daytime SBP	140.1 ± 17.2	122.5 ± 7.2	145.6 ± 15.7	<.001
Daytime DBP	82.6 ± 10.5	74.8 ± 5.0	85.1 ± 10.6	<.001
Thiazide-like	461 (98.5%)	110 (99.1%)	351 (98.3%)	.886
Renin-angiotensin system blocker	454 (97.0%)	106 (95.5%)	348 (97.5%)	.452
Calcium channel blocker	458 (97.9%)	108 (97.3%)	350 (98.0%)	.923
Beta-blocker	387 (82.7%)	97 (87.4%)	290 (81.2%)	.176
Alpha-blocker	37 (7.9%)	5 (4.5%)	32 (9.0%)	.187
Mineralocorticoid antagonist	84 (17.9%)	30 (27.0%)	54 (15.1%)	.007
Minoxidil	2 (0.4%)	0 (0.0%)	2 (0.6%)	1.00
Number of medications				
3	68 (14.5%)	8 (7.2%)	60 (16.8%)	
4	327 (69.9%)	85 (76.6%)	242 (67.8%)	.144
5	62 (13.2%)	15 (13.5%)	47 (13.2%)	
6	10 (2.1%)	3 (2.7%)	7 (2.0%)	
7	1 (0.2%)	0 (0.0%)	1 (0.3%)	

Note: Data are presented as mean ± standard deviation or number (%).

Abbreviations: BC, both controlled; BU, both uncontrolled; BP, Blood pressure; DBP, diastolic blood pressure; DU, daytime uncontrolled; HU, home uncontrolled; SBP, systolic blood pressure.

of 140/90 mmHg, and the NRI was 0.255. The accuracy of office BP threshold of 130/80 mmHg for identifying uncontrolled out-of-office BP was higher than that of office BP threshold of 140/90 mmHg (74.1% vs. 60.9%; Table S1 and Table S2). In terms of the AOBP threshold for diagnosing uncontrolled out-of-office BP, the AOBP of 130/80 mmHg revealed better diagnostic accuracy than the AOBP of 140/90 mmHg; the NRI was 0.543. The accuracy of AOBP threshold of 130/80 mmHg was higher than that of office BP threshold of 140/90 mmHg (73.1% vs. 54.1%; Table S3 and Table S4). In addition, with the same threshold of 130/80 mmHg, AOBP, compared to office BP, revealed a slightly improved diagnostic accuracy for identifying uncontrolled out-of-office BP (Table 4, NRI = 0.076).

3.3 | Comparison of office BP and AOBP thresholds for uncontrolled out-of-office BP in patients with resistant hypertension

The prevalence of hypertension phenotypes was different between office BP and AOBP thresholds of 130/80 mmHg and of 140/90 mmHg (Figure 2). The prevalence of controlled and masked uncontrolled hypertension was lower, and the prevalence of white-coat and sustained uncontrolled hypertension was higher, with a threshold of 130/80 mmHg than of 140/90 mmHg, for both office BP and AOBP. With the same BP threshold, the prevalence of white-coat uncontrolled hypertension was lower with AOBP measurement than with office BP measurement.

In this study, 230 subjects had an office BP less than 140/90 mmHg (Table 5). However, of these, 128 subjects (56%) had uncontrolled daytime BP and 66 subjects (29%) had uncontrolled home BP. There were 151 subjects (66%) who had uncontrolled home BP and/or uncontrolled daytime BP. Among 98 subjects whose office BP was controlled below 130/80 mmHg, 54 subjects (55%) had uncontrolled home BP and/or uncontrolled daytime BP. Even though the proportion of subjects with uncontrolled out-of-office BP was still high (55%), it was lower than that when the threshold of 140/90 mmHg was applied (66%).

Among 282 subjects who had an AOBP of less than 140/90 mmHg, 193 subjects (68%) had uncontrolled out-of-office BP. The proportion of subjects with uncontrolled out-of-office BP was 56% among 127 subjects who had an AOBP < 130/80 mmHg.

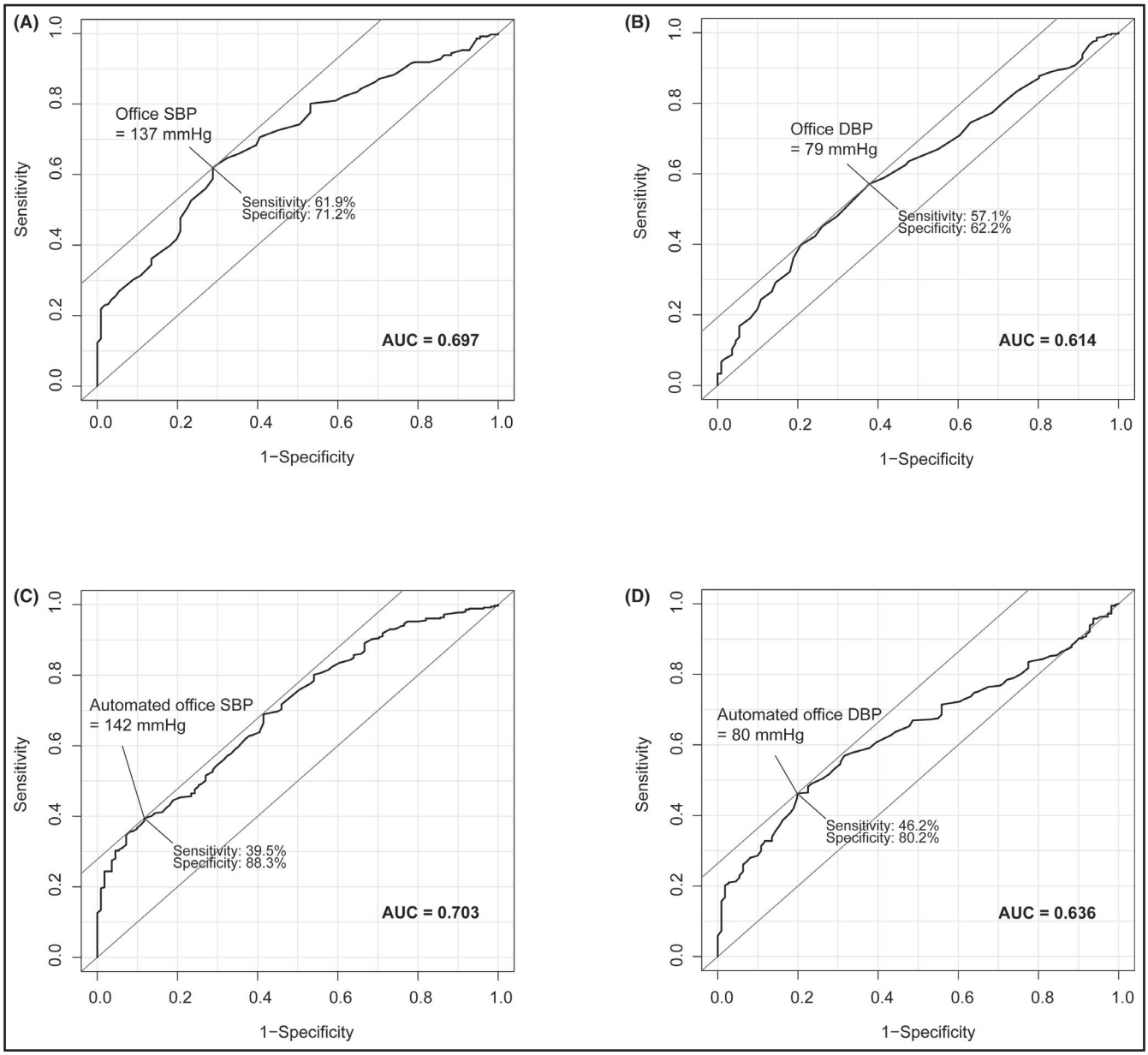

FIGURE 1 Receiver operating curve analyses of office systolic (A), diastolic (B), automated office systolic (C), and diastolic (D) blood pressure for identifying uncontrolled out-of-office blood pressure (BP)

4 | DISCUSSION

The key findings from this study are as follows. First, office BP or AOBP threshold of 130/80 mmHg better predicts uncontrolled out-of-office BP than threshold of 140/90 mmHg. Second, the proportion of subjects who had uncontrolled out-of-office BP is relatively high even if office BP or AOBP is controlled. Lowering office BP threshold to 130/80 mmHg makes it slightly more likely that out-of-office BP is also within the threshold of 135/85 mmHg. This should be considered for better BP control in subjects with resistant hypertension.

Using an office BP or AOBP threshold of 130/80 mmHg showed better correspondence to uncontrolled out-of-office BP, based on both ABPM and home BP monitoring. The increase in white-coat uncontrolled hypertension was offset by a decrease in masked uncontrolled hypertension so that overall BP control could be improved if the lower diagnostic threshold for aTRH is adopted. If resistant hypertension is defined as only uncontrolled office BP despite using 3 or more antihypertensive agents including diuretics without consideration for out-of-office BP measurements, then adopting an office BP threshold of 140/90 mmHg would seem logical, since lowering the threshold to 130/80 mmHg would increase the prevalence of white-coat uncontrolled hypertension. In a study by de la Sierra et al, among 8295 subjects with resistant hypertension, defined as an office BP ≥ 140/90 mmHg while being treated with three or more antihypertensive drugs including a diuretic, 37.5% had white-coat resistant hypertension.[5] Since white-coat uncontrolled hypertension has been shown to have a better prognosis than true resistant

TABLE 3 Reclassification tables for uncontrolled out-of-office blood pressure (BP) according to change of office BP threshold from 140/90 to 130/80 mmHg and according to change of automated office BP threshold from 140/90 to 130/80 mmHg

Daytime BP 135/85 mmHg or Home BP 135/85 mmHg	Office BP 140/90 mmHg	Office BP 130/80 mmHg	Reclassification improvement	Automated office BP 140/90 mmHg	Automated office BP 130/80 mmHg	Reclassification improvement
Controlled (*N* = 111)	Controlled (*N* = 79)[a]	Controlled (*N* = 44)	−0.152[i]	Controlled (*N* = 89)[k]	Controlled (*N* = 56)	−0.113[s]
		Uncontrolled (*N* = 35)[e]			Uncontrolled (*N* = 33)[o]	
	Uncontrolled (*N* = 32)[b]	Controlled (*N* = 0)[f]		Uncontrolled (*N* = 22)[l]	Controlled (*N* = 0)[p]	
		Uncontrolled (*N* = 32)			Uncontrolled (*N* = 22)	
Uncontrolled (*N* = 357)	Controlled (*N* = 151)[c]	Controlled (*N* = 54)	0.407[j]	Controlled (*N* = 193)[m]	Controlled (*N* = 71)	0.656[t]
		Uncontrolled (*N* = 97)[g]			Uncontrolled (*N* = 122)[q]	
	Uncontrolled (*N* = 206)[d]	Controlled (*N* = 0)[h]		Uncontrolled (*N* = 164)[n]	Controlled (*N* = 0)[r]	
		Uncontrolled (*N* = 206)			Uncontrolled (*N* = 164)	

Note: i = (f − e)/(a + c); j = (g − h)/(b + d); Net reclassification improvement = i + j = 0.255.
s = (p − o)/(k + m); t = (q − r)/(l + n); Net reclassification improvement = s + t = 0.543.

hypertension (sustained uncontrolled hypertension) and masked uncontrolled hypertension, avoiding the misclassification of white-coat uncontrolled hypertensive patients as true resistant hypertensive is important.[19] However, among aTRH subjects who have controlled office BP with four or more antihypertensive medications, identification of the appropriate office BP threshold to minimize the number of subjects with masked uncontrolled hypertension is imperative, because out-of-office BP measurements are more predictive of cardiovascular events than are office BP measurements.[20,21] The results from this study clearly show that lowering the office BP threshold lowers the prevalence of masked uncontrolled HT. This may be particularly important in the Asia/Pacific region, where masked hypertension is more prevalent.[22]

According to the Spanish ABPM registry study, 31.1% of the subjects with treated and controlled office BP had masked uncontrolled hypertension (uncontrolled out-of-office BP).[23] In our study, it is noticeable that the prevalence of masked uncontrolled hypertension in resistant hypertension is quite high. Among the 98 subjects whose office BP was controlled below 130/80 mmHg, 54 subjects (55%) had uncontrolled home BP or uncontrolled daytime BP (Table 5). Even though the proportion of subjects with out-of-office BP above the threshold was still high, it was lower than that when the threshold of 140/90 mmHg was applied (66%). With further treatment to lower blood pressure, the office BP threshold should be targeted to 130/80 mmHg as true controlled hypertension (controlled out-of-office BP) is more likely to be identified, conferring a better prognosis.[24] Despite this, when considering the relatively high number of cases of uncontrolled out-of-office BP, measured via home BP or ABPM, in subjects with office BP below 130/80 mmHg, the use of out-of-office BP monitoring is imperative in the management of resistant hypertension. We used a threshold ABPM daytime BP of 135/85 mmHg and a home BP of 135/85 mmHg for diagnosing true resistant hypertension, despite the 2017 ACC/AHA guidelines recommending a threshold of 130/80 mmHg as the corresponding value for a clinic BP of 130/80 mmHg.[7] This was because the European Society of Cariology/European Society of Hypertension still defines elevated daytime ABPM BP and home BP as 135/85 mmHg or above, and most of the studies that demonstrate the prognostic significance of ABPM and home BP have been validated using this threshold.[13] As an uncontrolled BP above the threshold of prognostic significance is of importance in resistant hypertension, we wanted to demonstrate the predictive value of a lower office BP threshold in better predicting the current definition of uncontrolled ABPM and home BP. Even when the out-of-office BP threshold was defined as 130/80 mmHg in accordance with the 2017 AHA/ACC guidelines,[7] office BP threshold 130/80 mmHg showed better accuracy than 140/90 mmHg (Table S5, Table S6, Table S7, Table S8). The NRIs of Office BP and AOBP thresholds of 130/80 mmHg were 0.461 and 0.490, respectively (Table S9).

Another important finding from this study was the relatively high disagreement between ABPM daytime BP and home BP. In subjects with an office BP < 140/90 mmHg (*N* = 230), 85 subjects (37%) with uncontrolled daytime BP had controlled home BP, while 23 subjects

TABLE 4 Reclassification tables for uncontrolled out-of-office blood pressure (BP) according to office BP threshold of 130/80 and automated office BP threshold of 130/80 mmHg

Daytime BP 135/85 mmHg or Home BP 135/85 mmHg	Office BP 130/80 mmHg	Automated office BP 130/80 mmHg	Reclassification improvement
Controlled (*N* = 111)	Controlled (*N* = 44)[a]	Controlled (*N* = 40)	0.122[i]
		Uncontrolled (*N* = 4)[e]	
	Uncontrolled (*N* = 67)[b]	Controlled (*N* = 16)[f]	
		Uncontrolled (*N* = 51)	
Uncontrolled (*N* = 357)	Controlled (*N* = 54)[c]	Controlled (*N* = 35)	−0.046[j]
		Uncontrolled (*N* = 19)[g]	
	Uncontrolled (*N* = 303)[d]	Controlled (*N* = 36)[h]	
		Uncontrolled (*N* = 267)	

Note: i = (f − e)/(a + c); j = (g − h)/(b + d). NRI = i + j = 0.076.

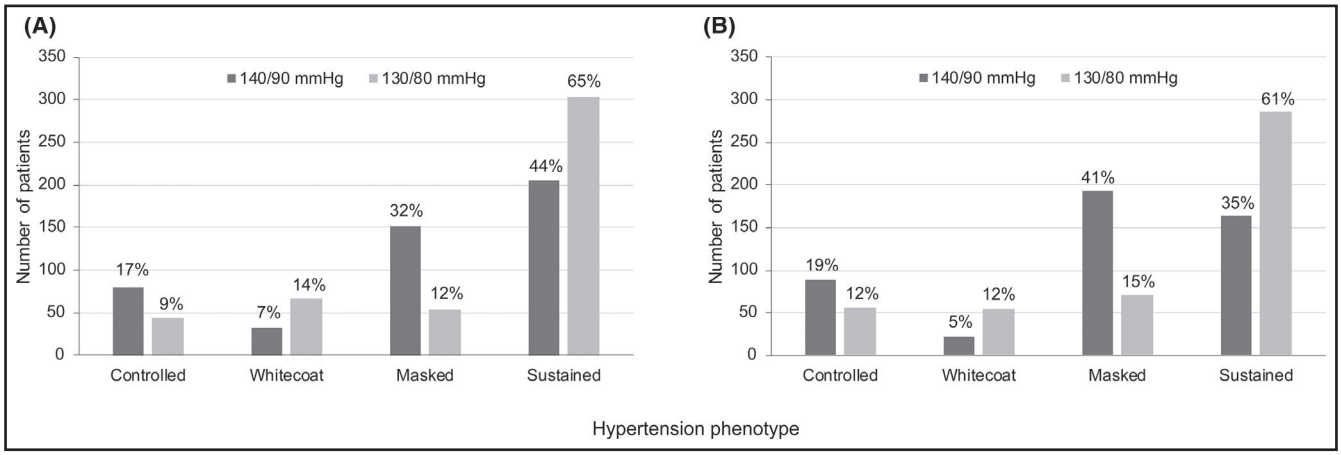

FIGURE 2 Hypertension phenotype according to different office blood pressure (A) and automated office blood pressure (BP) (B) thresholds

(10%) who had controlled daytime BP had uncontrolled home BP (Table 5). In subjects with an office BP < 130/80 mmHg (*N* = 98), the extent of discord was similar, with 31 subjects (32%) with uncontrolled daytime BP and controlled home BP, and 11 subjects (11%) with controlled daytime BP and uncontrolled home BP. This may have important implications as partial masked hypertension, defined as either home or 24-h ambulatory hypertension and office normotension, increased the risk of long-term stroke compared to sustained normotension.[25] Despite this discordance, home BP monitoring has been shown to have better prognostic value than clinic BP monitoring. In an observational cohort study by Kario et al including 21 591 treated hypertensive subjects, those with a well-controlled clinic SBP of <130 mmHg and an elevated morning home SBP of ≥145 mmHg had increased cardiovascular risk compared to those with both controlled clinic SBP and home morning SBP.[26] In the Dallas Heart Study, masked hypertension was associated with an unfavorable prognosis compared to the normal blood pressure group among 3027 subjects with home BP data, although they were not self-measured home BP data.[27,28] The findings from this study suggest that the use of both ABPM and home BP monitoring is important for obtaining appropriate classification of BP control status and optimal 24-hour BP control.

When using the same threshold of 130/80 mmHg, AOBP, compared to office BP, only slightly improved the accuracy of uncontrolled out-of-office BP identification. This is the first study to compare the accuracy of AOBP and office BP in identifying true resistant hypertension. Most studies validating the accuracy of AOBP were done in subjects with uncontrolled hypertension.[29] Therefore, the accuracy of AOBP compared to office BP measurement is not clear in subjects with treated hypertension. Our results showed that when office BP is measured according to the standard protocol, it is as reliable as AOBP measurement in treated hypertensive subjects. Additionally, with the lower threshold for aTRH diagnosis, the prevalence of masked uncontrolled hypertension in those with controlled office BP and controlled AOBP were comparable and still high. In a sub-study of the SPRINT (Systolic Blood Pressure Intervention Trial) trial, ambulatory BP measurement was performed in 897 SPRINT participants. The daytime average SBP was 6.85 mmHg higher than the clinic BP in the intensive treatment group, compared to 3.30 mmHg higher in the conventional treatment group, suggesting that AOBP measurements similarly risk missing masked uncontrolled hypertension without out-of-office BP measurements.[30]

TABLE 5 Proportion of uncontrolled hypertension according to out-of-office blood pressure (BP) among patients who had controlled office BP or automated office BP

Office BP		
Office BP < 140/90 mmHg (*N* = 230)	Home BP < 135/85 mmHg	Home BP ≥ 135/85 mmHg
Daytime BP < 135/85 mmHg (*N* = 102)	79 (34%)	23 (10%)
Daytime BP ≥ 135/85 mmHg (*N* = 128)	85 (37%)	43 (19%)
Office BP < 130/80 mmHg (*N* = 98)	Home BP < 135/85 mmHg	Home BP ≥ 135/85 mmHg
Daytime BP < 135/85 mmHg (*N* = 55)	44 (45%)	11 (11%)
Daytime BP ≥ 135/85 mmHg (*N* = 43)	31 (32%)	12 (12%)
Automated office BP		
Automated office BP < 140/90 mmHg (*N* = 282)	Home BP < 135/85 mmHg	Home BP ≥ 135/85 mmHg
Daytime BP < 135/85 mmHg (*N* = 118)	89 (32%)	29 (10%)
Daytime BP ≥ 135/85 mmHg (*N* = 164)	106 (38%)	58 (20%)
Automated office BP < 130/80 mmHg (*N* = 127)	Home BP < 135/85 mmHg	Home BP ≥ 135/85 mmHg
Daytime BP < 135/85 mmHg (*N* = 67)	56 (44%)	11 (9%)
Daytime BP ≥ 135/85 mmHg (*N* = 60)	46 (36%)	14 (11%)

There are several limitations that need to be addressed. First, although the study protocol recommended the measurement of unattended AOBP, this decision was left to the discretion of the investigators at each institution, based on the research facilities available. Because the majority of the measurements were attended AOBP, we cannot rule out the possibility that the diagnostic accuracy of AOBP was weakened. However, there are studies suggesting that attended AOBP may be used in place of unattended AOBP. In a recent study by Andreadis et al,[31] involving 146 subjects, there was minimal difference between attended AOBP and unattended AOBP, with both measurements showing no significant difference in daytime ABPM meausurements. Additionally, in a recent analysis of the SPRINT trial, 4082 participants had BP measured by unattended AOBP while 2247 participants were measured by attended AOBP. Similar SBP and DBP were demonstrated during follow-up, with no significant difference in the degree of reduction in the primary outcome in the intensive treatment arm, whose BP was measured using either unattended or attended AOBP.[32] Second, for measurement of AOBP, we did not use the validated AOBP measurement device which has been specifically designed for professional use. Instead, we used an automated home BP device that has a nocturnal automatic BP measurement algorithm. Previous studies have suggested that validated automatic home BP devices can be used for AOBP measurement and that HEM 7080-IC can be a good device to use for AOBP measurement in place of the validated standard devices.[33,34]

Third, since this study is a cross-sectional analysis of baseline BP measurements when patients were enrolled in the cohort, there is no information on drug compliance. However, this cohort is on-going and drug compliance will be investigated at follow-up. Further research in the future may address issue regarding drug compliance. Fourth, this study enrolled people with an office BP of 130/80 mmHg or higher, according to the definition of resistant hypertension. Therefore, it cannot be ruled out that more patients with white-coat uncontrolled out-of-office BP were enrolled. This is an inevitable limitation because the definition of resistant hypertension is based on office BP, and it is worth noting that the proportion of masked uncontrolled out-of-office BP in this study is, nevertheless, quite high.

In conclusion, in subjects with aTRH diagnosed with threshold of 130/80 mmHg, an office BP threshold of 130/80 mmHg showed better than 140/90 mmHg in terms of the correspondence to out-of-office BP, defined by a daytime ambulatory BP and/or home BP threshold of 135/85 mmHg regardless of using either conventional office BP or AOBP measurement.

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AUTHOR CONTRIBUTIONS

S Park is the principal investigator of the study and supervised its conduct and data analysis. S Park and J Shin had primary responsibility for the writing of this paper. CJ Lee and HJ Ha performed the data analysis, wrote, and revised the manuscripts. CJ Lee, JY Kim, IC Kim, SK Ryu, MY Rhee, JH Lee, JH Lee, HY Lee, SH Ihm, JW Chung, JH Choi, J Shin, and S Park enrolled the subjects and collected the data. K kario advised on the data analysis and reviewed the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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