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Optimal combinations of systolic and diastolic blood pressure in Korea: A nationwide population-based cohort study

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Abstract

We investigated the optimal combinations of systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels for lowest mortality in participants not taking hypertensive medication at the study baseline using nationwide representative databases. Survival rates and hazard ratios (HRs) were calculated using Kaplan-Meier curves and multivariable Cox regression analyses. The discriminatory ability for clinical outcomes was assessed by Harrell's C-index analysis. A survival spline curve was presented, and Classification and Regression Tree (CART) analysis was performed. SBP ≥ 140 group and DBP ≥ 90 group had the highest risk of mortality. Within SBP < 120, the HR (95% CIs) for all-cause mortality (ACM) was the lowest for DBP 70-79. Within SBP 120-139, the HR (95% CIs) for ACM was significantly lower for DBP 70-79. Within SBP ≥ 140, the HR (95% CIs) for ACM was significantly lower for DBP 80-89. Conversely, within SBP ≥ 140, DBP < 70 showed the highest risk for ACM. Similar relationships were observed when survival spline curves and CART analysis were used. The combination of SBP and DBP discriminated better than SBP or DBP alone for mortality. The effect of DBP on mortality varies according to the SBP range. It is more effective to evaluate the effect of SBP and DBP jointly for clinical outcomes.

Won-Jun Choi and Hye-Sun Lee contributed equally to this work.

Hyuk-Jae Chang and Ji-Won Lee contributed equally to this work.

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1 | INTRODUCTION

Hypertension is a well-established major risk factor for cardiovascular morbidity and mortality.[1] Largely based on the results of SPRINT (Systolic Pressure Intervention Trial), the 2017 American College of Cardiology/American Heart Association (AHA/ACC) guideline changed the landscape for blood pressure (BP) control goals, with a new definition for hypertension starting at a BP of 130/80 mmHg.[2] The new guideline additionally recommends antihypertensive medication for adults at high risk of cardiovascular disease (CVD) with SBP 130-139 mmHg or DBP 80-89 mmHg. This is supported by the recent large-scale systematic reviews and meta-analyses that intensive BP lowering is beneficial in reducing CV outcomes, especially for those with high CV risk.[3] However, conflicting reports still exist. Intensive BP lowering is associated with increased incidence of treatment-associated adverse events, and several studies suggest that achieving both SBP < 120 mmHg and DBP < 70 mmHg increases the risk of cardiovascular events.[4] In addition, strict BP lowering in the elderly was significantly associated with myocardial infarction and chronic heart failure.[5,6] Unlike SBP, the J-curve phenomenon between low DBP and cardiovascular events has been reported.[7]

Most recent studies have independently examined the effects of SBP or DBP on clinical outcomes, and few studies have considered SBP and DBP levels concurrently. Therefore, we hypothesized that ideal combinations of SBP and DBP levels would differ according to BP level. We investigated the optimal combinations of SBP and DBP levels to decrease all-cause and cardiovascular mortality in middle-aged and elderly adults using nationwide representative databases. To analyze long-term blood pressure control and its effects, we selected participants who were not diagnosed with hypertension and did not take hypertensive medication at the baseline of the study.

2 | METHODS

2.1 | Study population and data collection

This study used data obtained from the National Health Insurance System–National Health Screening Cohort (NHIS-HEALS), a national retrospective cohort study conducted by the Korea Centers for Disease Control and Prevention. The NHIS is a universal health coverage program, and all insured individuals and their dependents are required to undergo general health examinations every 2 years. Study populations were followed from January 1, 2006, until the date of a cardiovascular event, death, or December 31, 2015, whichever came first.

We extracted 1 021 208 participants whose data were available and excluded individuals who met any of the following criteria: younger than 40 or older than 75 years of age; history of hospitalization for a diagnosis of myocardial infarction (MI; Korean Standard Classification of Diseases, KCD codes I21-I23) or stroke (KCD codes I60-I64); any type of malignant cancer; death in the year of enrollment; single medical record after 2006; and those with missing SBP, DBP, or death data. Hypertension was defined as having a record of prescriptions for antihypertensive medications or diagnosis of hypertension (KCD codes I10-I13). Participants who had prescription records for antihypertensive medications were also excluded. Following these exclusions, 79 983 participants were included in the final analysis (Figure 1).

Blood pressure was measured at local hospitals and clinics, each of which met the internal and external quality control procedures of the Korean Association of External Quality Assessment Service. After 5 minutes of rest in the sitting position, BP measurements were taken by digital or automatic monitors during the health examination. If the SBP measurement was > 120 mmHg, or the DBP > 80 mmHg,

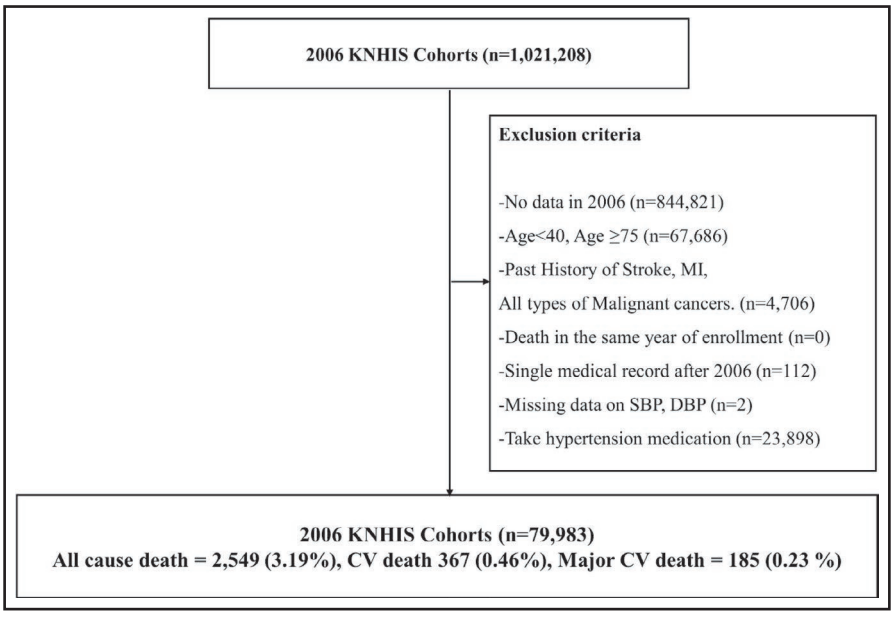

FIGURE 1 Flow chart of the study population

TABLE 1 Baseline characteristics according to SBP and DBP

Do not take hypertension medication (*n* = 79 983)													
	SBP					DBP							
	<120 (*n* = 31 842)	120 ~ 129 (*n* = 27 311)	130 ~ 139 (*n* = 15 428)	≥140 (*n* = 5402)	*p*-Value[a]	<70 (*n* = 14 845)	70 ~ 79 (*n* = 49 297)	80 ~ 89 (*n* = 34 386)	≥90 (*n* = 5353)	*p*-Value[a]	Total	Hypertension (*n* = 23 898)	*p*-Value[a]
Age	48.84 ± 7.4	51.12 ± 8.33	53.16 ± 9.08	55.58 ± 9.69	<.001	49.41 ± 7.95	50.95 ± 8.48	51.6 ± 8.61	51.58 ± 8.96	<.001	50.91 ± 8.48	57.85 ± 9.17	<.001
Female sex, *N* (%)	17 933 (56.32)	11 071 (40.54)	5897 (38.22)	2018 (37.36)	<.001	9205 (68.53)	18 809 (46.98)	8076 (34.5)	829 (26.75)	<.001	36 919 (46.16)	10 887 (45.56)	.101
Height, m^2	161.74 ± 8.3	163.19 ± 8.7	162.85 ± 8.84	162.11 ± 8.89	<.001	160.08 ± 7.82	162.37 ± 8.63	163.75 ± 8.69	164.5 ± 8.53	<.001	162.48 ± 8.61	160.99 ± 9	<.001
Weight, kg	60.06 ± 9.44	64.14 ± 10.14	65.14 ± 10.62	64.99 ± 10.77	<.001	57.81 ± 8.67	62.38 ± 9.8	65.67 ± 10.48	67.43 ± 11.07	<.001	62.77 ± 10.25	64.82 ± 10.54	<.001
BMI, kg/m^2	22.89 ± 2.61	24.01 ± 2.73	24.48 ± 2.87	24.65 ± 3.07	<.001	22.51 ± 2.54	23.59 ± 2.72	24.41 ± 2.84	24.84 ± 3.06	<.001	23.69 ± 2.82	24.94 ± 3.05	<.001
Physical activity, *N* (%)													
0	16 011 (51.74)	13 151 (49.58)	7503 (49.98)	2746 (52.24)	<.001	6912 (53)	19 834 (50.96)	11 170 (49.06)	1495 (49.67)	<.001	39 411 (5037)	11 811 (50.95)	<.001
1-2	8703 (28.12)	7686 (28.98)	4284 (28.54)	1341 (25.51)		3476 (26.65)	10 895 (27.99)	6768 (29.72)	875 (29.07)		22 014 (28.32)	5693 (24.56)	
3-4	3813 (12.32)	3342 (12.6)	1822 (12.14)	593 (11.28)		1602 (12.28)	4757 (12.22)	2861 (12.57)	350 (11.63)		9570 (12.31)	2825 (12.19)	
5-6	901 (2.91)	782 (2.95)	423 (2.82)	147 (2.8)		388 (2.98)	1147 (2.95)	620 (2.72)	98 (3.26)		2253 (2.9)	789 (3.4)	
Almost everyday	1518 (4.91)	1562 (5.89)	981 (6.53)	430 (8.18)		663 (5.08)	2286 (5.87)	1350 (5.93)	192 (6.38)		4491 (5.78)	2062 (8.9)	
Household income, *N* (%)													
1-2	4775 (15.21)	4226 (15.75)	2597 (17.07)	960 (17.95)	<.001	2080 (15.64)	6331 (16.08)	3667 (15.92)	480 (15.63)	<.001	12 558 (15.94)	4008 (17)	<.001
3-4	3901 (12.43)	3414 (12.73)	2027 (13.33)	805 (15.06)		1640 (12.33)	5109 (12.97)	2956 (12.84)	442 (14.39)		10 147 (12.88)	3118 (13.23)	
5-6	4162 (13.26)	3941 (14.69)	2321 (15.26)	965 (18.05)		1733 (13.03)	5662 (14.38)	3468 (15.06)	526 (17.12)		11 389 (14.46)	3497 (14.83)	
7-8	7029 (22.39)	6343 (23.64)	2609 (23.73)	1189 (22.24)		2824 (21.24)	9187 (23.33)	5441 (23.63)	718 (23.37)		18 170 (23.07)	5373 (22.79)	
9-10	11 524 (36.71)	8903 (33.19)	4657 (30.62)	1428 (26.71)		5021 (37.76)	13 088 (33.24)	7497 (32.55)	906 (29.49)		26 512 (33.65)	7578 (32.15)	
Smokers, *N* (%)	8446 (27.33)	9277 (35.05)	5332 (35.53)	1884 (36)	<.001	2743 (21.09)	12 229 (31.45)	8658 (38.11)	1309 (43.62)	<.001	24 939 (32.13)	6383 (27.53)	<.001
Alcohol drinkers, *N* (%)													
Non-drinker	19 306 (61.85)	14 149 (52.86)	7824 (51.59)	2663 (50.31)	<.001	9053 (68.79)	22 554 (57.43)	11 112 (48.37)	1223 (40.34)	<.001	43 942 (56.02)	14 251 (60.88)	<.001
Intermittent drinker	11 340 (36.33)	11 716 (43.77)	6655 (43.88)	2294 (43.34)		3916 (29.75)	15 598 (39.72)	10 860 (47.27)	1631 (53.79)		32 005 (40.8)	8209 (35.07)	
Daily drinker	568 (1.82)	901 (3.37)	688 (4.54)	336 (6.35)		192 (1.46)	1121 (2.85)	1002 (4.36)	178 (5.87)		2493 (3.18)	948 (4.05)	
SBP, mmHg	111.67 ± 10.32	123.89 ± 10.31	133.81 ± 11.58	146.61 ± 15.3	<.001	108.68 ± 11	120.14 ± 11.98	131.42 ± 13.31	144.77 ± 16.28	<.001	122.47 ± 15.22	133.91 ± 17.79	<.001
DBP, mmHg	70.71 ± 8.04	77.94 ± 8.01	83.24 ± 8.85	89.47 ± 10.85	<.001	66.14 ± 6.94	75.16 ± 7.44	83.64 ± 8.04	94.15 ± 10.43	<.001	76.86 ± 10.23	82.76 ± 11.26	<.001
Fasting Glucose, mg/dl	92.66 ± 20.06	96.49 ± 24.61	98.73 ± 25.55	102.28 ± 31.14	<.001	91.78 ± 18.93	95.59 ± 24.08	97.84 ± 25.05	100.25 ± 26.95	<.001	95.79 ± 23.81	104.24 ± 32.85	<.001
Total cholesterol, mg/dl	193.25 ± 35.36	199.4 ± 36.12	202.09 ± 36.39	204.22 ± 38.15	<.001	191.62 ± 35.52	197.44 ± 36.06	201.18 ± 36.22	203.5 ± 37.44	<.001	197.8 ± 36.23	200.37 ± 38.17	<.001
AST, mg/dl	24.23 ± 15.32	26.24 ± 21.44	27.64 ± 32.8	29.19 ± 24.15	<.001	23.7 ± 19.05	25.54 ± 24.65	27.24 ± 18.04	30.08 ± 31.15	<.001	25.91 ± 22.36	27.48 ± 17.83	<.001
ALT, mg/dl	22.57 ± 20.33	26.11 ± 23.12	27.62 ± 35.9	28.21 ± 25.79	<.001	21.11 ± 20.86	24.61 ± 27.5	27.71 ± 23.49	29.88 ± 26.21	<.001	25.14 ± 25.41	27.2 ± 21.37	<.001

Note: Data are expressed as the mean ± SD or frequency (percentage).

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]*p*-Values were calculated using ANOVA, Chi-square test.

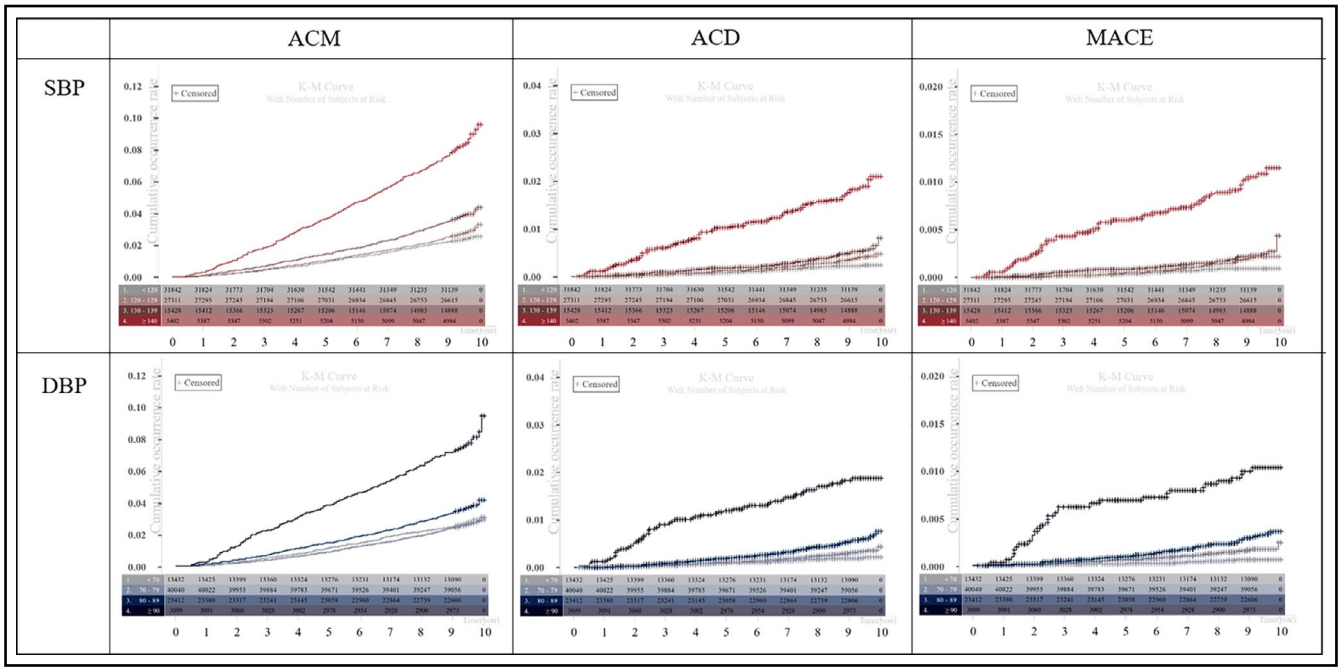

FIGURE 2 Kaplan-Meier curves and log-rank test for all-cause death, all cardiovascular death, and major cardiovascular death according to blood pressure (BP) groups

BP was measured repeatedly. All BP measurements, including BP data before the index period, were used to calculate mean BP.

Self-reported physical activity, cigarette smoking, and alcohol consumption were determined from questionnaires. Physical activity was divided into five groups: 0, 1-2, 3-4, 5-6, and "almost every day" according to the number of days of exercise during the week. Current smokers were classified as smokers. Alcohol drinkers were categorized as non-drinker, intermittent drinker (≤3-4 times a week), or daily drinker. Household income is divided into five groups based on decile data from the NHIS-HEALS dataset.

The study was approved by the Institutional Review Board of Yonsei University Health System (IRB number: 3-2018-0160), and the requirement for informed consent was waived.

2.2 | Outcome measurement

The primary outcomes of the study were all-cause mortality (ACM) and all cardiogenic mortality. All cardiovascular death (ACD) was defined as death from a disease of the circulatory system (KCD codes I00-I99). We selected MI (KCD codes I21-I23), hemorrhagic stroke (KCD codes I60-I62), and ischemic stroke (KCD code I63) among the detailed causes of cardiovascular mortality and named it as major cardiovascular death (MACE).

2.3 | Statistical analysis

Systolic blood pressure and DBP were classified into 4 groups. For SBP groups, <120, 120-129, 130-139, and ≥ 140 were categorized. For DBP groups, <70, 70-79, 80-89, and ≥ 90 were categorized. We performed analyses of combinations of SBP and DBP, more specifically by categorizing DBP groups within the same SBP group. For example, the SBP < 120 mmHg group was subdivided into 4 groups according to DBP as follows: SBP < 120/DBP < 70, SBP < 120/DBP 70-79, SBP < 120/DBP 80-89, and SBP < 120/DBP ≥ 90.

The characteristics of the study population were compared using one-way analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables, respectively.

The survival rates of each group according to the adjustment criteria presented in each BP group were analyzed by Kaplan-Meier curve and log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated according to BP levels using multivariable Cox regression analysis after adjusting for age, sex, BMI, physical activity, household income, smoking status, alcohol status, fasting glucose, and total cholesterol.

Harrell's C-index analysis was performed to evaluate the discrimination ability of SBP, DBP, and combination BP status. A survival spline curve was presented, and Classification and Regression Tree (CART) analysis was performed.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC, USA), which incorporates sample weights and adjusts for the complex sample design of the survey. All statistical tests were two-sided, and statistical significance was determined at $p < .05$.

3 | RESULTS

Table 1 presents baseline characteristics according to SBP and DBP. At baseline in 2006, 23% (n = 23 898) of participants had a previous hypertension diagnosis and were taking antihypertensive

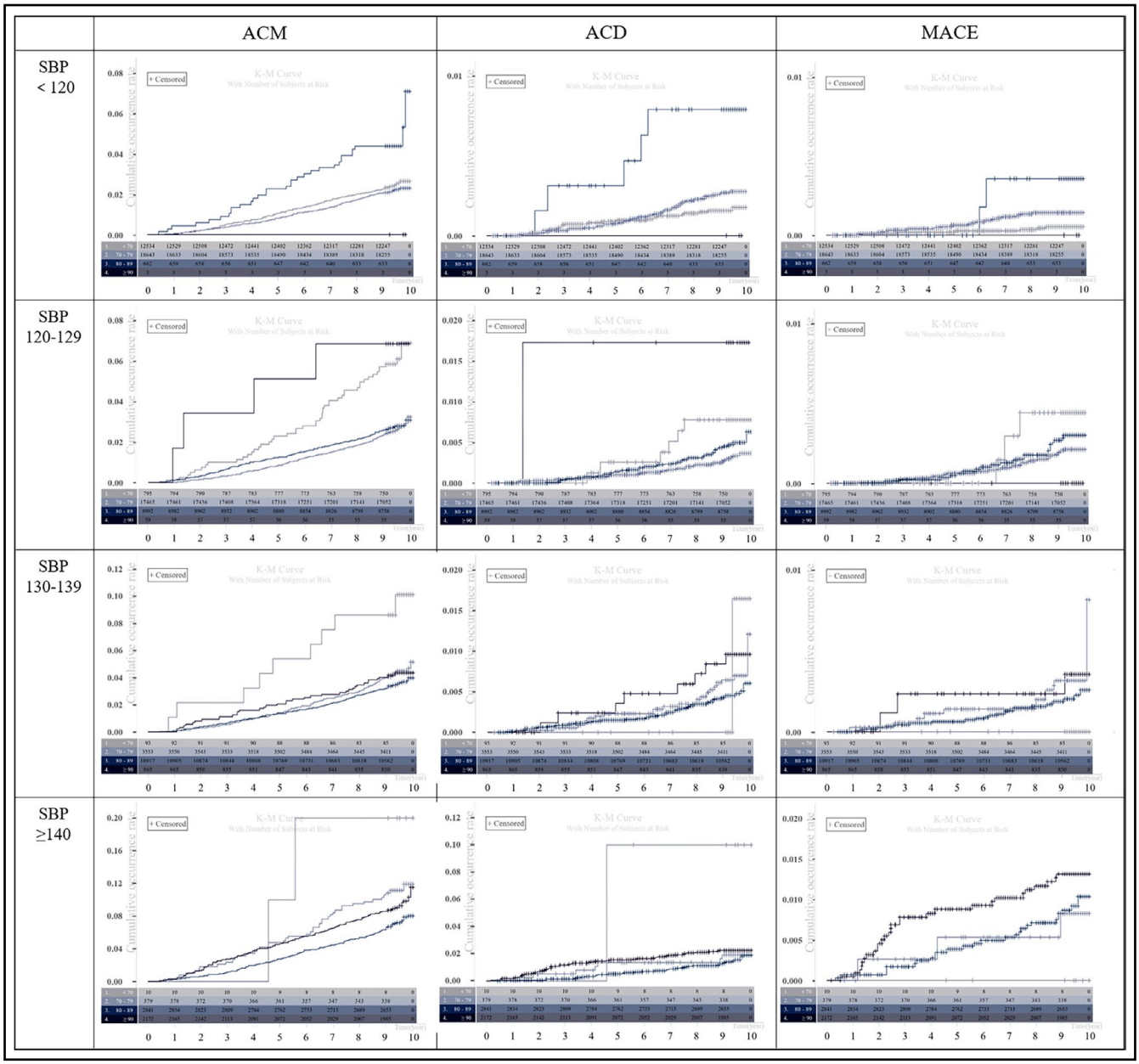

FIGURE 3 Kaplan-Meier curves and log-rank test for all-cause death, all cardiovascular death, and major cardiovascular death according to DBP levels within the same SBP levels. DBP, diastolic blood pressure; SBP, systolic blood pressure

medications, and 77% (*n* = 79 983) of participants had no hypertension history. There was a significant difference in all variables between participants taking antihypertensive medications or not. As SBP and DBP increased, participants not taking medication for hypertension at the study baseline tended to be older, men, current smokers, consumed more alcohol, had a higher BMI, and had higher fasting glucose, total cholesterol, and liver function enzymes.

Figure 2 shows the cumulative incidence of the three outcomes: ACM, ACD, and MACE (acute myocardial infarction, ischemic strokes, hemorrhagic strokes) according to BP using Kaplan-Meier curves and log-rank test. A total of 2549 ACM, 367 ACD, and 185 MACE events occurred during follow-up. There was a significant linear trend toward an increased risk of all three outcomes, with worse SBP and DBP control. As a result, the SBP ≥ 140 and DBP ≥ 90 groups had the highest risk of mortality. Within the same SBP levels, we analyzed the risk of mortality according to DBP levels (Figure 3). For SBP 120-129, ACM was higher in the DBP ≥ 90 group. Within the SBP 130-139 and ≥ 140 groups, ACM was higher in the DBP < 70 group.

Tables 2, 3, and 4 show HRs (95% CIs) for ACM, ACD, and MACE according to separated SBP and DBP groups or combinations of SBP and DBP groups after adjusting for age, sex, BMI, physical activity, household income, smoking status, alcohol status, fasting glucose, and total cholesterol. Because SBP is more discriminating than DBP,

TABLE 2 Hazard ratios for all-cause death according to blood pressure groups

Groups		HR (95% CI)	Pairwise comparison *p*-Value		
SBP	<120	0.633 (0.557-0.72)	<.001	.212	.003
	120 ~ 129	0.539 (0.477-0.61)	<.001	.129	ref
	130 ~ 139	0.588 (0.518-0.668)	<.001	ref	
	≥140	1	ref		
DBP	<70	0.529 (0.445-0.629)	<.001	.490	<.001
	70 ~ 79	0.39 (0.337-0.452)	<.001	<.001	ref
	80 ~ 89	0.505 (0.436-0.586)	<.001	ref	
	≥90	1	ref		
SBP < 120	DBP < 70	0.043 (0.003-0.71)	.028	.003	.005
	70 ~ 79	0.035 (0.002-0.568)	.018	<.001	ref
	80 ~ 89	0.077 (0.005-1.292)	.075	ref	
	≥90	1	ref		
120 ~ 129	DBP < 70	0.346 (0.124-0.968)	.043	.662	.025
	70 ~ 79	0.242 (0.09-0.648)	.005	<.001	ref
	80 ~ 89	0.322 (0.119-0.866)	.025	ref	
	≥90	1	ref		
130 ~ 139	DBP < 70	0.644 (0.295-1.404)	.269	.896	.401
	70 ~ 79	0.475 (0.323-0.697)	<.001	.011	ref
	80 ~ 89	0.615 (0.431-0.875)	.007	ref	
	≥90	1	ref		
≥140	DBP < 70	1.603 (0.395-6.502)	.509	.158	.218
	70 ~ 79	0.655 (0.463-0.926)	.017	.521	ref
	80 ~ 89	0.586 (0.477-0.72)	<.001	ref	
	≥90	1	ref		

Note: Adjusted for age, sex, BMI, physical activity, household income, smoking status, alcohol status, fasting glucose, total cholesterol.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

we performed SBP and DBP combination analysis by categorizing DBP groups within the same SBP group.

Table 2 shows the HRs (95% CIs) for ACM analysis. The HR (95% CIs) was highest for the SBP ≥ 140 and DBP ≥ 90 groups, and this trend was similar in ACD and MACE analyses. Similar relationships were observed when survival spline curves were used to treat SBP and DBP as continuous variables (Figure 4). SBP higher than 120 mmHg was associated with a risk for all three outcomes in a dose-responsive manner. Similarly, DBP higher than 70 mmHg gradually increased the risk of clinical outcomes. Within SBP < 120, the HR (95% CIs) for ACM was lowest in the DBP 70-79 group, followed by the DBP < 70, DBP 80-89, and DBP ≥ 90 groups. Within SBP 120-139, the HR (95% CIs) for ACM was significantly lower in the DBP 70-79 group. Within SBP ≥ 140, the HR (95% CIs) for ACM was significantly lower in the DBP 80-89 group. Conversely, within SBP ≥ 140, the DBP < 70 group showed the highest risk for ACM. In other words, the effect of DBP on ACM varies according to the range of SBP.

We observed a similar trend in ACD analysis. As for ACM, HRs (95% CIs) for ACD were highest for the SBP ≥ 140 and DBP ≥ 90 groups. Within the SBP < 120 and SBP 120-129 groups, the HRs (95% CIs) for ACD were significantly lower in the DBP < 70 group. But within the SBP 130-139 and SBP ≥ 140 groups, the HRs (95% CIs) for ACD showed the lowest risk in the DBP 70-79 group. Consistent with the ACM analysis, the DBP < 70 group showed the highest risk for ACD within the SBP ≥ 140 group. (Table 3).

Table 4 shows HR (95% CIs) analysis for MACE. HRs (95% CIs) for MACE were highest for the SBP ≥ 140 and DBP ≥ 90 groups. The DBP 70-79 group showed the lowest HRs (95% CIs) for MACE in all SBP ranges. As in the two analyzes described above, the DBP < 70 group showed the highest risk for MACE within the SBP ≥ 140 group.

To evaluate the potential discriminatory ability of SBP, DBP, and SBP and DBP in combination for clinical outcomes, Harrell's C-indexes were calculated (Table 5). These results suggest that SBP alone and the combination of SBP and DBP are more discriminating than DBP alone in all three outcomes. In ACM analysis, the combination of SBP and DBP discriminated better than SBP alone. But in ACD and MACE analyses, there was no difference in discrimination ability between SBP alone and the combination of SBP and DBP.

TABLE 3 Hazard ratios for all cardiovascular death according to blood pressure groups

Groups		HR (95% CI)	Pairwise comparison *p*-Value		
SBP	<120	0.301 (0.215-0.42)	<.001	.152	.136
	120 ~ 129	0.381 (0.286-0.507)	<.001	.954	ref
	130 ~ 139	0.384 (0.284-0.52)	<.001	ref	
	≥140	1	ref		
DBP	<70	0.155 (0.093-0.258)	<.001	<.001	.0914
	70 ~ 79	0.229 (0.165-0.318)	<.001	<.001	ref
	80 ~ 89	0.372 (0.269-0.513)	<.001	ref	
	≥90	1	ref		
SBP < 120	DBP < 70	0.003 (0.001-0.059)	<.001	.004	.087
	70 ~ 79	0.005 (0.001-0.095)	<.001	.033	ref
	80 ~ 89	0.013 (0.001-0.315)	.007	ref	
	≥90	1	ref		
120 ~ 129	DBP < 70	0.142 (0.016-1.296)	.084	.163	.931
	70 ~ 79	0.149 (0.02-1.093)	.061	.001	ref
	80 ~ 89	0.298 (0.04-2.199)	.235	ref	
	≥90	1	ref		
130 ~ 139	DBP < 70	0.257 (0.031-2.103)	.205	.882	.952
	70 ~ 79	0.241 (0.104-0.562)	.001	.421	ref
	80 ~ 89	0.299 (0.14-0.639)	.002	ref	
	≥90	1	ref		
≥140	DBP < 70	3.255 (0.441-24.012)	.247	.085	.077
	70 ~ 79	0.487 (0.215-1.104)	.085	.719	ref
	80 ~ 89	0.564 (0.366-0.87)	.010	ref	
	≥90	1	ref		

Note: Adjusted for age, sex, BMI, physical activity, household income, smoking status, alcohol status, fasting glucose, total cholesterol.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

According to the result of Harrell's C-indexes, we performed CART analysis, considering the joint effects of SBP and DBP simultaneously for the lowest mortality (Figure 5). In ACM analysis, regardless of DBP, the SBP < 120 group had low risk and SBP ≥ 140 had high risk. Prognosis was poor in the SBP 120-129 group when DBP was < 70 and ≥ 90, and in the SBP 130-139 group when DBP was < 70. In the ACD analysis, as in the ACM analysis, the SBP < 120 group had low risk and SBP ≥ 140 had high risk regardless of DBP. The SBP 120-129 group showed poor prognosis with DBP ≥ 90, and SBP 130-139 showed poor prognosis with DBP < 70 and ≥ 90. In MACE analysis, there was no cut-off value of poor prognosis in SBP < 120, 120-129, and 130-139. Poor prognosis in the SBP ≥ 140 group was when DBP < 70.

4 | DISCUSSION

The 2017 ACC/AHA guideline emphasized strict BP control and recommended to reduce SBP/DBP < 130/80 mmHg.[2] The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines maintain the diagnostic threshold of hypertension at 140/90 mmHg and redefined office BP treatment targets according to age stratification and CV risk profiles.[8] It is still unknown whether excessive BP reduction results in improved clinical outcomes. Previous studies did not account for the complex relationships between BP components and mortality. We examined the effects of SBP and DBP on mortality simultaneously, rather than assessing each BP component separately. Although high BP (SBP ≥ 140 and DBP ≥ 90) has a poor prognosis and is consistent with the results of previous experiments, prognosis was poor in the SBP 120-129 group when DBP was < 70 and ≥ 90, and in the SBP 130-139 group when DBP was < 70. In addition, the lowest risk of DBP was 70-79, not < 70, with a J-shape in the spline curve analysis, meaning it is more effective and appropriate to evaluate the effect of SBP and DBP jointly in clinical outcomes. This is supported by our Harrell's C-index analysis, and the combination analysis showed higher discrimination ability than that of SBP or DBP alone.

Previous studies have shown similar results. Glynn et al (2000) showed the lowest mortality at SBP ≤ 130 and DBP 80-90, and

TABLE 4 Hazard ratios for major cardiovascular death according to blood pressure groups

Groups		HR (95% CI)	Pairwise comparison *p*-Value		
SBP	<120	0.197 (0.121-0.319)	<.001	.120	.023
	120 ~ 129	0.335 (0.229-0.489)	<.001	.540	ref
	130 ~ 139	0.294 (0.193-0.447)	<.001	ref	
	≥140	1	ref		
DBP	<70	0.08 (0.034-0.191)	<.001	.001	.02
	70 ~ 79	0.211 (0.136-0.327)	<.001	.004	ref
	80 ~ 89	0.344 (0.224-0.53)	<.001	ref	
	≥90	1	ref		
SBP < 120	DBP < 70	0.001 (0.001-0.011)	<.001	.005	.029
	70 ~ 79	0.001 (0.001-0.035)	<.001	.098	ref
	80 ~ 89	0.004 (0.001-0.136)	.002	ref	
	≥90	1	ref		
120 ~ 129	DBP < 70	0.264 (0.013-5.467)	.389	.760	.504
	70 ~ 79	0.179 (0.01-3.106)	.238	.042	ref
	80 ~ 89	0.316 (0.018-5.533)	.431	ref	
	≥90	1	ref		
130 ~ 139	DBP < 70	0.358 (0.016-8.042)	.518	.995	.972
	70 ~ 79	0.34 (0.094-1.225)	.099	.873	ref
	80 ~ 89	0.361 (0.112-1.162)	.088	ref	
	≥90	1	ref		
≥140	DBP < 70	2.814 (0.155-51.063)	.484	.270	.212
	70 ~ 79	0.4 (0.126-1.276)	.122	.582	ref
	80 ~ 89	0.552 (0.315-0.967)	.038	ref	
	≥90	1	ref		

Note: Adjusted for age, sex, BMI, physical activity, household income, smoking status, alcohol status, fasting glucose, total cholesterol.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

the highest mortality at SBP > 160 and DBP < 70.[9] In a recent study, patients with atrial fibrillation (AF) undergoing hypertension treatment showed a U-shaped relationship of major cardiovascular events, with SBP 120-129 and DBP < 80 mmHg as the optimal BP treatment target.[10] Several studies suggested that 70 mmHg was the optimal DBP target and an increased risk of death for DBP ≤ 70 mmHg, especially in the elderly.[11,12] Recently, our group found that participants in the DBP < 70 mmHg group who took hypertension drugs had a high risk of mortality regardless of SBP status, and the highest mortality was observed in the DBP < 70 mmHg and SBP ≥ 140 mmHg groups.[13]

Although the precise mechanism for the relationship between SBP, DBP, and mortality remains unknown, this could be partly explained by pulse pressure (PP). PP is higher due to the tendency of SBP to increase and DBP to decrease with age, which is attributed to a loss of arterial wall elasticity and arterial stiffness.[14] Apart from high BP, wide PP is also known to increase cardiovascular or all-cause mortality.[15] The association between PP and CVD incidence was previously reported by Blacher et al, in which hypertensive patients had a 17% increased risk of CVD per 10 mmHg higher PP.[16] However, PP alone, without appropriate attention to SBP and DBP components, is an inadequate risk indicator for prognostic and therapeutic decisions.[17] Increasing PP by increasing SBP was consistently associated with increased risk, while increasing PP by decreasing DBP could be associated with increased risk, decreased risk, or no change in risk depending on age and BP level.[17] Similarly in our results, for a fixed DBP, increasing PP by increasing SBP was associated with higher mortality, while decreasing PP by increasing DBP above 90 mmHg increased risk for death. Overall, our observations emphasize that PP in conjunction with SBP and DBP might be effective to identify patients at high risk of CVD and all-cause mortality. Future clinical studies are needed to validate these findings.

There are some limitations in this study. First, because the current study was an observational study, potentially unmeasured confounding factors could overestimate or underestimate the impact of BP on clinical outcomes. Second, although BP-measuring equipment of all health examination institutions is

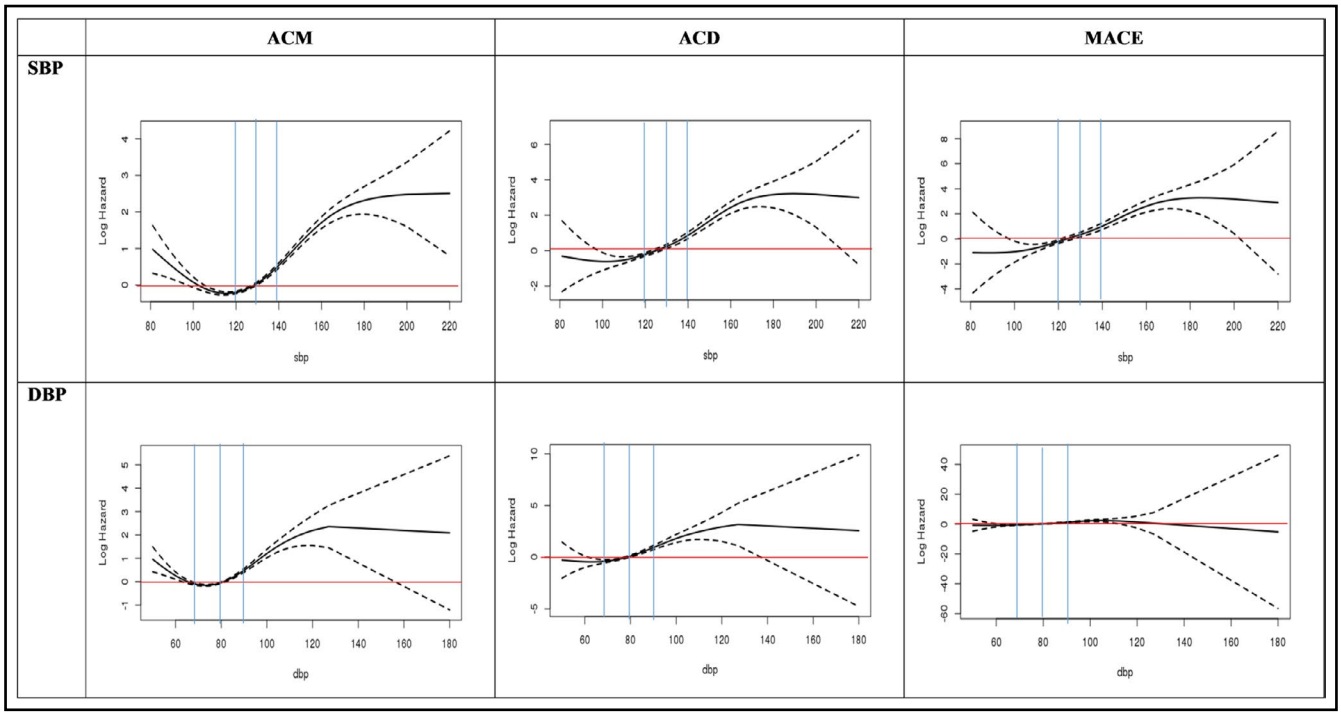

FIGURE 4 Survival spline curve for all-cause mortality, all cardiovascular death, and major cardiovascular death according to blood pressure (BP) groups

TABLE 5 Discrimination ability for all-cause death, all cardiovascular death and major cardiovascular death according to systolic blood pressure

ACM	C-index (95% CI)	Pairwise comparison P-value	
SBP	**0.581(0.568-0.593)**	**ref**	
DBP	0.542(0.529-0.553)	<0.001	ref
SBP + DBP	0.588(0.576-0.6)	0.008	<0.001
ACD			
SBP	0.668(0.636-0.7)	ref	
DBP	0.628(0.601-0.659)	<0.001	ref
SBP + DBP	0.667(0.635-0.7)	0.739	0.003
MACE			
SBP	0.7(0.661-0.739)	ref	
DBP	0.659(0.617-0.739)	0.008	ref
SBP + DBP	0.699(0.662-0.737)	0.617	0.012

Abbreviations: ACD, all cardiovascular death; ACM, all causes mortality; C-index, Concordance-index; MACE, major cardiovascular death.

quality-qualified according to the Basic Act on National Health Examination, a lack of device uniformity and single visit measurements may have caused slight variability within results. However, recent guidelines have advocated that single visit measurements with automatic office-based devices represent a less resource-intensive yet equally or more precise measurement of BP than multiple clinic visits.[18] Third, our study participants are all Korean adults, so the results may not be generalized to other races or ethnic groups. Fourth, some of the 16 categories had small sample and event sizes, potentially limiting their statistical accuracy. Further research is needed with a larger sample size. Nevertheless, this study has several strengths. We used a large-scale Asian cohort in a real-world setting from the National Health Insurance System–National Health Screening Cohort (NHIS-HEALS), a reliable large national data set sampled from most adult health insurance subscribers in Korea. We also used various statistical approaches to adjust for multiple types of bias and improve the accuracy of predictive survival models with SBP and DBP in combination.

Taken together, the results are summarized as follows. High BP (SBP ≥ 140 and DBP ≥ 90) has a poor prognosis and is consistent with the results of previous experiments. However, lower BP does not always yield a better prognosis. With SBP 130 as the boundary, high DBP with lower SBP, and low DBP with higher SBP, showed high risk for mortality. In particular, the lowest DBP (<70) had a worse prognosis than other groups with the highest SBP. This study used a statistical model to examine a new perspective using a statistical model. If clinical research supports these findings, primary care providers may consider the optimal combination of SBP and DBP, rather than SBP or DBP alone, in clinical decision-making.

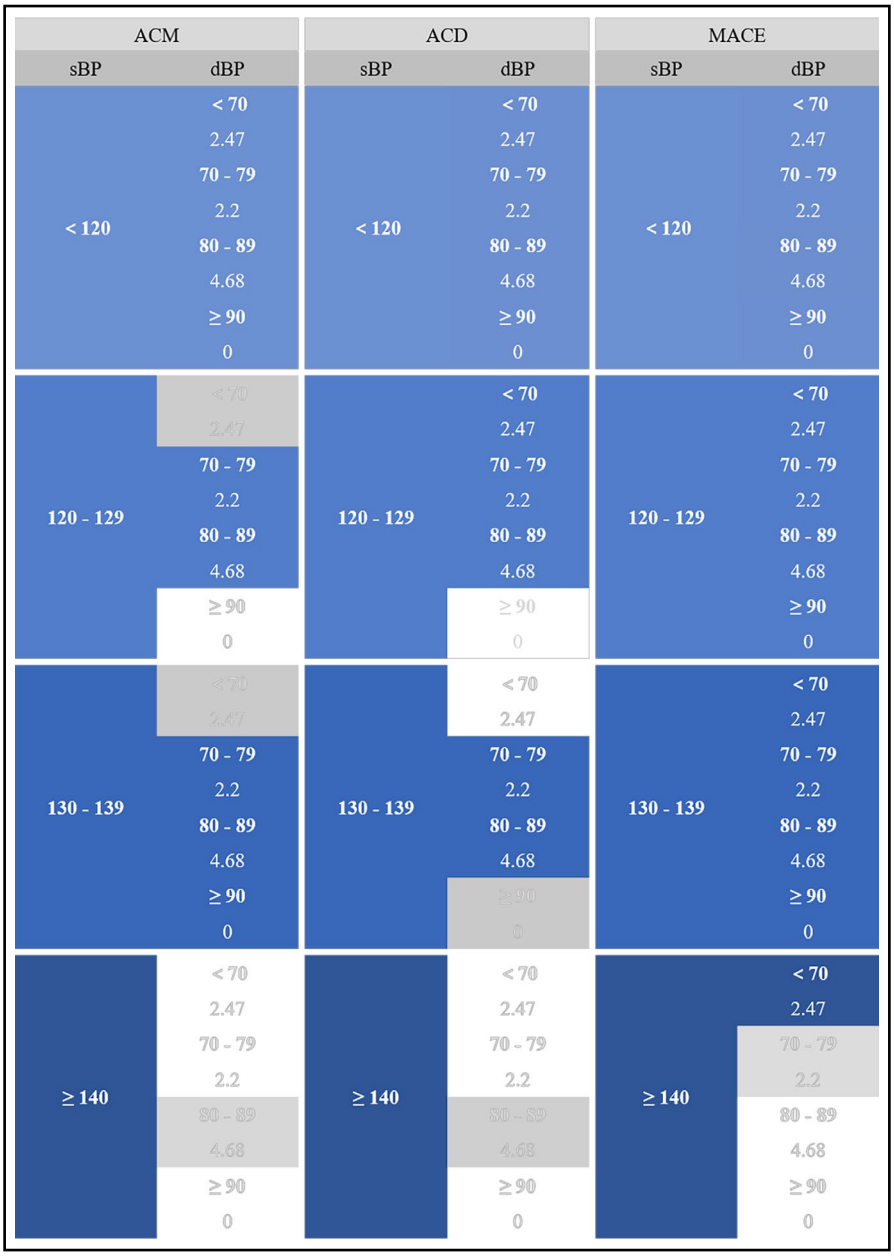

FIGURE 5 Classification and Regression Tree analysis of the joint effects of SBP and DBP. DBP, diastolic blood pressure; SBP, systolic blood pressure

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

WJC, HSL, HJC, and JWL contributed to conceptualization. HSL contributed to methodology. HSL contributed to software. WJC and HSL contributed to validation. HSL and JWH contributed to formal analysis. WJC and HSL contributed to investigation. JWL contributed to resources and data curation. WJC and HSL contributed to

writing—original draft preparation. HJC and JWL contributed to writing—review and editing. JWH contributed to visualization. HJC and JWL contributed to supervision. HJC and JWL contributed to project administration. JWL contributed to funding acquisition.

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