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ARTICLE

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Prevalence and clinical characteristics of primary aldosteronism in a tertiary-care center in Korea

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Abstract

Approximately 29% of Korean adults have hypertension; however, the prevalence of primary aldosteronism among the hypertensive population is largely unknown. The aim of our study was to evaluate the prevalence and clinical characteristics of primary aldosteronism in a tertiary-care center in Korea. We retrospectively analyzed 1173 patients with newly diagnosed or preexisting hypertension who were referred to our tertiary-care hospital between January 2013 and December 2018. Patients were screened for primary aldosteronism with the aldosterone-renin ratio and underwent a saline infusion test for diagnostic confirmation. Adrenal computed tomography and adrenal venous sampling were performed for subtype classification for primary aldosteronism. Among the 1173 patients (mean age, 51.8 years; women, 53.2%), 360 (30.7%) had positive screening-test results, of whom 71 (6.1%) were finally diagnosed with primary aldosteronism. Conclusive subtype differentiation was made in 55 patients, of whom 15 (27%) had an aldosterone-producing adenoma, 4 (7%) had unilateral adrenal hyperplasia, and 36 (66%) had bilateral adrenal hyperplasia. Patients with primary aldosteronism had a higher ambulatory blood pressure, left ventricular mass index, and urinary albumin-to-creatinine ratio than those without. Moreover, the primary aldosteronism group had a higher prevalence of left ventricular hypertrophy and albuminuria than the non-primary aldosteronism group. Primary aldosteronism may be more common (6.1%) among Korean patients with hypertension than generally recognized. Primary aldosteronism was associated with a higher degree and prevalence of target organ damage and a higher blood pressure level. Wide application of screening tests for primary aldosteronism may be beneficial in detecting this potentially curable cause of hypertension.

Keywords Ambulatory blood pressure monitoring · Hypertension · Primary aldosteronism · Target-organ damage

Introduction

Primary aldosteronism (PA), characterized by autonomous aldosterone overproduction, is a common cause of secondary hypertension [1]. Such excess production of aldosterone causes hypertension, cardiovascular damage, sodium retention, and hypokalemia. Moreover, patients with PA have higher cardiovascular morbidity and mortality than patients with essential hypertension [2–4]. The recommended therapeutic management of PA is adrenalectomy for unilateral disease and mineralocorticoid receptor (MR) antagonists for bilateral disease. Both treatments are known to have benefits for controlling blood pressure (BP) and reducing cardiovascular complications [5, 6].

Until the 1990s, most experts recommended that PA should be suspected in patients with severe hypertension with spontaneous hypokalemia. The disease was thought to be uncommon, as the reported prevalence of PA was less than 2% [7–9]. However, studies have revealed that only 9–37% of patients

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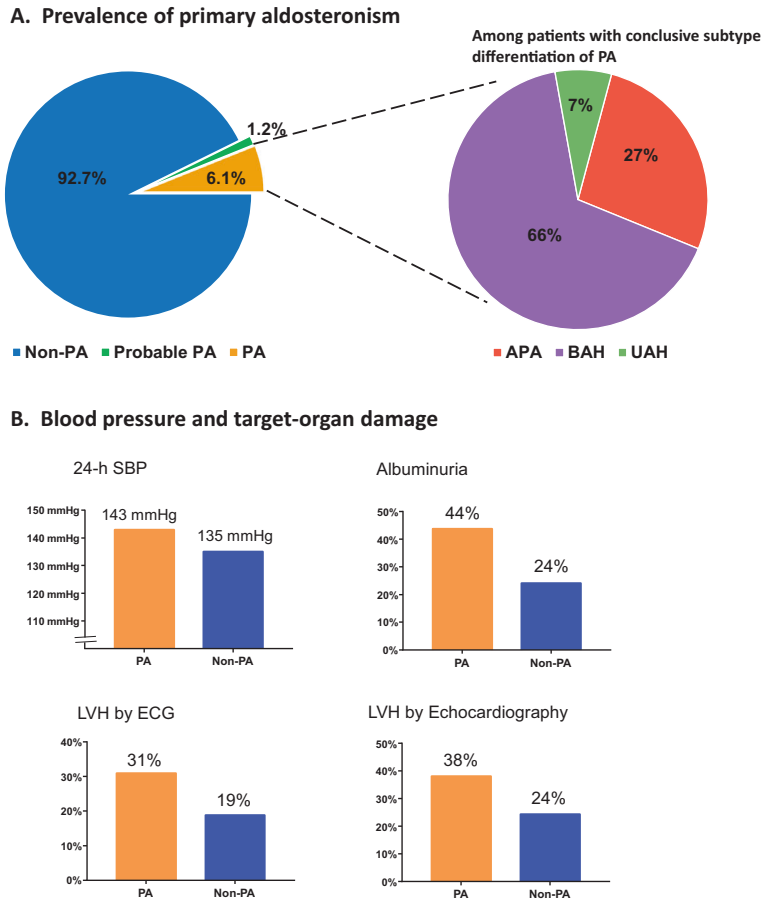
Graphical Abstract

(A) The prevalence of PA was 6.1% of the total population. Among 55 patients with conclusive subtype differentiation of PA, 27% had APA, 65% had BAH, and 7% had UAH. (B) Patients with PA had a higher blood pressure and higher prevalence of target-organ damage than patients without PA. APA, aldosterone-producing adenoma; BAH, bilateral adrenal hyperplasia; ECG, electrocardiogram; LVH, left ventricular hypertrophy; PA, primary aldosteronism; SBP, systolic blood pressure; UAH, unilateral adrenal hyperplasia.



Point of view

- Clinical relevance

  Primary aldosteronism may be more common (prevalence of 6.1%) among Korean patients with hypertension than has been generally recognized. In addition, primary aldosteronism is associated with a higher degree and prevalence of target organ damage and a higher blood pressure level.
- Future direction

  Further research is warranted to elucidate whether wide screening and earlier detection of primary aldosteronism would reduce the incidence of cardiovascular events in clinical practice.
- Consideration for the Asian population

  In the Asian population, widespread screening for primary aldosteronism may be beneficial in detecting this potentially curable cause of hypertension.

with PA have hypokalemia and that the absence of hypokalemia has a low negative predictive value for the diagnosis of PA [1, 10, 11]. The wide use of the aldosterone-to-renin ratio (ARR) as a screening test in patients with hypertension has led to an increase in the detection rate of PA [10]. In a recent meta-analysis, the prevalence of PA was 4.3% in primary care centers and 9.5% in referral centers [12]. The reported prevalence of PA varies greatly among studies, as patients' characteristics are heterogeneous and different diagnostic methods are used [10, 13].

In Korea, ~29% of adults have hypertension [14], and it is important to identify the existence of PA among them. An understanding of the prevalence and clinical characteristics of PA can improve its diagnosis and management. However, the prevalence of PA among Korean patients with hypertension is not well known, and we are aware of only a few analyses that have been conducted to evaluate the clinical manifestations of PA in Korea [15–17]. The aim of

this study was to evaluate the prevalence and clinical manifestations of PA in a tertiary-care center in Korea.

Methods

Study population

We retrospectively analyzed a total of 1173 patients with newly diagnosed or preexisting hypertension who were referred to a single tertiary hospital (Severance Hospital) between January 2013 and December 2018. These patients were consecutively screened for PA by a single hypertension specialist. A diagnosis of hypertension was made if the office systolic BP (SBP) was ≥140 mmHg and/or the diastolic BP (DBP) was ≥90 mmHg, or if the patient was using antihypertensive medication according to the current guidelines [14, 18].

This study was approved by the Institutional Review Board of the Yonsei University Health System (4–2021-0174) and was conducted in accordance with the Declaration of Helsinki. Informed consent was waived by the board, as personal identifying information was removed after cohort creation according to strict confidentiality guidelines.

Diagnosis of PA

The diagnosis of PA was made according to the recommendation in the Endocrine Society guideline [1]. Patients were screened for PA by using the ARR, defined as the ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA), both of which were measured using a gamma counter and radioimmunoassay using commercial kits (Fujirebio Inc., Tokyo, Japan and Beckman Coulter Immunotech, Marseille, France). MR antagonists were stopped for at least 4 weeks before ARR testing. Calcium channel blockers and/or α-adrenergic receptor blockers and/or hydralazine, which are known to have a minimal effect on ARR, were the preferred medications for BP control when discontinuation of all antihypertensive medications was not feasible because of the risk of uncontrolled hypertension. A positive screening result was defined as an ARR > 30 ng/dL per ng/mL/h, or an ARR > 20 ng/dL per ng/mL/h together with a PAC > 15 ng/dL. The ARR test could be repeated if the initial results were inconclusive or difficult to interpret because of medications that could affect it. Among patients with a positive initial screening result, those who were considered to have a low probability of PA (and, thus, a high probability of the result being a false positive) by the physician (i.e., because of normalization of the ARR during the follow-up period or the use of beta-blockers or nonsteroidal anti-inflammatory drugs at initial screening) did not have to undergo a confirmatory test. Moreover, those who were unwilling or unable to undergo further investigations because of loss to follow-up, old age, heart failure, chronic kidney disease, or severe uncontrolled hypertension could not proceed to confirmatory testing. Among the patients who did not undergo a confirmatory test, those who exhibited clinically suspected features of PA, such as uncontrolled HTN, and were started on MR antagonists for BP control were considered to have "probable PA." Patients with spontaneous hypokalemia and PRA below detection levels with PAC > 20 ng/dL were diagnosed with PA at the physician's discretion, without confirmatory testing, in line with recommendations from the Endocrine Society [1].

In patients with a positive screening result, a saline infusion test (SIT) was performed to confirm the diagnosis of PA [1, 11, 19]. Specifically, 2 L of 0.9% saline was infused over 4 h in the recumbent position, starting between 8:00 and 9:30 AM. A blood sample was drawn at baseline and after infusion; a postinfusion PAC ≥ 10 ng/dL confirmed the diagnosis of PA, and a postinfusion PAC < 5 ng/dL excluded the diagnosis of PA. A PAC of ≥5 and <10 ng/dL was considered indeterminate and classified as PA or non-PA at the physician's discretion, considering uncontrolled hypertension or an increase in the PAC during the follow-up period. We also performed a supplementary analysis, in which we classified patients as having PA using a cutoff postinfusion PAC of 6.8 ng/dL, according to a previous study [20].

Subtype classification for PA

All patients with a confirmed diagnosis of PA underwent adrenal computed tomography (CT) for preliminary classification. Patients willing to undergo adrenalectomy underwent adrenal venous sampling (AVS). AVS was conducted in the morning with adrenocorticotropic hormone stimulation by an experienced radiologist [21, 22]. The selectivity index was calculated as the ratio of the cortisol level in each adrenal vein to the peripheral cortisol level. AVS was regarded as successful if the selectivity index was >5.0 [23, 24]. Patients with an adequate AVS on at least one side were further assessed for lateralization. In the case of adequate bilateral AVS, a lateralization index greater than 4 or between 3 and 4 with contralateral suppression (a cortisol-corrected aldosterone ratio between the nondominant adrenal vein and peripheral vein, known as the contralateral suppression index, of <1) was used as the lateralization criterion. For adequate unilateral AVS, the presence of contralateral suppression was considered sufficient evidence of lateralization. Some younger patients (<35 years) with radiologic features consistent with a cortical adenoma on CT and apparent PA features (uncontrolled hypertension,

hypokalemia) did not undergo AVS before proceeding to unilateral adrenalectomy at the physician's discretion.

PA was subclassified as aldosterone-producing adenoma (APA), bilateral adrenal hyperplasia (BAH), and unilateral adrenal hyperplasia (UAH). A diagnosis of APA or UAH was pathologically confirmed after surgery [1, 25]. If no adrenalectomy was performed, radiologic features of adrenal CT and lateralization of AVS were used for the diagnosis. Patients without evidence of lateralization of aldosterone secretion were diagnosed with BAH by exclusion.

Data collection

Baseline characteristics, including demographic data, comorbidities, current medication use, laboratory data, and echocardiographic parameters, were collected for all patients by reviewing their medical records. Biochemical parameters, including creatinine, electrolytes, cholesterol, and glucose, were measured simultaneously with the PAC and ARR. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2. We defined hypokalemia as a serum potassium level <3.5 mmol/L. The risk of cardiovascular complications was assessed by identifying the presence of left ventricular hypertrophy (LVH) upon electrocardiogram (ECG) or echocardiography. By ECG, LVH was diagnosed if the sum of the S wave in lead V1 and the R wave in lead V5 or V6, whichever was larger, exceeded 35 mm or if the R wave in lead aVL exceeded 11 mm, according to the current guideline and a similar previous study [16, 18]. Echocardiography was performed in 980 patients (83.5%). The left ventricular mass index (LVMI) was calculated by using the left ventricular diameter and body surface area, and an LVMI ≥ 95 g/m^2 in women and ≥115 g/m^2 in men was defined as LVH [26]. Albuminuria was defined as a spot urinary albumin-to-creatinine ratio (UACR) of ≥30 mg/g.

BP measurements

Baseline BP was obtained from the record of the patient's first visit for evaluation of PA. Office BP measurements were not standardized; both office aneroid BP measurements (Mercury sphygmomanometer until 2013, thereafter by Welch Allyn, Inc., Skaneateles Falls, NY, USA) and automated oscillometric BP measurements (A&D Medical, Tokyo, Japan) were used because of the retrospective study design.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) was performed by using the Takeda TM-2430 instrument (A&D Medical), with readings taken every 30 min [27, 28]. We considered an ABPM record of at least 70% of the expected measurements and at least 14 measurements during the day and 7 during the night as being adequate [29, 30]. Daytime and nighttime were determined according to information provided in the patients' diaries. Ambulatory BP readings were averaged for the 24-h, daytime, and night-time values [31]. If the period between the office BP and ABPM measurements exceeded 3 months, only the office BP measurements were included in the analyses. ABPM was performed prior to PA-specific treatment. Patients remained on their usual antihypertensive medications during ABPM. In cases where more than one 24-h ABPM test was performed, only the first measurement was collected.

Dipping categories were defined according to the night-to-day SBP ratio as follows: riser (ratio > 1.0); nondipper (0.9< ratio ≤1.0); dipper (0.8< ratio ≤0.9); and extreme dipper (ratio ≤ 0.8) [30].

Statistical analysis

Descriptive statistics were used to characterize baseline characteristics and comorbidities. Categorical variables are reported as frequencies (percentages). Continuous variables are expressed as the means ± standard deviations or medians with interquartile ranges. Categorical variables were compared by using Fisher's exact test or the Pearson chi-square test, and continuous variables were compared by using Student's *t* test or the Mann–Whitney *U* test.

All tests were two-tailed, and a *P* value of <0.05 was considered statistically significant. Statistical analyses were performed by using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient enrollment and clinical characteristics

Between January 2013 and December 2018, a total of 1173 patients with newly diagnosed or preexisting hypertension underwent a screening test for PA at our tertiary hospital. The mean age of these patients was 51.8 years, and 53.2% were women (Table 1). Overall, the average office SBP and DBP were 148.6 ± 21.2 mmHg and 90.1 ± 12.4 mmHg, respectively.

Diagnosis of PA

The flow chart of the diagnostic work-up for PA is presented in Fig. 1. Among the 1173 patients who were screened, 360 (30.7%) patients exhibited positive results on the screening test for PA. Among the 360 patients who were screened positive, 155 patients were considered by the physician to have a low probability of PA or a high probability of a false-

Table 1 Baseline characteristics according to PA diagnosis

Variables	Overall ($n = 1173$)	PA ($n = 71$)	Non-PA[a] ($n = 888$)	P value
Clinical characteristics				
Age, years	51.8 ± 15.9	50.4 ± 13.7	50.3 ± 16.2	0.961
Female	624 (53.2)	37 (52.1)	448 (50.5)	0.884
Height, cm	164.3 ± 9.6	165.5 ± 8.3	164.9 ± 9.7	0.639
Weight, kg	68.5 ± 15.2	73.6 ± 17.5	69.0 ± 15.4	0.015
Body mass index, kg/m²	25.2 ± 4.0	26.6 ± 4.6	25.2 ± 4.2	0.007
Diabetes	87 (7.4)	11 (15.5)	51 (5.7)	0.003
Atrial fibrillation	25 (2.1)	2 (2.8)	11 (1.2)	0.566
Coronary artery disease	80 (6.8)	7 (9.9)	45 (5.1)	0.149
Previous stroke	57 (4.9)	5 (7.0)	33 (3.7)	0.286
Chronic kidney disease	48 (4.1)	2 (2.8)	33 (3.7)	0.952
Laboratory data				
Creatinine, mg/dL	0.84 ± 0.58	0.79 ± 0.20	0.83 ± 0.49	0.222
eGFR, ml/min/1.73 m^2	95.9 ± 19.4	97.3 ± 18.3	97.2 ± 19.1	0.961
Serum potassium, mmol/L	4.3 ± 0.4	4.0 ± 0.5	4.4 ± 0.4	<0.001
Hypokalemia (potassium < 3.5 mmol/L)	24 (2.0)	6 (8.5)	13 (1.5)	<0.001
Serum glucose, mg/dL	106 ± 25	106 ± 18	105 ± 25	0.721
Total cholesterol level, mg/dL	191 ± 38	180 ± 30	193 ± 37	0.001
UACR, mg/g[b]	13 (8–30)	22 (9–93)	13 (7–26)	0.021
Albuminuria[b]	145 (25.6)	14 (43.8)	97 (22.0)	0.010
ARR, ng/dL per ng/mL/h	12.4 (5.3–27.9)	56.7 (39.2–96.7)	8.6 (3.8–15.2)	<0.001
PAC, ng/dL	17.3 (13.0–23.6)	25.4 (20.0–32.6)	16.6 (1278–22.5)	<0.001
PRA, ng/mL/h	1.34 (0.63–3.55)	0.43 (0.26–0.72)	1.97 (1.04–4.51)	<0.001
LVH by ECG	232 (19.8)	22 (31.0)	164 (18.5)	0.016
Echocardiographic parameters[c]				
LVEF, %	67.7 ± 6.6	67.4 ± 6.5	67.8 ± 6.5	0.702
LVMI, g/m^2	92.9 ± 25.4	100.2 ± 6.5	91.4 ± 26.2	0.003
LAVI, ml/m^2	27.2 ± 8.5	28.3 ± 8.2	26.4 ± 7.8	0.076
E/e'	9.9 ± 3.7	10.4 ± 3.3	9.6 ± 3.5	0.105
LVH by Echocardiography	256 (26.1)	24 (38.1)	172 (22.9)	0.011
Medication at the time of referral				
Number of antihypertensive medication	1.8 ± 1.2	2.4 ± 1.3	1.6 ± 1.1	<0.001
RAS inhibitor (ACEi/ARB)	662 (56.4)	48 (67.6)	485 (54.6)	0.046
Beta-blocker	299 (25.5)	31 (43.7)	180 (20.3)	<0.001
Calcium channel blocker	775 (66.1)	55 (77.5)	568 (64.0)	0.030
Diuretic	286 (24.4)	25 (35.2)	191 (21.5)	0.012
Alpha-blocker or others	47 (4.0)	11 (15.5)	21 (2.4)	<0.001
Statin	362 (30.9)	23 (32.4)	259 (29.2)	0.661

Values are expressed as number (%), mean ± standard deviation, or median (interquartile range)

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARR* aldosterone-to-renin ratio, *ECG* electrocardiogram, *eGFR* estimated glomerular filtration rate, *LAVI* left atrial volume index, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *LVMI* left ventricular mass index, *PA* primary aldosteronism, *PAC* plasma aldosterone concentration, *PRA* plama renin activity, *RAS* renin-angiotensin system, *UACR* urinary albumin-to-creatinine ratio

[a]Excluding patients with positive initial screening result not undergoing confirmatory test ($n = 214$)

[b]UACR and albuminuria data were available for 567 (48.3%) participants ($n = 440$ in non-PA group, $n = 32$ in PA group)

[c]Echocardiographic data were available for 987 (84.1%) participants ($n = 751$ in non-PA group, $n = 63$ in PA group)

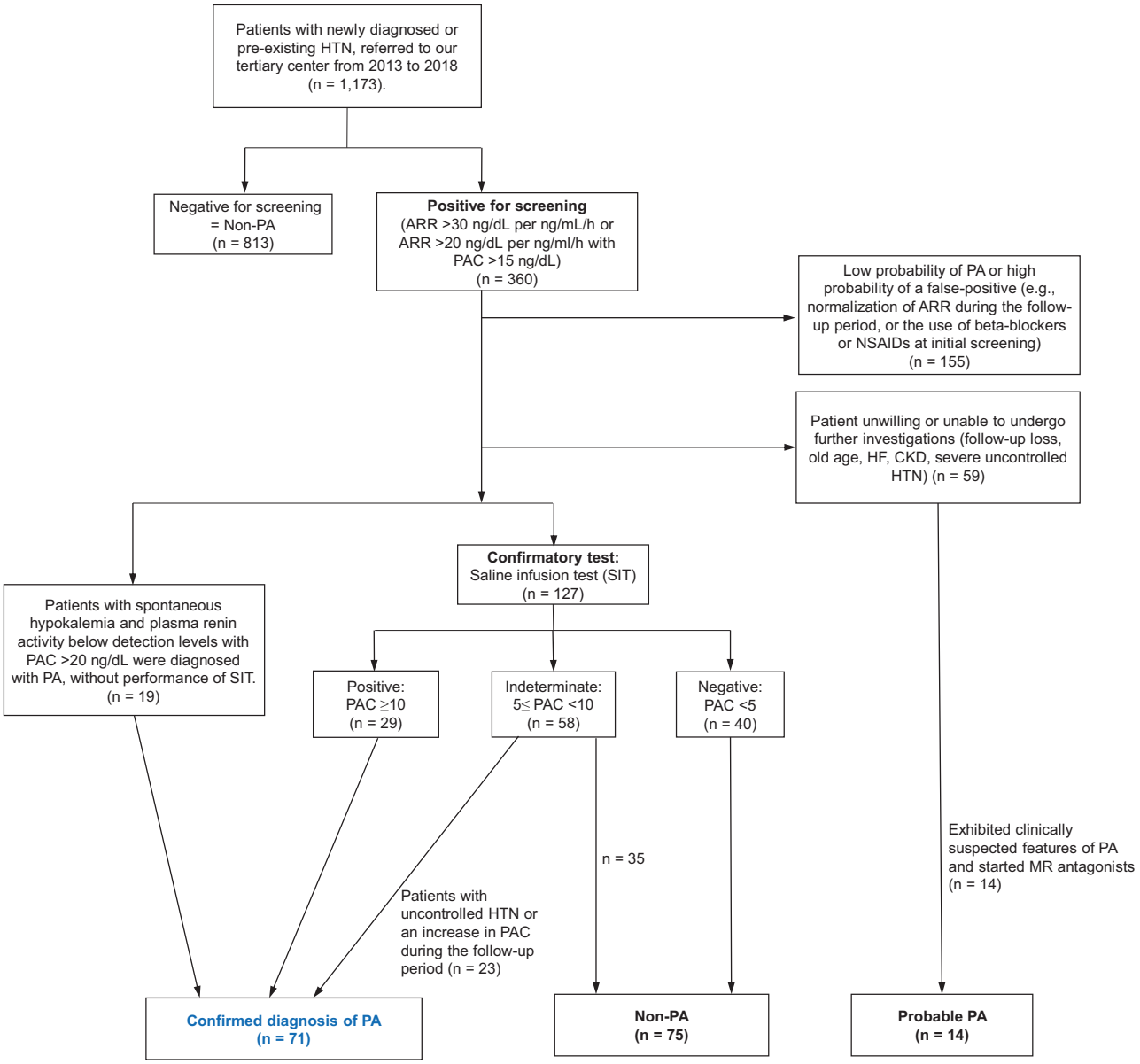


Fig. 1 Study flow chart for diagnosis of PA. Among the 1173 patients with hypertension who were initially included in the study and screened for PA, 71 (6.1%) were diagnosed with PA. ARR aldosterone-to-renin ratio, CKD chronic kidney disease, HF heart failure, HTN hypertension, NSAID nonsteroidal anti-inflammatory drug, PA primary aldosteronism, PAC plasma aldosterone concentration, SIT saline infusion test

positive test. Fifty-nine patients were unwilling or unable to undergo further investigations, among which 14 had clinically suspected features of PA and were started on MR antagonists for BP control. These 14 cases (1.2%) were classified as probable PA. Nineteen patients with spontaneous hypokalemia and PRA below detection levels with PAC > 20 ng/dL were diagnosed with PA without performance of the SIT. The remaining 127 patients underwent SIT.

Upon performance of the SIT in these 127 patients, the PA diagnosis was confirmed in 29, excluded in 40, and indeterminate in 58 according to the postinfusion PAC level. Of the 58 patients with an indeterminate diagnosis, 23 with uncontrolled hypertension or an increase in the PAC during the follow-up period were diagnosed with PA. Finally, 71 (6.1%) patients were confirmed to have PA among the total study sample.

When applying a cutoff value of 6.8 ng/dL during supplementary analysis, among 1173 patients with hypertension, 80 (6.8%) were diagnosed with PA.

Subtype classification for PA

Adrenal CT was performed for all 71 patients confirmed to have PA, and AVS was performed in 53 (74.6%) of them

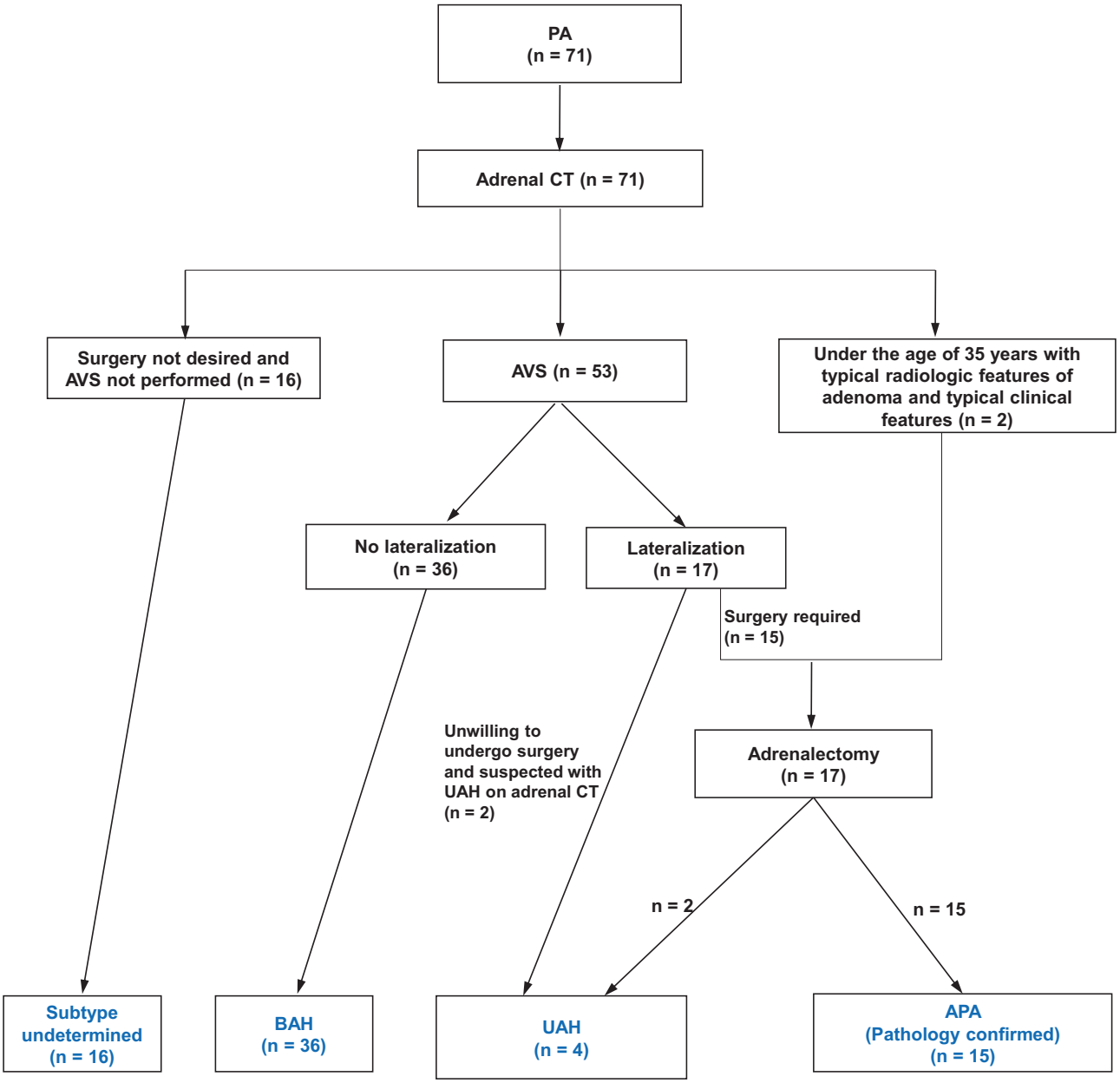


Fig. 2 Study flow chart for subtype classification of PA. APA aldosterone-producing adenoma, AVS adrenal venous sampling, BAH bilateral adrenal hyperplasia, CT computed tomography, PA primary aldosteronism

(Fig. 2). Sixteen patients were unwilling to undergo adrenalectomy and therefore did not undergo AVS. Two patients under the age of 35 years with typical radiologic features of adenoma on CT and clinical features of PA bypassed AVS and proceeded directly to surgery. Among 53 patients who underwent AVS, unilateral aldosterone overproduction was observed in 17 and bilateral secretion in 36. Among the 17 patients with unilateral aldosterone overproduction, 2 declined adrenalectomy, both of whom were suspected to have UAH based on adrenal CT characteristics. As such, a total of 17 patients (15 who underwent AVS and 2 who did not) underwent unilateral adrenalectomy. Finally, among the 55 patients with conclusive subtype differentiation of PA, 15 (27%) had APA, 4 (7%) had UAH, and 36 (66%) had BAH. The remaining 16 patients did not undergo AVS and had an undetermined subtype of PA.

Differences between the PA and non-PA groups

The baseline characteristics according to PA diagnosis are summarized in Table 1. The non-PA group excluded

patients with a positive initial screening result who were not undergoing a confirmatory test ($n = 214$). Patients with PA had a higher ARR and PAC and lower PRA than patients without PA ($P < 0.001$). The mean serum potassium level at the time of diagnosis was lower in patients with PA than in patients without PA (4.0 mmol/L vs. 4.4 mmol/L, $P < 0.001$), and the proportion of hypokalemia was much higher in the PA group than in the non-PA group (8.5% vs. 1.5%, $P < 0.001$). Patients with PA were taking more antihypertensive agents (2.4 vs. 1.6, $P < 0.001$) and had a higher body weight and body mass index than patients with non-PA. Diabetes was also more prevalent in the PA group than in the non-PA group. Among patients with diabetes, HbA1c did not significantly differ between those with PA and those without (6.52% vs. 7.05%, $P = 0.195$). No statistically significant differences were observed in other characteristics between these groups, including age, sex, other comorbidities, and creatinine level.

In terms of target-organ damage (Table 1), patients with PA presented with a higher LVMI (100.2 g/m^2 vs. 91.4 g/m^2, $P = 0.003$) and more frequently presented with LVH upon ECG (31.0% vs. 18.5%, $P = 0.016$) and/or echocardiography (38.1% vs. 22.9%, $P = 0.011$) than patients without PA; furthermore, they had a higher UACR value. Albuminuria was more prevalent in the PA group than in the non-PA group (43.8% vs. 22.0%, $P = 0.010$).

BP data according to PA diagnosis are summarized in Table 2. Patients with PA seemed to have a higher baseline office SBP and DBP than patients without PA, but this difference was not statistically significant. Patients with PA exhibited higher 24-h, daytime, and nighttime BP values than patients without PA. There were no statistically significant differences in the night-to-day SBP ratio or the proportion of risers/nondippers between the two groups.

Table 2 Blood pressure measurements according to PA diagnosis

Variables	PA ($n = 71$)	Non-PA[a] ($n = 888$)	P value
Office SBP, mmHg	152.3 ± 20.2	147.7 ± 21.1	0.076
Office DBP, mmHg	92.7 ± 13.4	90.2 ± 12.3	0.103
24-h SBP, mmHg[b]	143.1 ± 14.5	135.0 ± 14.9	<0.001
24-h DBP, mmHg[b]	85.8 ± 9.8	82.0 ± 9.6	0.005
Daytime SBP, mmHg[b]	148.2 ± 14.5	140.2 ± 15.2	<0.001
Daytime DBP, mmHg[b]	89.0 ± 9.3	85.7 ± 10.2	0.018
Nighttime SBP, mmHg[b]	133.5 ± 18.1	123.9 ± 16.5	<0.001
Nighttime DBP, mmHg[b]	79.5 ± 12.1	74.3 ± 10.2	<0.001
SBP night/day ratio[b]	0.90 ± 0.09	0.89 ± 0.08	0.158
Risers/non-dipper[b]	24 (42.9)	267 (35.7)	0.352

Values are expressed as number (%), mean ± standard deviation, or median (interquartile range)

ABPM ambulatory blood pressure monitoring, *DBP* diastolic blood pressure, *PA* primary aldosteronism, *SBP* systolic blood pressure

[a]Excluding patients with positive initial screening result not undergoing confirmatory test ($n = 214$)

[b]ABPM data were available for 973 (82.9%) participants ($n = 748$ in non-PA group, $n = 56$ in PA group)

Differences between unilateral and bilateral PA groups

Patients with APA were characterized by a higher PAC and ARR and lower potassium levels than patients with BAH (Table 3). The BP measurements neither did statistically significantly differ between the two groups nor did any other characteristics.

Follow-up according to treatment

The fifteen patients with APA were confirmed to have PA after adrenalectomy. Among the four patients with UAH, two were confirmed after surgery, and the remaining were confirmed with AVS and adrenal CT and treated with MR antagonists, as they declined surgery. Among the 52 patients with BAH and indeterminate subtype, 49 were treated with MR antagonists. Among the remaining three patients with BAH, one declined the use of MR antagonists, and two exhibited controlled BP without the use of MR antagonists.

The baseline and follow-up clinical characteristics of patients with PA, stratified according to the treatment method, are summarized in Table 4. Patients with PA exhibited a BP reduction after treatment, regardless of the treatment method. Patients with PA also exhibited a higher serum potassium level after treatment. Moreover, the follow-up ARR was lower than that at baseline. Patients treated with surgery but not with medication exhibited a lower follow-up than baseline PAC.

Discussion

The main findings of the present study are as follows: (1) Among a total of 1173 hypertensive patients, 71 were diagnosed with PA, with a prevalence of 6.1%. (2) Among the 55 patients with a conclusive subtype differentiation of PA, 15 (27%) had APA, 4 (7%) had UAH, and 36 (66%) had BAH, indicating a higher prevalence of bilateral than unilateral PA. (3) Patients with PA had higher BPs than those without PA; moreover, LVH and albuminuria were more prevalent in the PA group than in the non-PA group.

The prevalence of PA (6.1%) among patients with hypertension in our study was similar to that in previous studies [12, 13, 32, 33]. Notably, 59 patients with positive screening test results were unwilling or unable to undergo

Table 3 Baseline characteristics according to subtype classification of PA

Variables	BAH ($n = 36$)	APA ($n = 15$)	P value
Clinical characteristics			
Age, years	49.4 ± 13.1	46.0 ± 9.4	0.373
Female	20 (56)	9 (60)	0.999
Height, cm	165.7 ± 8.8	166.6 ± 7.5	0.722
Weight, kg	72.7 ± 21.0	76.4 ± 15.9	0.546
Body mass index, kg/m²	26.1 ± 5.2	27.3 ± 4.0	0.419
Diabetes	2 ^6)	3 (20)	0.287
Laboratory data			
Creatinine, mg/dL	0.77 ± 0.16	0.74 ± 0.19	0.522
eGFR, ml/min/1.73 m^2	99.2 ± 15.5	102.3 ± 17.5	0.537
Serum potassium, mmol/L	4.2 ± 0.4	3.8 ± 0.6	0.016
Hypokalemia (potassium < 3.5 mmol/L)	0 (0)	2 (13)	0.149
Serum glucose, mg/dL	103.6 ± 14.1	111 ± 25	0.311
Total cholesterol level, mg/dL	183.8 ± 29.3	178 ± 32	0.559
UACR, mg/g[a]	17 (9–52)	118 (25–166)	0.344
Albuminuria[a]	9 (38)	5 (71)	0.248
ARR, ng/dL per ng/mL/h	49.5 (37.4–63.2)	101.7 (48.6–161.6)	0.038
PAC, ng/dL	22.2 (18.6–27.8)	30.1 (26.1–45.6)	0.001
PRA, ng/mL/h	0.47 (0.33–0.67)	0.39 (0.21–0.73)	0.488
LVH by ECG	11 (31)	4 (27)	0.999
Echocardiographic parameters[b]			
LVEF, %	68.6 ± 5.7	65.4 ± 8.4	0.144
LVMI, g/m^2	95.8 ± 19.3	105.2 ± 24.7	0.176
LVH by Echocardiography	10 (33)	7 (50)	0.468
Medication			
Number of antihypertensive medication	1.9 ± 1.0	2.7 ± 1.2	0.022
Blood pressure measurements			
Office SBP, mmHg	149.1 ± 20.0	152.6 ± 16.2	0.553
Office DBP, mmHg	91.8 ± 14.6	93.9 ± 10.7	0.623
24-h SBP, mmHg[c]	143.1 ± 15.1	141.9 ± 15.0	0.828
24-h DBP, mmHg[c]	85.4 ± 10.2	86.8 ± 9.3	0.686
Daytime SBP, mmHg[c]	149.4 ± 15.2	146.1 ± 13.1	0.527
Daytime DBP, mmHg[c]	89.2 ± 9.8	89.4 ± 9.3	0.952
Nighttime SBP, mmHg[c]	131.3 ± 17.6	133.0 ± 19.4	0.793
Nighttime DBP, mmHg[c]	78.0 ± 11.5	80.6 ± 11.8	0.521
SBP night/day ratio[c]	0.89 ± 0.08	0.91 ± 0.09	0.297
Risers/non-dipper[c]	12 (39)	5 (45)	0.973

Values are expressed as number (%), mean ± standard deviation, or median (interquartile range)

APA aldosterone-producing adenoma, *ARR* aldosterone-to-renin ratio, *BAH* bilateral adrenal hyperplasia, *ECG* electrocardiogram, *eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *LVMI* left ventricular mass index, *PA* primary aldosteronism, *PAC* plasma aldosterone concentration, *PRA* plama renin activity, *UACR* urinary-albumin-to-creatinine ratio

[a]UACR and albuminuria data were available only for 24 (47%) participants, among which 17 had BAH and 7 had APA

[b]Echocardiographic data were available only for 44 (86%) participants, among which 30 had BAH and 14 had APA

[c]ABPM data were available only for 42 (82%) participants, among which 31 had BAH, and 11 had APA

confirmatory tests. Of these, 14 patients had clinically suspected features of PA, were started on MR antagonists and were classified as "probable PA." If these patients were taken into account, the prevalence of PA increased to 7.2%. However, a survey of general practitioners in Europe revealed that only 7–8% of patients with hypertension are screened for PA [34]. Moreover, only 2% of patients with resistant hypertension are reportedly screened for PA [35]. PA is not uncommon in the hypertensive population, and considering that 29% of the adult Korean population has hypertension, the identification of patients with PA among that hypertension may be important. To the best of our knowledge, ours is the first report of the prevalence and clinical characteristics of PA among the Korean hypertensive population, and our findings may be of use in clinical practice.

Additionally, differences in hypertension severity or patient characteristics between primary or tertiary care facilities may affect the prevalence of PA. Referral bias may result in a slightly higher prevalence of PA in tertiary care facilities than in primary care facilities, as supported by previous studies [12]. Further studies regarding the prevalence of PA in Korean primary-care practice are warranted.

Hypokalemia is no longer a requisite for the diagnosis of PA, considering that only 9–37% of patients with PA reportedly have hypokalemia [10, 11, 13]. According to our data, among 71 patients with PA, only 6 (8.5%) had hypokalemia, which approximates the lower bound of the abovementioned range. Additionally, it is well known that target-organ damage, including LVH and albuminuria, is associated with PA [32, 36, 37]. Moreover, patients with PA have a high prevalence of diabetes and obesity [38, 39]. Similar to these previous studies, our study revealed that patients with PA displayed a higher degree and prevalence of target organ damage than patients without PA, suggesting that a high aldosterone concentration may be responsible for such damage.

In our study, patients with PA had a higher overall BP than patients without PA, despite using a similar number of antihypertensive medications. Furthermore, patients with PA exhibited a statistically significant BP reduction after treatment, whether by surgery or by MR antagonists. This may emphasize the need for proper diagnosis and treatment for PA to optimize BP control and minimize the risk of cardiovascular complications.

One surprising finding from our study was the lack of a difference in the nocturnal dipping pattern during 24-h ambulatory monitoring between the PA and non-PA groups. Previous studies yielded inconsistent results in this regard. In some studies, there was no difference in the diurnal dipping pattern between patients with and without PA [40, 41]. However, in others, the nocturnal BP decline was lower in those with PA than in those without PA, and impaired nocturnal dipping was more prevalent in patients with PA [42–44]. However, these studies all differed in their diagnostic criteria for PA, their policies on continuation or discontinuation of antihypertensive medication

Table 4 Baseline and follow-up clinical characteristics according to treatment method for PA

Variables	Surgery PA ($n = 17$)	Medication PA ($n = 54$)
Baseline		
Office SBP, mmHg	152.1 ± 15.9*	152.4 ± 21.5*
Office DBP, mmHg	94.1 ± 11.3*	92.2 ± 14.1*
Serum potassium, mmol/L	3.9 ± 0.5*	4.1 ± 0.4*
ARR, ng/dL per ng/mL/h	77.1 (30.4–157.4)*	55.1 (41.2–83.2)*
PAC, ng/dL	30.1 (25.4–41.5)*	22.5 (18.9–31.2)
PRA, ng/mL/h	0.42 (0.21–0.76)*	0.44 (0.32–0.63)*
Number of antihypertensive medication	2.6 ± 1.2	2.6 ± 1.2
Follow-up (After treatment)		
Office SBP, mmHg	126.9 ± 16.4*	126.4 ± 13.4*
Office DBP, mmHg	82.2 ± 13.1*	77.3 ± 7.8*
Serum potassium, mmol/L	4.6 ± 0.4*	4.5 ± 0.4*
ARR, ng/dL per ng/mL/h[a]	9.3 (5.5–11.9)*	24.4 (6.2–41.2)*
PAC, ng/d[a]	15.9 (11.9–19.8)*	23.8 (20.7–31.7)
PRA, ng/mL/h[a]	1.74 (1.12–3.36)*	1.04 (0.51–6.93)*
Number of antihypertensive medication	2.3 ± 1.1	2.3 ± 1.1

Values are expressed as number (%), mean ± standard deviation, or median (interquartile range)

APA aldosterone-producing adenoma, *ARR* aldosterone-to-renin ratio, *BAH* bilateral adrenal hyperplasia, *DBP* diastolic blood pressure, *PA* primary aldosteronism, *PAC* plasma aldosterone concentration, *PRA* plasma renin activity, *SBP* systolic blood pressure

*P value <0.05 between baseline and follow-up

[a]The ARR, PAC, and PRA were available only for 32 (45%) participants, among which 16 were treated with surgery and 16 were treated with medication

before ABPM, and patient inclusion criteria, which may explain the inconsistency in results.

The prevalence of APA among patients with PA also differs among studies, probably because of the heterogeneity in patients' characteristics, diagnostic criteria, and the frequency of AVS [11, 12]. In our study, BAH was more prevalent than APA, with only 27% of patients with PA having APA, consistent with the results of recent studies [32, 33]. In addition, biochemical and hormonal abnormalities tended to be milder in patients with BAH than in those with APA. Although APA is thought to be a more severe form of PA, there were no statistically significant differences in the prevalence of LVH and parameters of ABPM, including in the number of risers/nondippers, between these subgroups.

Perspective of Asia

Studies have shown that obesity is associated with an increase in inappropriate aldosterone secretion [45]. Additionally, Asians are more likely to have higher salt sensitivity than Westerners [46]. Therefore, the prevalence of PA reported in Western countries may not be directly applicable to Asian countries. The important finding from this study was that the prevalence of PA was similar to that in the Western population and to that reported for other Asian countries, such as Singapore and China [33, 47]. The results of this study suggest that widespread screening for PA may be beneficial in detecting this potentially curable cause of hypertension in the Asian population.

Limitations

This study has several limitations. First, it was a retrospective, single-center study in a tertiary hospital. As many patients who are referred to tertiary hospitals are at high risk and need evaluation for secondary hypertension or have uncontrolled hypertension, the results from this study cannot be generalized to the general hypertension population. Second, confirmatory tests were not performed for all patients with positive screening results. Patients deemed by the physician to have a low probability of PA and those who were unwilling or unable to undergo further investigations did not receive a SIT in our study. Additionally, patients with indeterminate SIT results were classified as having or not having PA at the physician's discretion. The retrospective design and the use of the physician's discretion in the diagnostic process might have given rise to bias and inaccuracy in terms of the prevalence of PA, which was a major limitation of our study. Third, although antihypertensive medication with minimal effect on the ARR was preferentially prescribed during the initial screening, we could not exclude the possibility that patients were using other medications with possible effects on the ARR, which might have affected the ARR values in this study. Fourth, we did not perform another confirmatory test, such as the fludrocortisone suppression test or the captopril challenge test, for those patients with a contraindication or an indeterminate result on the SIT. Hence, the true prevalence of PA might be higher than 6.1%. Fifth, the duration of hypertension and the BP level without antihypertensive medication could not be evaluated because of the retrospective design. Additionally, antihypertensive medications were not withheld before ABPM and echocardiography were performed, which may have interfered with the overall BP burden, nocturnal dipping, and LVMI. However, withdrawal of antihypertensive medications can lead to a hypertensive crisis and is, therefore, not routinely performed prior to ABPM. As the objective of the current study was to determine indicators of PA in routine ABPM studies, the continuation of medications was not a hindrance. Sixth, AVS was not performed on all patients with PA. Sixteen patients did not undergo AVS and could

therefore be considered of an indeterminate subtype of PA. Seventh, other forms of secondary hypertension were not systematically excluded because of the retrospective study design.

Despite these limitations, our study also had certain strengths, including the large number of participants who underwent the screening test for PA. Furthermore, our study had the advantage of the availability of data on ABPM and target organ damage. To our knowledge, this was the first large study in which the prevalence of PA was evaluated among Korean patients with hypertension. Considering the relatively high prevalence of PA, our study provides evidence and a rationale for routine screening for PA in patients with hypertension during their initial evaluation. Further research is warranted to elucidate whether wide screening and earlier detection for PA would reduce the incidence of real-world cardiovascular events.

Conclusion

PA may be more common among Korean patients with hypertension than generally recognized, with a prevalence of 6.1%. Patients with PA may have a higher degree and prevalence of target organ damage and a higher BP level than those without PA. Wide application of screening tests for PA among patients with hypertension may be beneficial in detecting this potentially curable cause of hypertension.

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Compliance with ethical standards

Conflict of interest CJL has received honoraria from Novartis, Daewoong Pharmaceutical, Servier, Hanmi Pharmaceutical, Yuhan, Boryung Pharmaceutical, and Daiichi Sankyo. YR has received an honorarium from Amgen and has been a consultant for Amgen and Pharmanovia. SP has received honoraria from Pfizer, Boryoung, Hanmi, Daewoong, Donga, Celltrion, Servier, Daiichi Sankyo, and Daewon. SP has also received a research grant from Daiichi Sankyo. The remaining authors have nothing to declare.

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