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Primary Aldosteronism in Patients in China With Recently Detected Hypertension

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ABSTRACT

BACKGROUND A total of 44.7% adults in China have hypertension, but the prevalence of primary aldosteronism (PA) in Chinese hypertensive patients is unknown.

OBJECTIVES This study prospectively investigated the prevalence, characteristics, and outcomes of PA in newly diagnosed hypertensive patients.

METHODS In a large community health center, consecutive hypertensive patients with an aldosterone-renin ratio >20 ng/mIU and plasma aldosterone concentration >10 ng/dl underwent captopril challenge test and/or saline infusion test for confirmation of PA. Adrenal computed tomography scan and adrenal vein sampling were used for subtyping. PA patients treated with surgery or medication were followed up for 1 year, and outcomes after treatment were evaluated.

RESULTS In total, 1,020 newly diagnosed hypertensive patients were screened over 16 months, of whom 40 were diagnosed with PA, 948 with non-PA, 32 with probable PA, resulting in a prevalence of more than 4.0%. Compared with non-PA, PA patients more frequently displayed microalbuminuria ($p = 0.031$), but the incidence of cardiovascular events was not different ($p = 0.927$). For surgically treated patients ($n = 7$), a complete biochemical success rate was 100% and a complete clinical success rate was 85.7%. For medically treated patients ($n = 29$), the proportion with optimal blood pressure control was 79%, and among them, 91% (21 of 23) only needed 1 antihypertensive drug: the mineralocorticoid receptor antagonist.

CONCLUSIONS The prevalence of PA in patients with newly diagnosed hypertension in China was at least 4%. PA screening in newly diagnosed hypertensive patients leads to good clinical outcomes. (Primary Aldosteronism In Hypertensive Patients in China [PA-China]; NCT03155139) (J Am Coll Cardiol 2020;75:1913-22) © 2020 by the American College of Cardiology Foundation.

Primary aldosteronism (PA) is a common cause of secondary hypertension. It is characterized by autonomous hypersecretion of aldosterone from the adrenal cortex, leading to an increase in plasma aldosterone concentration and suppression of renin (1). The treatment of PA is different from that of essential hypertension (EH) with targeted medical therapy available and a potential surgical cure for those with a unilateral aldosterone-producing adenoma (APA). The accurate diagnosis of this disease can greatly improve patient prognosis.

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ABBREVIATIONS AND ACRONYMS

APA = aldosterone-producing adenoma

ARR = aldosterone-to-renin ratio

AVS = adrenal vein sampling

BAH = bilateral adrenal hyperplasia

CV = cardiovascular

DDD = defined daily dose

PA = primary aldosteronism

PAC = plasma aldosterone concentration

PRC = plasma renin concentration

UACR = urinary albumin to creatinine ratio

China bears a considerable proportion of the global burden of morbidity and mortality due to hypertension. The latest epidemiological survey of hypertension based on community populations showed that 44.7% of Chinese age 35 to 75 years experienced hypertension (2). More recently, approximately 244.5 million Chinese adults age ≥18 years are reported to have hypertension (3). Based on prevalence estimates of PA in the general hypertensive population of 5% to 10% (4,5), it is estimated that there might be at least 12 million patients with PA in China, including potentially curable subtypes. However, the actual prevalence of PA in China is unclear.

SEE PAGE 1923

Experimental and clinical studies suggest that long-term exposure to increased aldosterone levels result in cardiovascular (CV) and renal structural damage, independent of blood pressure (BP) (6,7). There is growing evidence for the significantly higher risk of target organ damage and CV events in patients with PA compared with those with age- and BP-matched EH (8–10). However, most of the PA patients in these studies were diagnosed decades after the onset of hypertension. Previous studies demonstrated that a shorter duration of hypertension prior to the diagnosis of PA is associated with a greater probability of surgical cure of unilateral disease (11,12). Thus, it is probable that PA patients identified from a newly diagnosed hypertensive population will have better clinical outcomes following both medical and surgical treatment than those with prolonged hypertension.

Our study aimed to determine the prevalence of PA in China by screening for PA in a large cohort of newly diagnosed hypertensive patients and to evaluate the outcomes of PA by following 1 year of targeted treatment.

METHODS

STUDY DESIGN AND PATIENT COHORTS. This is a prospective study. Newly diagnosed hypertensive patients were consecutively screened for PA at the Community Physical Examination Center affiliated with the First Affiliated Hospital of Chongqing Medical University from May 2017 to September 2018. It is one of the largest primary care centers in Southwest China and takes charge of the annual health check for a population of 147,000. Patients were recruited based on the inclusion criteria: age 18 to ~75 years, with a new (within the previous 12 months) diagnosis of hypertension, with a diagnosis of hypertension made by systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg on at least 3 occasions on different days (including at least 1 out-of-office BP measurement), and not taking antihypertensive drugs. The classification of BP for adults (age 18 years and older) was stratified according to the Joint National Committee VI (13). Patients were excluded if they had: 1) other known causes of secondary hypertension; 2) severe renal insufficiency (estimated glomerular filtration rate <30 ml/min/1.73 m^2), calculated using the CKD-EPI formula; or 3) severe heart failure (New York Heart Association functional class III or above).

All included patients gave a medical and pharmacological history; underwent a physical examination, including measurement of height, weight, waist circumference, and BP; and had blood collected for the measurement of plasma aldosterone and direct renin concentration. Hypokalemia was defined as serum potassium <3.5 mmol/l. Microalbuminuria was defined by spot urinary albumin to creatinine ratio (UACR) of 30 to 300 mg/g. CV events identified from hospital records at baseline included myocardial infarction, unstable angina pectoris requiring angioplasty, stroke, or transient ischemic attack.

All patients with PA were followed up for at least 1 year after surgery or medical treatment for assessment of outcomes, including BP, antihypertensive requirement, serum potassium, aldosterone, and renin.

This study was approved by the ethical committee of Chongqing Medical University, and written informed consent was obtained from all patients participating in the study.

SCREENING TEST FOR PA. For screening, blood samples for plasma renin concentration (PRC) and plasma aldosterone concentration (PAC) were collected in the morning after the subjects were out of bed and in the upright position for at least 2 h. Patients with severe hypertension were commenced on antihypertensive agents that did not interfere with aldosterone and renin measurements, including nondihydropyridine calcium-channel blockers terazosin or doxazosin. A positive screening test was defined as an aldosterone-to-renin ratio (ARR) >20 ng/mIU (~55 $pmol \cdot l^{-1}/mIU \cdot l^{-1}$) together with a plasma aldosterone level >10 $ng \cdot dl^{-1}$ (277 pmol/l). Patients who tested positive proceeded to the confirmatory test, whereas patients who tested negative were considered to not have primary aldosteronism.

CONFIRMATORY TESTS FOR PA. Based on our previous study (14) and taking into account the safety

and convenience of diagnostic tests, we selected the captopril challenge test (CCT) as the first confirmatory test for all patients who screened positive. For patients with an indeterminate result after the CCT (aldosterone concentration after CCT in the gray zone: 8 to 11 ng·dl^{-1} or 220 to 280 pmol/l), a second confirmatory test, the saline infusion test (SIT), was conducted. The diagnosis of PA was established if post-CCT aldosterone concentration was >11 ng·dl^{-1} (>280 pmol/l) or post-SIT aldosterone concentration was >6 ng·dl^{-1} (>180 pmol/l).

For the CCT, patients received 50-mg captopril orally at 8:00 to 9:00 AM after sitting or standing for at least 1 h. Blood samples were drawn for the measurement of PRC and PAC at baseline and 2 h after the challenge, with the patient remaining seated during this period.

For the SIT, patients stayed in the seated position for at least 1 h before and during the infusion of 2 l of 0.9% saline over 4 h, starting at 8:00 AM. Blood samples were drawn at baseline and after 4 h for PRC, cortisol, and PAC determination. During the test, the patients remained seated, and BP and heart rate were monitored hourly.

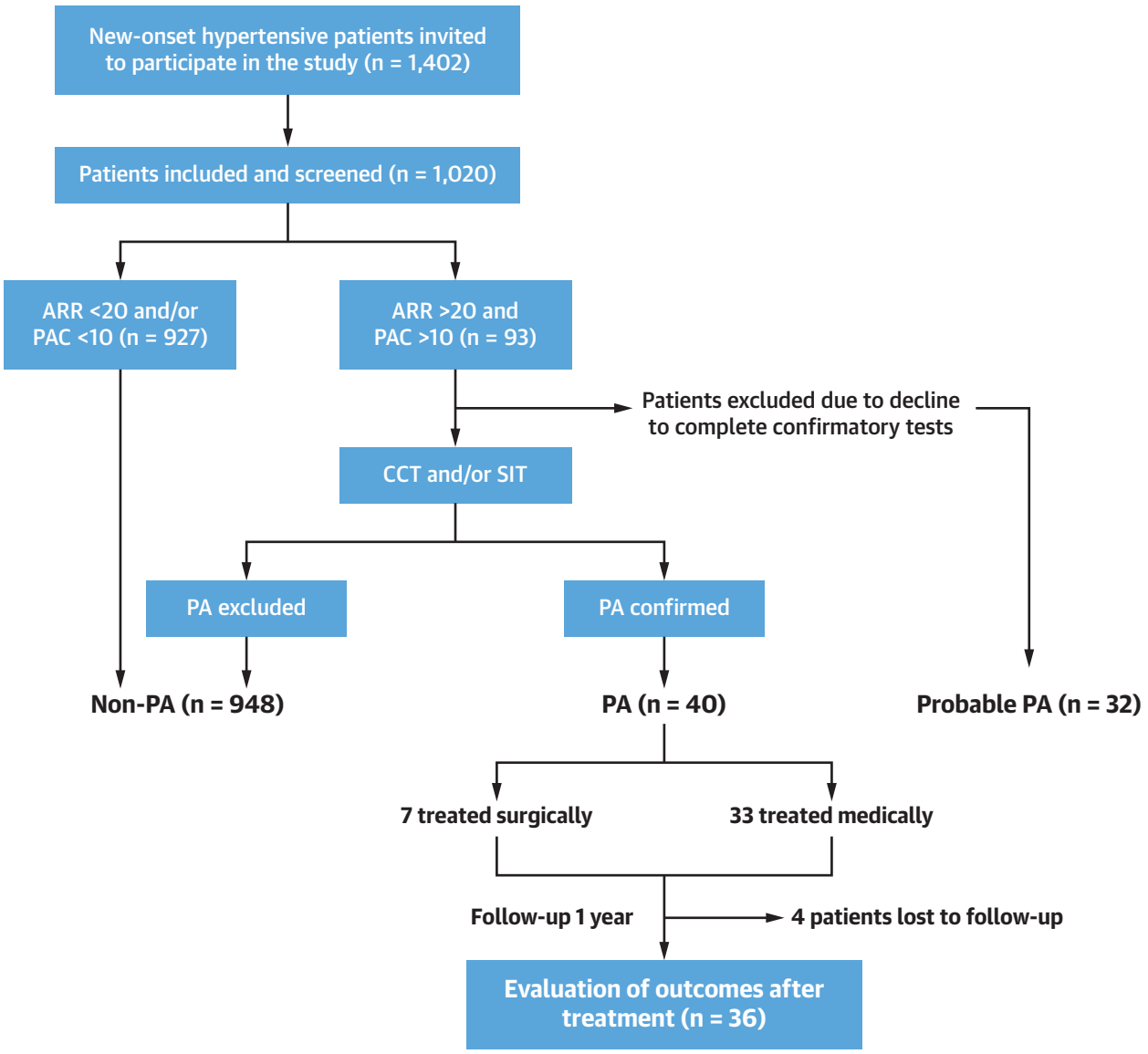
SUBTYPE CLASSIFICATION FOR PA. All patients with a confirmed diagnosis of PA underwent adrenal computed tomography (CT) scanning for preliminary classification. The findings of the adrenal CT scan were evaluated by the same radiologist and divided into 3 types: unilateral lesions, bilateral disease, and bilateral normal. A nodule on CT was defined as a nodule ≥1 cm in diameter. Bilateral normal appearance was defined if the size of the nodule or thickness of adrenal gland was <1 cm on both sides (15). Patients willing to undergo adrenalectomy were submitted to adrenal vein sampling (AVS). AVS was performed in the morning between 8:00 AM and 12:00 PM without ACTH stimulation, the procedures of which have been described in detail elsewhere (14). The criterion used to determine the lateralization of aldosterone hypersecretion was established according to consensus (16). The right and left selectivity index (SI) was calculated as the ratio of each adrenal vein cortisol level to peripheral cortisol level. AVS was regarded as successful if the SI was >2.0. Lateralization of aldosterone hypersecretion was assessed by the lateralization index (the aldosterone to cortisol concentration ratio on the dominant side to the aldosterone-to-cortisol concentration ratio on the contralateral side). Lateralization of aldosterone secretion was defined as a lateralization index ≥2. The diagnosis of aldosterone-producing adenoma (APA) was defined as: 1) unilateral lesion determined by CT and adrenal cortical adenoma confirmed by post-operative pathological examination, with complete biochemical remission after adrenalectomy according to Primary Aldosteronism Surgery Outcome (PASO) consensus (17); or 2) lateralization of aldosterone secretion at AVS if surgery was not performed. The diagnosis of bilateral adrenal hyperplasia (BAH) was confirmed by AVS; if AVS failed or was not performed, BAH was established by a previously reported subtype prediction score of at least 8, which had a positive predictive value of 93.5% for BAH (15). The details of the prediction score can be seen in Supplemental Table 1. An indeterminate subtype was defined as patients who did not meet the diagnostic criteria for APA or BAH. Genetic testing was performed in patients with an onset of confirmed PA earlier than age 20 years and in those with a family history of PA or strokes at a young age for exclusion of glucocorticoid-remediable aldosteronism.

EVALUATION OF CLINICAL OUTCOME OF PA. According to PASO criteria (17), outcomes of adrenalectomy for unilateral primary aldosteronism were classified into complete, partial, and absent success, for both clinical and biochemical outcomes. A detailed description of the outcomes can be found in Supplemental Table 2. For PA patients treated medically, clinical outcomes were determined by the BP response to treatment and the number and dosage of antihypertensive medications. Antihypertensive medication is expressed as defined daily dose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication in adults (ATC/DDD Index 2019). Hypertension was considered "optimally controlled" when home-based monitoring revealed 3 consecutive readings of SBP <140 mm Hg and DBP <90 mm Hg, after the dose of antihypertensive drugs remained stable for more than 1 month.

BIOCHEMICAL MEASUREMENTS. PRC and PAC were measured by automated chemiluminescence immunoassays (LIAISON, DiaSorin, Saluggia, Italy). The analytical sensitivity was 0.53 mIU/l, and the functional sensitivity was 1.6 mIU/l. The PAC assay has a measuring range from 2.2 ng/dl (56 pmol/l) (analytical sensitivity) to 100 ng/dl (2,545 pmol/l), with a functional sensitivity of 3 ng/dl (76.4 pmol/l).

STATISTICAL ANALYSIS. Data were analyzed with the Kolmogorov-Smirnov test to determine their distributions. Normally distributed variables were expressed as the mean ± SD, non-normally distributed variables were expressed as the median (interquartile range), and categorical variables were described as absolute numbers and percentages.

FIGURE 1 Study Flow Chart



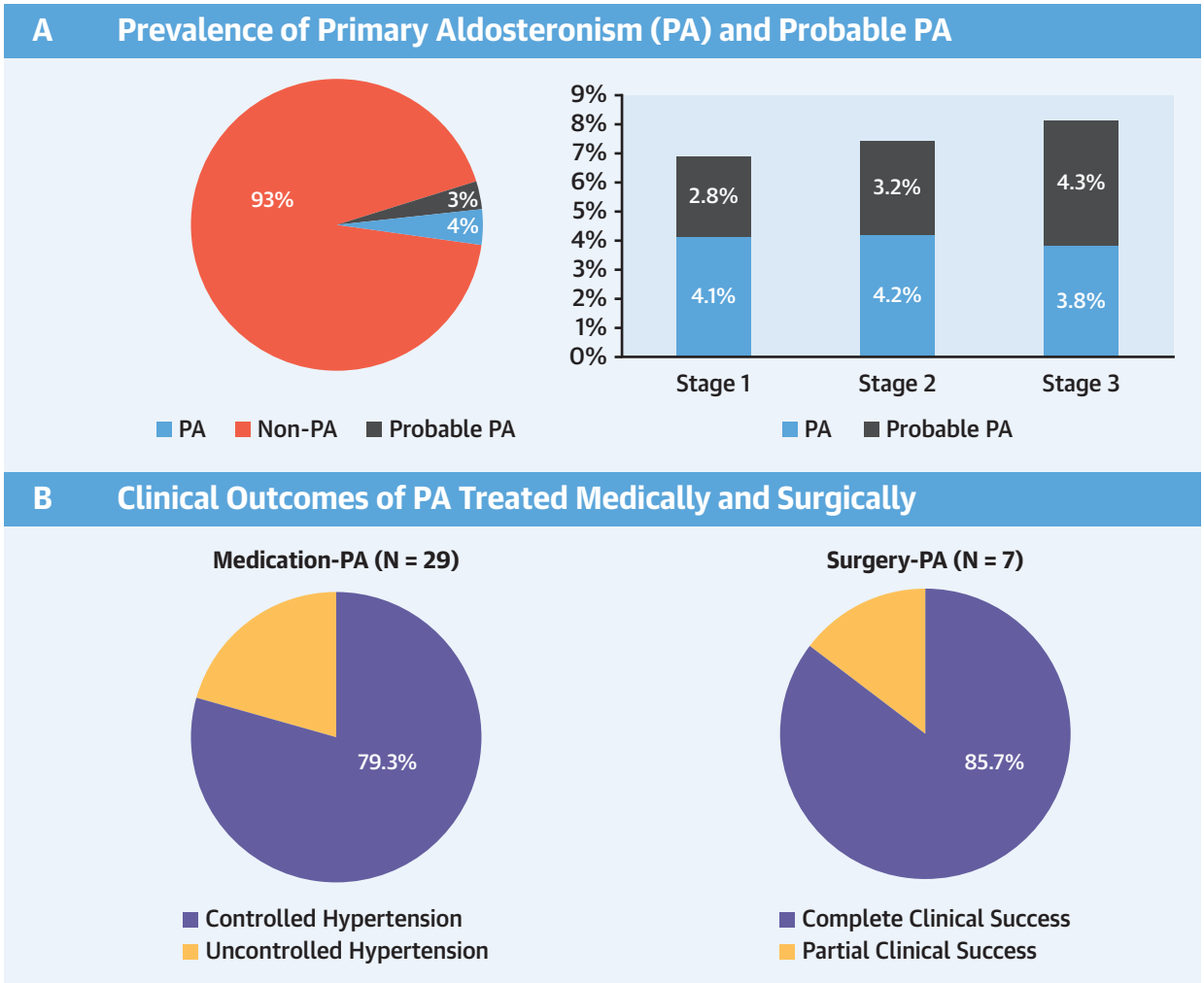
From the 1,020 patients with newly diagnosed hypertension for primary aldosteronism (PA), 40 patients were diagnosed as PA and 36 of them with targeted treatment were followed-up for 1 year. ARR = aldosterone-to-renin ratio; CCT = captopril challenge test; PAC = plasma aldosterone concentration; SIT = saline infusion test.

Statistical significance between groups was calculated in normally distributed data by 1-way analysis of variance with a post hoc Bonferroni analysis. Differences between groups were calculated in non-normally distributed data using Kruskal-Wallis or Mann-Whitney *U* tests. Covariate-adjusted UACR was derived from the univariate analysis using the general linear model (8). Categorical variables were analyzed by chi-square or Fisher exact test. SPSS Statistics version 22.0 (IBM, Armonk, New York) was used for statistical analysis.

RESULTS

From May 2017 to September 2018, 1,402 newly diagnosed hypertensive patients were invited to participate in the study, of whom 1,020 had the screening test, with an overall response rate of 73%. There were no significant differences in age, sex, and BP between the included patients and those who did not participate (n = 382) (Supplemental Figure 1). The average age of included patients was 51 years and 35% were women; included were 533 cases (52%) with

CENTRAL ILLUSTRATION **Prevalence and Clinical Outcomes of PA in Patients With Newly Diagnosed Hypertension**



Xu, Z. et al. J Am Coll Cardiol. 2020;75(16):1913–22.

(A) Overall, the prevalence of primary aldosteronism (PA) was 4%, with 4.1% in stage 1 hypertension, 4.2% in stage 2 hypertension, and 3.8% in stage 3 hypertension. The prevalence of probable PA was 3%, with 2.8% in stage 1 hypertension, 3.2% in stage 2 hypertension, and 4.3% in stage 3 hypertension. **(B)** At the end of 1-year follow-up, 85.7% of PA patients treated surgically achieved complete clinical success and 79.3% of PA patients treated medically had good blood pressure control. Controlled hypertension: when home-based monitoring revealed 3 consecutive readings of systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg, after the dose of antihypertensive drugs remained stable for more than 1 month. Complete clinical success: normal blood pressure without the aid of antihypertensive medication. Partial clinical success: the same blood pressure as before surgery with less antihypertensive medication or a reduction in blood pressure with either the same amount or less antihypertensive medication.

stage 1 hypertension, 348 cases (34%) with stage 2 hypertension, and 139 cases (14%) with stage 3 hypertension.

The flow of the study, including the diagnostic work-up for PA, is shown in Figure 1. A total of 93 patients (9%) screened positive by pre-specified criteria. These patients were then divided into 3 groups: "PA," "non-PA," and "probable PA." Of these 93 patients, 40 were found to have PA, including 29 with a post-CCT PAC >11 ng·dl^{-1} and 11 with a post-SIT PAC >6 ng·dl^{-1}; 21 were classified as non-PA, including 14 with post-CCT PAC <8 ng·dl^{-1} and 7 with post-SIT PAC <6 ng·dl^{-1}; and 32 were classified as "probable PA" including 20 who declined the CCT and 12 who declined the SIT following an indeterminate CCT. Overall, a conclusive diagnosis was

TABLE 1 Clinical and Biochemical Characteristics of the Subjects

	Non-PA (n = 948)	PA (n = 40)	Probable PA (n = 32)	p Value
Age, yrs	50 (43-60)	47 (35-55)	54 (49-66)	0.002
Male	636 (67.1)	19 (47.5)	9 (28.1)	<0.0001
BMI, kg/m^2	25.6 (23.2-27.7)	24.2 (22.6-26.1)	24.8 (22.7-27.4)	0.026
Waist circumference, cm	86 (81-93)	83 (76.0-89.5)	84 (77.0-87.8)	0.002
SBP, mm Hg	153 (145-164)	151 (144-162)	161 (144-174)	0.481
DBP, mm Hg	95 (89-102)	95 (91-102)	93 (86-97)	0.464
Stage of HT				0.931
1	497 (52.4)	21 (52.5)	15 (46.8)	
2	323 (34.1)	14 (35)	11 (34.4)	
3	128 (13.5)	5 (12.5)	6 (18.8)	
Family history				
Stroke	159 (16.8)	10 (25.0)	6 (18.8)	0.389
Hypertension	523 (55.2)	29 (72.5)	22 (68.8)	0.034
Diabetes at diagnosis	21 (2.2)	1 (2.5)	2 (6.3)	0.461
Serum potassium, mmol/l	4.0 (3.8-4.2)	3.9 (3.6-4.2)	4.0 (3.8-4.4)	0.062
PRC, mIU/l	14 (6.7-26.7)	3.6 (1.1-6.6)	2.7 (1.7-5.8)	<0.0001
PAC, ng/dl	8.2 (6.1-11.2)	16.5 (13.2-21.5)	13.2 (11.4-16.4)	<0.0001
ARR, ng/mIU	6.3 (3-12)	45 (27-138)	56 (27-93)	<0.0001
FPG, mmol/l	5.5 (5.1-6.1)	5.3 (5.1-5.7)	5.7 (5.2-6.0)	0.195
TC, mmol/l	5 (4.4-5.7)	4.7 (4.2-5.4)	5.4 (4.6-5.9)	0.08
TG, mmol/l	1.6 (1.1-2.4)	1.9 (1.1-3.0)	1.4 (1.1-1.9)	0.238
HDL, mmol/l	1.3 (1.1-1.5)	1.3 (1.0-1.6)	1.5 (1.2-1.7)	0.032
LDL, mmol/l	3.3 (2.8-3.8)	3 (2.6-3.7)	3.6 (2.8-4.0)	0.205
Cr, mg/dl	71 (60-82)	66 (48.5-89.0)	59 (50.5-69.8)	0.003
eGFR, ml/min/1.73 m^2	104.5 (94.7-113.1)	110.1 (95.8-121.2)	110.3 (98.1-115.1)	0.085
Uric acid, mg/dl	373 (307.0-445.8)	326 (281.0-415.5)	321.5 (270.5-361.0)	<0.0001
BUN, mmol/l	5.3 (4.5-6.3)	4.9 (4.2-6.2)	5.3 (4.8-6.6)	0.167
UACR, mg/g	15.6 (7.9-32)	19.2 (10.3-52.6)	24.3 (8.9-49.8)	0.121
Adjusted UACR, mg/g*	31.7 (29.3-34.4)	59 (55.7-62.7)	31.6 (30.0-33.1)	0.021
CV events	31 (3.3)	1 (2.5)	1 (3.1)	0.927
Stroke	20 (2.1)	1 (2.5)	1 (3.1)	
Coronary artery disease†	14 (1.5)	1 (2.5)	0 (0.0)	

Values are median (interquartile range) or n (%). *Adjusted UACR indicates UACR adjusted for eGFR. †Documented coronary artery disease included myocardial infarction and unstable angina pectoris requiring angioplasty.

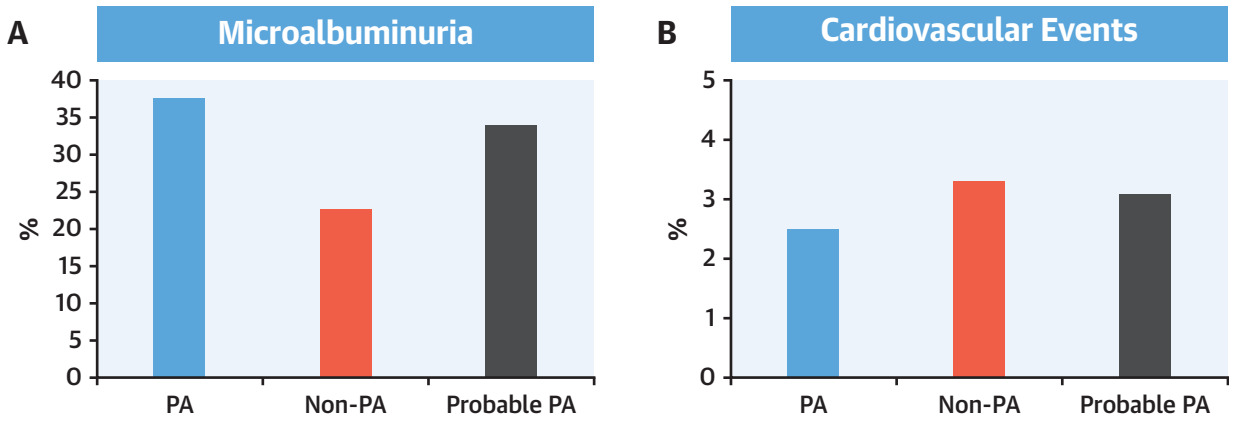
ARR = aldosterone-to-renin ratio; BMI = body mass index; BUN = blood urea nitrogen; Cr = creatinine; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; HDL = high-density lipoprotein; HT = hypertension; LDL = low-density lipoprotein; PA = primary aldosteronism; PAC = plasma aldosterone concentration; PRC = plasma renin concentration; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride; UACR = urinary albumin creatinine ratio.

attained in 96.9% (n = 988) of the 1,020 patients, including 40 cases diagnosed as PA and 948 cases as non-PA (including 927 who screened negative and 21 who failed the confirmatory test). The overall prevalence of PA in our primary care cohort was 4.0% (40 of 988). The prevalence was not different between the hypertension stages in PA patients, with 21 cases (4.1%) in stage 1, 14 cases (4.2%) in stage 2, and 5 cases (3.8%) in stage 3 (p = 0.981). The results were similar in patients with probable PA, with 2.8% in stage 1, 3.2% in stage 2, and 4.3% in stage 3 hypertension (p = 0.632) (**Central Illustration**).

The clinical and biochemical data of the included patients are shown in **Table 1**. There was no significant difference in the distribution of hypertension severity among the 3 groups. Patients with PA and patients with probable PA had higher plasma aldosterone and ARR, and lower renin levels than patients in the non-PA group. Patients with PA tended to have lower serum potassium (p = 0.062); however, the proportion of patients with hypokalemia was much higher in the PA and probable PA groups (at 17.5% and 12.0%, respectively) than the non-PA group (at 4.7%) (p < 0.001).

The incidence of microalbuminuria was significantly higher in PA than in non-PA patients (37.5% vs. 22.8%; p = 0.031), and similar to that in the probable PA patients (34.4%; p = 0.784) (**Figure 2A**). UACR was not significantly higher in PA patients; however, after adjustment for estimated glomerular filtration rate

FIGURE 2 Target Organ Damage and Cardiovascular Events in 3 Groups of Hypertensive Patients



(A) Incidence of microalbuminuria in PA patients (15 of 40) was similar to that in patients in probable PA (11 of 32) and higher than that in patients in non-PA (216 of 948). **(B)** Incidence of cardiovascular events were not significantly different for PA (1 of 40), non-PA (31 of 948), and probable PA (1 of 32). Cardiovascular events included myocardial infarction, unstable angina pectoris requiring angioplasty, stroke, or transient ischemic attack.

(considering that patients have hyperfiltration), the UACR was significantly higher in those with PA than non-PA (Table 1). However, there was no significant difference in the prevalence of diagnosed CV events between the 3 groups (2.5% vs. 3.3% vs. 3.1% for PA, non-PA, and probable PA, respectively; $p = 0.927$) (Figure 2B).

Of the 40 patients diagnosed with PA, 4 patients underwent AVS, of whom 3 were confirmed to have unilateral PA and 1 had bilateral PA. According to the guideline (1), 5 other patients with typical APA (younger than age 35 years and with spontaneous hypokalemia, marked aldosterone excess, and a cortical adenoma on adrenal CT scan) bypassed AVS and proceeded to surgery directly. Among the remaining 31 patients with PA, 6 patients refused any subtyping test, including adrenal CT scan. In total, 25 patients completed their adrenal CT, and the results did not show typical nodules in 23 patients, but revealed unilateral nodules in 2 patients. All of them were unwilling to have surgery; therefore, AVS was not recommended to them. According to pre-defined criteria, of the 40 patients with PA, there were 8 with APA, 21 with BAH, and 11 with indeterminate subtypes. Of 8 APAs, 7 were confirmed through PASO criteria after surgery and 1 was confirmed by AVS because the patient postponed surgery for personal reasons. This patient is being treated with spironolactone until she is ready for adrenal surgery. One BAH was confirmed through AVS, whereas the other 20 cases of BAH were diagnosed using the prediction score (15), which is based on sex, serum potassium, adrenal nodule on CT scan (yes or no), baseline PAC, and ARR; those who had more than 8 points were categorized as BAH. Clinical and biochemical data of PA subgroups showed that there were more women; higher ARR, baseline PAC, PAC post-CCT, and PAC post-SIT; and lower serum potassium, body mass index, and waist circumference in patients with unilateral hyperaldosteronism (Supplemental Table 3).

At 12 months after treatment, 4 PA patients were lost to follow-up, while clinical and biochemical data were collected from the remaining patients treated with surgery ($n = 7$) or medication ($n = 29$) (baseline and follow-up data in Table 2). All patients treated surgically achieved complete biochemical success (Supplemental Table 4). Complete clinical success was defined as normal BP without the aid of antihypertensive medication. In total, 6 of 7 patients treated surgically achieved complete clinical success after surgery, resulting in a high complete clinical success rate of 85.7%. For patients receiving medical treatment for PA, the proportion with optimal BP control was 79.3% and among them, 91.3% (21 of 23) only needed 1 antihypertensive drug: the mineralocorticoid receptor antagonist. The mean value of DDD for antihypertensive drugs was as low as 1.0.

DISCUSSION

Our study demonstrates, for the first time, that PA is not uncommon in patients with newly diagnosed hypertension in China, with a prevalence of at least 4.0%.

TABLE 2 Baseline and Follow-Up Clinical Features of PA Patients With Targeted Treatment

	Surgery PA (n = 7)	Medication PA (n = 29)
Baseline		
Age, yrs	36 ± 8	48 ± 11
Female	6 (85.7)	13 (40.6)
SBP, mm Hg	152 ± 15	156 ± 16
DBP, mm Hg	99 ± 7	97 ± 9
Serum potassium, mmol/l	3.2 (2.9–3.5)	4 (3.7–4.3)
PAC, ng/dl	20.7 (20.6–27.0)	15.4 (12.7–19.9)
PRC, mIU/l	0.5 (0.5–4.1)	4 (2.7–6.6)
Follow-up		
SBP, mm Hg	116 ± 15	131 ± 9
DBP, mm Hg	81 ± 11	84 ± 8
Serum potassium, mmol/l	4.1 (3.9–4.5)	4.1 (3.7–4.5)
PAC, ng/dl	8.7 (6–11.1)	21.3 (15.9–25.9)
PRC, mIU/l	11.3 (3.9–15.3)	6.8 (2.9–14.3)
ΔSBP, mm Hg	−36 ± 12	−26 ± 3
ΔDBP, mm Hg	−18 ± 7	−13 ± 2

Values are mean ± SD, n (%), or median (interquartile range).
ΔDBP = diastolic blood pressure drop after treatment; ΔSBP = systolic blood pressure drop after treatment; other abbreviations as in Table 1.

The result is consistent with a recent study from Italy, which reported a prevalence of 5.9% in primary care, although the patients were not all antihypertensive treatment-naïve (4). Notably, 3% of the patients with newly diagnosed hypertension were classified as "probable PA"; their clinical and biochemical characteristics were similar to those with confirmed PA. Considering that the patients with probable PA had higher SBP, lower PRC, and higher ARR than those with confirmed PA, some of them could even have unilateral PA. If these patients are taken into account, the prevalence of PA in the treatment-naïve population will increase to 7% (**Central Illustration**).

Newly diagnosed hypertensive patients represent a population with a relatively short duration of disease who may have a higher chance of surgical cure or complete clinical response to MR antagonist treatment. The current study showed that PA patients with newly diagnosed hypertension treated surgically could achieve a complete clinical success rate of up to 85.7%, whereas those treated medically achieved optimal BP control in 79.3% (**Central Illustration**). Furthermore, we observed no significant difference in the prevalence of CV events between PA and non-PA groups at baseline, suggesting that PA-mediated CV injury can be mitigated if targeted treatment is started early. These findings justify early screening and timely diagnosis as key factors to optimize the clinical prognosis of patients with PA.

Previous studies have suggested that the prevalence of PA in newly diagnosed hypertension ranges between 2.6% and 11.2% (18–21). Race, selection of population, and study design are all important factors contributing to the heterogeneity of prevalence estimates. The prevalence of PA was only 2.6% in a Dutch population, but the small sample size (n = 361) and low response rate (<10%) may have influenced the result (19). Two studies had similar results to ours with a similar ARR cut-off. In a study from Sweden by Westerdahl et al. (20), using an ARR cutoff of >24 (ng/mIU) as a positive screening test, the prevalence was 5.5%. In a Japanese study by Omura et al. (21), using an ARR cutoff of >15 ng/mIU, the prevalence was 5.9% (21). In a multicenter study in Italy that involved 1,125 newly diagnosed hypertensive patients referred to hypertension centers, the prevalence of PA was 11.2%, which is higher than the current study. The author found a heterogeneity of PA prevalence across centers, suggesting underlying referral bias with an impact on prevalence (18). In our study, the 4% prevalence is most likely an underestimate of the true prevalence. When we take into account the "probable PA" group (n = 32), who did not complete their diagnostic work-up, if the rate of positive confirmatory testing is the same as the other patients (66% tested positive on the CCT or SIT), then another 21 patients would have been diagnosed with PA, increasing the total number of PA cases to 61, which leads to a PA prevalence of 6%. Furthermore, our study specified a PAC threshold of 10 ng/dl (277 pmol/l) as a criterion for positive screening, which can increase the risk of missing PA (22). Of note, our patient cohort included those with isolated systolic (≥140 mm Hg, n = 244) or isolated diastolic hypertension (≥90 mm Hg, n = 75). The current Endocrine Society Guidelines (1) suggest screening in patients with systodiastolic hypertension (both SBP >150 mm Hg and DBP >100 mm Hg). However, the aim of this study was to evaluate all hypertensive patients rather than just the ones suggested by the current guidelines. Having either SBP ≥140 mm Hg or DBP ≥90 mm Hg is considered stage 2 hypertension by the 2017 ACC/AHA guidelines (23). We found that 6 of 244 (2.5%) patients with isolated systolic hypertension and 5 of 75 (6.7%) with isolated diastolic hypertension had PA. Two patients with isolated diastolic hypertension had APA, which was surgically cured. If patients with isolated systolic or diastolic hypertension were excluded from the analysis, then the prevalence becomes 29 of 701 (4.1%), which is actually the same as the prevalence in the overall cohort. The data suggest that PA screening in patients with isolated systolic or diastolic hypertension is warranted.

Previous studies have shown that patients with PA are more likely to display target organ damage and CV events compared with those with age and BP matched EH (24). Some studies reported a higher CV risk even when the hypertension duration (5 to 10 years) was matched (25,26). Interestingly, in our study, there was no significant difference in the rate of diagnosed CV events among patients with or without PA. It is probable that high circulating aldosterone has not yet caused clinically evident damage to the target organs in the early stage of disease. Of interest, patients with PA displayed a higher rate of microalbuminuria in our study, which is consistent with previous reports (4,8), suggesting that high aldosterone level induces water and sodium retention and blood volume expansion in the early stage of the disease and leads to glomerular hyperfiltration (27). However, this damage is functional and reversible. Clinical evidence has shown that renal dysfunction in PA patients is reversible after normalization of aldosterone excess through surgery (28,29).

A large-scale study on the prognosis of patients with unilateral hyperaldosteronism after adrenalectomy showed a complete clinical success of 37% (17% to 62%) and a complete biochemical success of 94% (83% to 100%) (17). In our study, 86% of APA patients with newly diagnosed hypertension achieved complete clinical success and 100% achieved complete biochemical success. There is evidence that the duration of hypertension is closely related to the post-operative clinical outcome of PA patients (12,17). The longer the duration of hypertension, the less likely it is for patients with a resectable APA to achieve complete clinical success after adrenalectomy. For PA patients receiving medical treatment, the earlier initiation of targeted therapy at an early stage of hypertension leads to good control of BP, as demonstrated in our study. These findings underscore the benefits of screening for PA at the early stage of hypertension.

The strength of this study lies in its relatively large sample size, prospective study design, and strict diagnostic protocol. It is the first to systematically evaluate unselected hypertensive patients in a primary health center in China, which minimizes selection bias. The patients are then formally evaluated in a tertiary hospital following international guidelines. This study is also the first to evaluate the clinical outcomes of PA patients with newly diagnosed hypertension in the Chinese population, providing evidence for the benefits of early screening for PA in patients with newly diagnosed hypertension.

STUDY LIMITATIONS. First, the screening threshold is stringent, and the formal diagnostic test for PA was not performed on all patients who screened positive. Second, due to the limitations of currently available confirmatory tests, some PA patients may be missed, such as those with Ang II-responsive PA (30). These limitations may underestimate the prevalence of PA in our cohort. Third, most cases of BAH were diagnosed with the BAH score rather than AVS due to patient preference. Some of these patients may have had resectable APA. Finally, the ability to assess CV and renal outcomes after targeted treatment, including left ventricular mass, cardiac rhythm, 24-h BP, and albuminuria, was limited by the cost of these tests and the lack of commitment from patients to pursue investigations following clinically successful treatment.

CONCLUSIONS

The prevalence of PA in patients with newly diagnosed hypertension in China is at least 4.0%, indicating that PA is not uncommon in the Chinese hypertensive population. In the early stage of the disease, the risk of CV events is relatively low; an early diagnosis leads to optimal clinical outcomes for both surgically and medically treated PA patients. Urgent action is needed to increase the awareness of PA as a highly treatable cause of hypertension and translate our findings into revised guidelines for the early detection of PA through screening in community health centers in China.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Primary aldosteronism is more common than generally appreciated among patients with newly diagnosed hypertension, and early diagnosis coupled with surgical or medical treatment can lead to favorable clinical outcomes.

TRANSLATIONAL OUTLOOK: Extended follow-up of larger cohorts of patients with primary aldosteronism identified early in the course of hypertension is necessary to compare the long-term benefit of various approaches to management.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.