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# Basal Plasma Aldosterone Concentration Predicts Therapeutic Outcomes in Primary Aldosteronism

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**Purpose:** Normal basal plasma aldosterone concentration (PAC) reflects mild aldosterone excess compared to high basal PAC. We previously reported lower risk for cardiovascular and cerebrovascular events in patients with primary aldosteronism (PA) and normal basal PAC (nPA) than in those with high basal PAC (hPA). However, the differences in therapeutic outcomes between nPA and hPA are unclear. The aim of this multi-institutional, retrospective cohort study was to determine the clinical significance of nPA to therapeutic outcomes, including adrenalectomy (ADX) and treatment with mineralocorticoid receptor antagonists (MRAs).

**Methods:** A total of 1146 patients with PA who were diagnosed and underwent adrenal venous sampling (AVS) between January 2006 and October 2016 were enrolled. The clinical parameters at baseline and after ADX or treatment with MRA were compared between the nPA and hPA groups.

**Results:** Significantly higher rates of absent clinical success (36.6 vs. 21.9%, $P = 0.01$) and absent biochemical success (26.4 vs. 5.2%, $P < 0.01$) were found for the nPA group than for the hPA group, respectively. Logistic regression analysis identified baseline PAC as a significant independent predictor of absent clinical success of ADX and MRAs.

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**Conclusions:** Plasma aldosterone concentration at baseline was a significant and independent predictor of absent clinical success of ADX and MRA. Mineralocorticoid receptor antagonist treatment appeared to be a better therapeutic choice than ADX in the nPA group.



**Freeform/Key Words:** primary aldosteronism (PA), plasma aldosterone concentration (PAC), adrenalectomy, mineralocorticoid receptor antagonist

Primary aldosteronism (PA) is major cause of secondary hypertension [1, 2]. Since autonomous aldosterone hypersecretion induces a rise in blood pressure and direct damage to the myocardium and arterial wall, PA patients are at higher risk of cardiovascular and cerebrovascular (CCV) events than those with essential hypertension [3–5]. This difference in the risk of cardiovascular events is reversed by the management of aldosterone excess by either adrenalectomy (ADX) or treatment with mineralocorticoid receptor antagonists (MRAs) [6]. The outcome of treatment suggests that aldosterone excess plays an important role in cardiovascular risk. Previous studies showed that higher plasma aldosterone concentration (PAC) [7, 8], hypokalemia [8, 9], unilateral subtype [8], positive results on the saline infusion test [10], and positive results on various other confirmatory tests [11] were associated with the risk of CCV events in PA patients. These findings suggest that the hormonal intensity of aldosterone reflects a CCV event risk. A previous study reported that basal PAC was less than 15 ng/dL in 36% of 74 PA patients [12]. We also reported previously that patients with PA and normal basal PAC (<16 ng/dL) (nPA) had clinical features of mild aldosterone excess, such as low incidence of hypokalemia and less use of antihypertensive medications than PA patients with high basal PAC (≥16 ng/dL) (hPA) [7]. In addition, nPA was associated with lower risk of CCV events than hPA [7]. However, there is no information on the differences in therapeutic outcomes between nPA and hPA.

The aim of this cross-sectional retrospective study was to determine the clinical significance of nPA in terms of therapeutic outcomes, such as ADX or treatment with MRA.

## 1. Materials and Methods

### *A. Subjects*

This study was conducted as part of the Japan Primary Aldosteronism Study (JPAS) with retrospective cross-sectional analysis. The nationwide PA registry in Japan was established at 28 centers. Patients with PA who were diagnosed and underwent adrenal venous sampling (AVS) between January 2006 and February 2018 were enrolled in this study. Patients eligible for JPAS were men and women aged 20 to 90 years. Patients whom the investigators judged unsuitable were excluded. The clinical characteristics, biochemical findings, results of confirmatory tests, imaging findings, results of AVS, treatment, surgical findings, and related follow-up data were collected electronically using the web-based registry system. System construction, data security, and maintenance of the registered data were outsourced to EPS Corporation (Tokyo, Japan).

The study was conducted using a valid data set of 2814 PA patients in February 2018. The PA patients with available data 1 year after ADX or treatment with MRA were selected. Of these, we excluded patients who had been treated with MRA at the time of diagnosis or after ADX and patients with suspected autonomous cortisol secretion defined by serum cortisol levels ≥ 3 μg/dL after 1 mg dexamethasone. Finally, 1146 patients in this study (nPA = 601, hPA = 545, Table 1) underwent ADX (n = 349) or were treated with MRA (n = 797) and included in this study (Fig. 1).

**Table 1. Baseline characteristics of the PA patients.**

| | Total (n = 1146) | nPA (n = 601) | hPA (n = 545) | *P* |
|---|---|---|---|---|
| Sex male/female (%, male) | 558/588 (48.7%) | 270/331 (44.9%) | 288/257 (52.8%) | <0.01 |
| Age (years) | 54 (45–62) | 56 (48–63) | 52 (43–61) | <0.01 |
| Duration of hypertension (years) | 6 (2–13) | 4 (1–11) | 8 (3–14) | <0.01 |
| Age of hypertension onset (years) | 45 (37–52) | 48 (40–55) | 41 (35–49) | <0.01 |
| Systolic blood pressure (mmHg) | 141 (129–152) | 141 (129–152) | 141 (130–152) | 0.77 |
| Diastolic blood pressure (mmHg) | 87 (78–96) | 87 (78–95) | 88 (79–96) | 0.39 |
| Defined daily dose of antihypertensive medications | 1.0 (0.7–2.0) | 1.0 (0.5–1.5) | 1.5 (1.0–2.2) | <0.01 |
| Body mass index (kg/m$^2$) | 24.4 (21.9–27.5) | 24.5 (21.8–27.3) | 24.2 (21.9–27.6) | 0.69 |
| Diabetes mellitus | 15.4% | 16.0% | 14.7% | 0.54 |
| Dyslipidemia | 29.4% | 31.0% | 27.7% | 0.23 |
| Ever smoker | 34.4% | 33.1% | 35.7% | 0.37 |
| Drinker | 53.1% | 50.1% | 56.3% | <0.05 |
| Serum potassium (mEq/L) | 3.8 (3.4–4.0) | 3.9 (3.7–4.1) | 3.5 (3.1–3.9) | <0.01 |
| Hypokalemia | 40.1% | 19.0% | 63.4% | <0.01 |
| eGFR (mL/min/1.73 m$^2$) | 77.8 (66.5–90.3) | 77.8 (67.7–90.2) | 77.7 (64.9–90.6) | 0.23 |
| Proteinuria | 12.2% | 6.9% | 18.0% | <0.01 |
| Cardiovascular and cerebrovascular events | 7.5% | 6.0% | 9.2% | <0.05 |
| Plasma aldosterone concentration (ng/dL) | 15.3 (10.9–23.5) | 11.1 (8.9–13.1) | 24.2 (19.1–35.9) | <0.01 |
| Plasma renin activity (ng/mL/hr) | 0.3 (0.2–0.5) | 0.3 (0.2–0.5) | 0.3 (0.2–0.5) | 0.63 |
| ARR (ng/dL)/(ng/mL/hr) | 49.6 (29.3–103.0) | 34.9 (22.8–60.0) | 84.0 (41.8–189.0) | <0.01 |
| Adrenal mass on CT | 45.4% | 33.0% | 59.1% | <0.01 |
| AVS LI ≤ 2/ 2 < LI ≤ 4/ 4 < LI | 52.5%/17.1%/30.4% | 69.9%/17.7%/12.5% | 33.6%/16.5%/49.9% | <0.01 |
| CLR < 1 | 35.5% | 15.2% | 57.6% | <0.01 |

Data are median (first and third quartile) values. Hypokalemia was considered present if serum potassium was < 3.5 mEq/L at the diagnosis of PA or a patient was taking a potassium supplement. Oral potassium was used in patients with hypokalemia. Estimated glomerular filtration rate was calculated using the following formula: estimated glomerular filtration rate (mL/min/1.73 m$^2$) = 194 × serum creatinine (-1.094) × age (-0.287) × 0.739 (if female). Proteinuria was defined as +, 2+, and 3 + protein in urinalyses. AVS was evaluated if cannulation was success (selectivity index > 5). The selectivity index was defined as cortisol concentration in the adrenal vein to that in the inferior vena cava. The LI was calculated by dividing the aldosterone to cortisol ratio on the dominant side by that on the nondominant side. The CLR was calculated by dividing the aldosterone to cortisol ratio on the nondominant side by that in the inferior vena cava. AVS data after ACTH stimulation were used for analysis in the present study. *P* value for differences between nPA vs. hPA.

Abbreviations: ARR, plasma aldosterone concentration/plasma renin activity ratio; AVS, adrenal venous sampling; CLR, contralateral ratio; CT, computed tomography; eGFR, estimate glomerular filtration rate; LI, lateralization index.

### *B. Diagnosis of PA*

Primary aldosteronism was diagnosed according to the guidelines of the Japan Endocrine Society [1] and Japan Society of Hypertension [13]. Primary aldosteronism was diagnosed by positive case detection with a ratio of PAC (measured in ng/dL) to plasma renin activity (PRA) (measured in ng/mL/h) aldosterone-to-renin ratio (ARR) of > 20 and at least 1 positive result on 4 confirmatory tests, including the captopril-challenge test, the saline-infusion test, the furosemide-upright test, and the oral salt-loading test. Antihypertensive medications were usually changed to calcium channel blockers and/or α-adrenergic blockers, as appropriate, until the final diagnosis was established. The PA patients were classified into the nPA group (normal PAC [<16 ng/dL]) or the hPA group (high PAC [≥16 ng/dL]) by using the PAC level measured before any confirmatory test and in a supine position for more than 30 minutes to avoid the effect of the sitting position and potential interference from antihypertensive drugs [7]. The PA subtype was diagnosed based on an AVS with adrenocorticotropic hormone (cosyntropin) stimulation, a procedure that was described in detail previously [14]. Adrenal vein cannulation was considered successful if the selectivity index was > 5 [15]. The selectivity index was defined as the ratio of cortisol concentration in

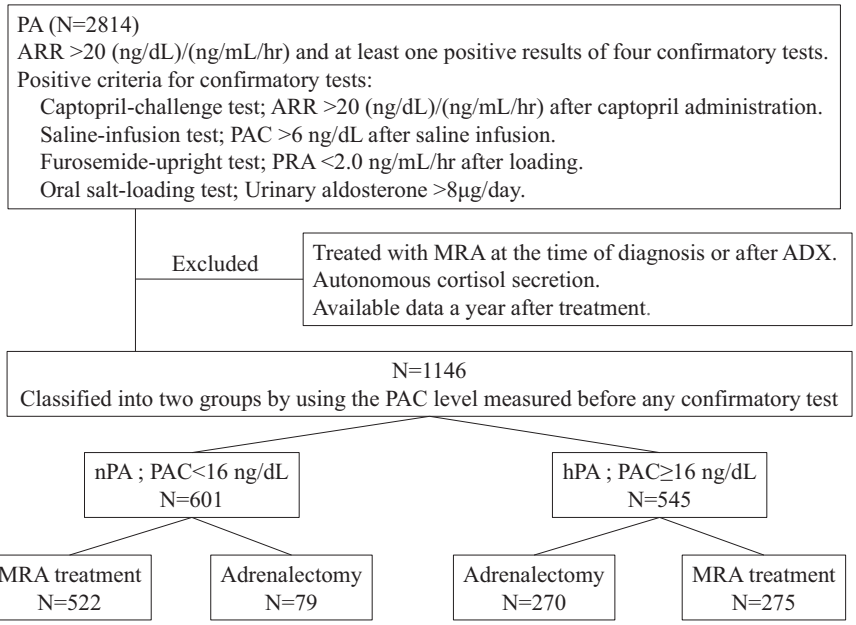


**Figure 1.** Classification strategy for primary aldosteronism with normal and high basal plasma aldosterone concentration.

the adrenal vein to that in the inferior vena cava. Unilateral subtype diagnosis of PA was defined as a lateralization index (LI) > 4. The LI was calculated by dividing the aldosterone-to-cortisol ratio on the dominant side by that on the nondominant side.

### *C. Assessment of Clinical and Biochemical Outcomes by International Consensus Criteria*

Various clinical parameters measured at baseline and 1 year after ADX were compared between the nPA and hPA groups. Individual surgical outcomes were evaluated using the international consensus criteria of the Primary Aldosteronism Surgical Outcome (PASO) study, which included 6 outcomes (complete, partial, and absent success of clinical and biochemical outcomes) based on blood pressure, defined daily dose (DDD) of antihypertensive medications, plasma potassium, PAC, and PRA [16]. In addition, individual clinical outcomes following MRA treatment were based on blood pressure and DDD excluding MRA.

### *D. Laboratory Tests*

Plasma aldosterone concentration and PRA were measured by commercially available kits. Plasma aldosterone concentration was determined by radioimmunoassay (SPAC-S Aldosterone Kit [17]; Fuji Rebio, Co., Tokyo, Japan) in 25 centers and chemiluminescent enzyme immunoassay (Accuraseed Aldosterone [18]; FUJIFILM Wako Pure Chemical, Co., Tokyo, Japan) in 3 centers. The reference ranges of PAC measured in the supine position were 3.0 to 15.9 ng/dL and 2.99 to 15.9 ng/dL, respectively. Plasma renin activity was measured by radioimmunoassay or enzyme immunoassay. The reference range of PRA in the supine position was 0.3 to 2.9 ng/mL/h (PRA radioimmunoassay kits [19]; Fuji Rebio, Co., Tokyo, Japan) in 15 centers, 0.2 to 2.3 ng/mL/h (PRA enzyme immunoassay kits [20]; Yamasa, Co., Choshi, Japan) in 9 centers, and 0.2 to 2.7 ng/mL/h (PRA radioimmunoassay kits [21]; Yamasa, Co., Choshi, Japan) in 3 centers. Plasma active renin concentration (ARC) was measured by chemiluminescent enzyme immunoassay in 1 center and the ARC value was used for analysis by converting to PRA. The reference range of ARC in the supine position was 2.5 to 21.0 pg/mL (Accuraseed Renin [Japanese patent number 2877222, monoclonal antibody 12-12 and 11–6]; Wako Pure Chemical, Co., Tokyo, Japan].

### *E. Statistical Analysis*

Data were expressed as median values (interquartile rage [IQR]). Differences between 2 groups were analyzed by the Wilcoxon test for continuous variables and by the chi-square test for categorical variables. For paired data comparing baseline and post-treatment, paired t-tests for variables and a McNemar's test for categorical data were used. Logistic regression analysis was performed to identify independent predictors of absent success of ADX and MRA treatment. The variables of PAC at baseline, sex, age, duration of hypertension, DDD before treatment, BMI, smoking and eGFR were selected for analysis based on the results of previous studies [7, 22–25]. Statistical significance was defined at the $P < 0.05$ significance level. All statistical analyses were performed using JMP Pro software for Windows (ver0.14, SAS Institute, Cary, NC).

## 2. Results

### *A. Clinical Characteristics of nPA and hPA Patients at Baseline*

The baseline clinical characteristics of nPA (n = 601) and hPA (n = 545) patients are shown in Table 1. Compared with the hPA group, the nPA group included older (56 vs. 52 years, $P < 0.01$) patients with a lower proportion of males (44.9% vs. 52.8%, $P < 0.01$) that had a shorter duration of hypertension (4 vs. 8 years, $P < 0.01$) and older age at onset of hypertension (48 vs. 41 years, $P < 0.01$). The DDD was smaller in the nPA group than in the hPA group (1.0 vs. 1.5, $P < 0.01$), but there was no significant difference in blood pressure between the 2 groups. Serum potassium level was higher (3.9 vs. 3.5, $P < 0.01$) and the prevalence of hypokalemia was lower (19.0 vs. 63.4%, $P < 0.01$) in the nPA group than in the hPA group. Adrenal masses were found on the CT in fewer patients (33.0 vs. 59.1%, $P < 0.01$), and the proportions of patients with high LI and contralateral ratio (CLR) were significantly lower in the nPA group than in the hPA group.

### *B. Comparison of Clinical Features at Baseline and 1-year Follow-up after ADX and MRA*

Table 2 lists differences in the clinical features of patients in the nPA and hPA groups recorded at baseline and 1 year after ADX. Compared with the baseline, ADX significantly improved blood pressure, DDD, and hypokalemia in both groups at 1-year follow-up. Although the estimated glomerular filtration rate (eGFR) decreased significantly in both groups, the prevalence of proteinuria was significantly lower only in the hPA group ($P < 0.01$) but not the nPA group ($P = 0.06$). While PAC at 1 year after ADX did not change in the nPA group ($P = 0.70$), it decreased significantly in the hPA group ($P < 0.01$). Furthermore, ARR decreased significantly in both groups due to significant increases in PRA.

Table 3 shows the changes in several clinical parameters associated with MRA treatment. Compared with the baseline, blood pressure, DDD excluding MRA, serum potassium level and the prevalence of hypokalemia improved in both the nPA and hPA groups after MRA treatment. In contrast to ADX, MRA treatment was associated with significant decreases in eGFR and improvement in the prevalence of proteinuria in both groups. Furthermore, ARR decreased significantly in both the nPA and hPA groups due to increases in both PAC and PRA.

### *C. Comparison of ADX Therapeutic Outcomes Between nPA and hPA Groups Using International Consensus Criteria*

The clinical success of surgical outcomes was evaluated based on the international consensus criteria [16] (Fig. 2A). The rate of absent clinical success was significantly higher in the nPA group (36.6%) than in the hPA group (21.9%, $P = 0.01$). Twenty-six nPA patients were classified as absent clinical success (age 54 [45–60] years; duration of hypertension,

**Table 2. Clinical characteristics of the 349 PA patients with adrenalectomy.**

| | nPA (n = 79) | | | | hPA (n = 270) | | | |
|---|---|---|---|---|---|---|---|---|
| | **n** | **Baseline** | **After ADX** | ***P*** | **n** | **Baseline** | **After ADX** | ***P*** |
| Systolic blood pressure (mmHg) | 79 | 141 (130–153) | 130 (120–140) | <0.01 | 270 | 141 (130–153) | 126 (118–136) | <0.01 |
| Diastolic blood pressure (mmHg) | 79 | 87 (78–91) | 82 (73–90) | <0.01 | 270 | 87 (80–96) | 80 (74–87) | <0.01 |
| Defined daily dose of antihypertensive medications | 71 | 1.0 (0.5–2.0) | 0.5 (0–1.3) | <0.01 | 251 | 1.8 (1.0–2.3) | 0.5 (0–1.3) | <0.01 |
| Serum potassium (mEq/L) | 75 | 3.8 (3.4–4.0) | 4.3 (4.1–4.6) | <0.01 | 244 | 3.3 (2.9–3.6) | 4.4 (4.1–4.7) | <0.01 |
| Hypokalemia | 72 | 36.1% | 0% | <0.01 | 233 | 84.6% | 0.4% | <0.01 |
| eGFR (mL/min/1.73 $m^2$) | 75 | 78.7 (65.4–92.9) | 67.1 (55.5–78.7) | <0.01 | 246 | 78.3 (64.6–91.6) | 62.1 (47.4–74.5) * | <0.01 |
| Proteinuria | 36 | 19.4% | 5.6% | 0.06 | 143 | 23.1% | 7.7% | <0.01 |
| Plasma aldosterone concentration (ng/dL) | 57 | 10.7 (8.9–13.1) | 10.8 (7.6–13.5) | 0.70 | 171 | 30.0 (21.5–44.9) | 10.5 (7.8–13.7) | <0.01 |
| Plasma renin activity (ng/mL/hr) | 57 | 0.2 (0.1–0.4) | 0.8 (0.4–1.5) | <0.01 | 162 | 0.3 (0.1–0.4) | 1.5 (0.6–2.7) ** | <0.01 |
| ARR (ng/dL)/(ng/mL/hr) | 57 | 44.0 (29.5–80.0) | 12.3 (6.4–22.1) | <0.01 | 161 | 123.5 (64.0–226.5) | 7.4 (4.3–14.9) ** | <0.01 |

Data are median (first and third quartile) values. See Table 1 for abbreviations.
*nPA After ADX vs. hPA after ADX, $P < 0.05$. ** nPA After ADX vs. hPA after ADX, $P < 0.01$.

**Table 3. Clinical characteristics of the 797 PA patients with MRA treatment.**

| | nPA (n = 522) | | | | hPA (n = 275) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Baseline | After MRA | *P* | n | Baseline | After MRA | *P* |
| MRA equivalent potency total daily dose (mg) | | - | 50 (50–100) | | | - | 100 (50–100) †† | |
| Spironolactone total daily dose (mg) | | - | 25 (25–50) | | | - | 50 (25–75) †† | |
| Eplerenone total daily dose (mg) | | - | 50 (50–100) | | | - | 100 (50–100) †† | |
| Systolic blood pressure (mmHg) | 522 | 141 (129–152) | 130 (120–138) | <0.01 | 275 | 141 (130–152) | 130 (123–140) | <0.01 |
| Diastolic blood pressure (mmHg) | 522 | 87 (78–96) | 80 (74–87) | <0.01 | 275 | 88 (79–96) | 82 (76–89) † | <0.01 |
| Defined daily dose of antihypertensive medications excluding MRA | 471 | 1.0 (0.5–1.5) | 0.5 (0–1.0) | <0.01 | 250 | 1.3 (1.0–2.0) | 1.0 (0.5–1.8) †† | <0.01 |
| Serum potassium (mEq/L) | 487 | 4.0 (3.7–4.2) | 4.2 (4.0–4.5) | <0.01 | 257 | 3.7 (3.4–4.0) | 4.2 (4.0–4.5) | <0.01 |
| Hypokalemia | 472 | 16.5% | 2.8% | <0.01 | 249 | 45.4% | 8.4%†† | <0.01 |
| eGFR (ml/min/1.73 $m^2$) | 488 | 77.2 (67.6–90.1) | 70.8 (60.4–81.7) | <0.01 | 257 | 76.4 (65.2–87.9) | 66.8 (56.8–78.8) †† | <0.01 |
| Proteinuria | 329 | 6.7% | 3.7% | 0.01 | 165 | 16.4% | 8.5% | 0.02 |
| Plasma aldosterone concentration (ng/dL) | 330 | 11.0 (8.8–13.0) | 20.2 (14.4–28.3) | <0.01 | 175 | 21.0 (17.6–25.7) | 30.9 (21.8–43.0) †† | <0.01 |
| Plasma renin activity (ng/mL/hr) | 324 | 0.3 (0.2–0.5) | 1.0 (0.5–1.8) | <0.01 | 172 | 0.4 (0.2–0.6) | 1.0 (0.4–2.1) | <0.01 |
| ARR (ng/dL)/(ng/mL/hr) | 324 | 31.8 (21.7–53.5) | 20.8 (12.4–40.0) | <0.01 | 172 | 55.5 (34.4–104.4) | 32.1 (16.6–71.3) †† | <0.01 |

Data are median (first and third quartile) values. The MRA equivalent potency dose is a metric to allow consolidation of spironolactone and eplerenone doses into a single MRA potency. Spironolactone is considered twice as potent as eplerenone for this calculation; therefore, the dosing was calculated by multiplying spironolactone total daily dose by two and eplerenone total daily dose by one.

†nPA After MRA treatment vs. hPA after MRA treatment, $P < 0.05$. ††nPA After MRA treatment vs. hPA after MRA treatment, $P < 0.01$.

Abbreviation: MRA, mineralocorticoid receptor antagonist. See Table 1 for additional abbreviations.

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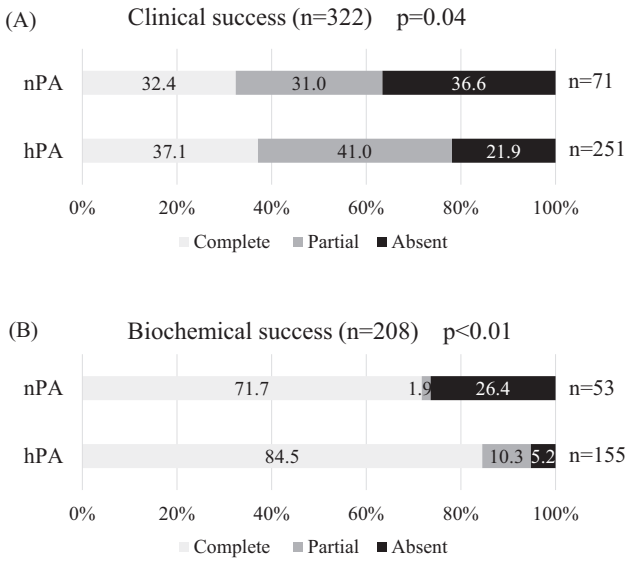


**Figure 2.** Clinical and biochemical outcomes after adrenalectomy in patients with primary aldosteronism. Clinical (n = 322) (**A**) and biochemical (n = 208) (**B**) outcomes were assessed by the international consensus criteria. *P* values for comparisons of the proportions of the 3 groups (complete, partial, and absent).

10 years[3–17]; BMI 25.8 (22.5–28.3) kg/m$^2$; diabetes mellitus, 19.2%, dyslipidemia, 46.2%; ever a smoker, 40.0%). Although serum potassium (baseline 3.8 [3.0–4.0], post-ADX 4.3 [4.0–4.5], $P < 0.01$) and ARR (baseline 50.0 [33.8–81.5], post-ADX 16.6 [9.1–30.5], $P < 0.01$) significantly improved after ADX in this absent clinical success group, DDD was significantly higher after ADX (baseline 1.0 [0.6–1.9], post-ADX 1.3 [0.8–2.2], $P = 0.02$), and blood pressure showed no improvement (systolic blood pressure, baseline 142 [126–146] mmHg, post-ADX 139 [129–148] mmHg, $P = 0.68$), (diastolic blood pressure, baseline 86 [77–90] mmHg, post-ADX 89 [80–90] mmHg, $P = 0.84$). Next, we evaluated the independent predictors of absent clinical success after ADX (Table 4). Univariate analysis showed that PAC at baseline, sex, duration of hypertension, BMI, smoking, and eGFR at baseline were significantly associated with absent clinical success after ADX. The above factors were entered into logistic regression analysis, and the results identified PAC at baseline, male sex, long duration of hypertension, and DDD as significant and independent predictors of absent clinical success after ADX.

With regards to the biochemical success of surgical outcomes, a significantly lower rate of complete biochemical success (71.7 vs. 84.5%, $P = 0.04$) and higher absent biochemical success (26.4 vs. 5.2%, $P < 0.01$) were noted in the nPA group than in the hPA group based on the international consensus criteria [16] (Fig. 2B).

### *D. Comparison of MRA Outcomes Between nPA and hPA Groups*

The clinical parameters at baseline and after MRA treatment for PA patients are shown in Table 3. The MRA equivalent potency total daily dose and DDD excluding MRA was significantly smaller in the nPA group than in the hPA group (50 [50–100] vs. 100 [50–100] mg/day; $P < 0.01$, 0.5 [0–1.0] vs. 1.0 [0.5–1.8], $P < 0.01$, respectively). However, the post-MRA diastolic blood pressure and the prevalence of post-MRA hypokalemia were significantly lower in the nPA group (80 [74–87] vs. 82 [76–89] mmHg; $P < 0.01$, 2.8% vs. 8.4%, $P < 0.01$, respectively) than in the hPA group. Although eGFR was higher in the nPA group (70.8 [60.4–81.7] vs. 66.8 [56.8–78.8], $P < 0.01$) than in the hPA group, there was no difference in eGFR (baseline, post-MRA) between the 2 groups (nPA 7.1 vs. hPA 8.2 mL/min/1.73 m$^2$, $P = 0.17$).

**Table 4. Results of logistic regression analysis of the 8 factors associated with absent clinical success after adrenalectomy.**

| | Unadjusted Analysis | | Adjusted Analysis | |
|---|---|---|---|---|
| **Variable** | **Odds ratio (95% CI)** | ***P*** | **Odds ratio (95% CI)** | ***P*** |
| Plasma aldosterone concentration at baseline (ng/dL) | 0.98 (0.97–0.99) | <0.01 | 0.97 (0.96–0.99) | <0.01 |
| Plasma aldosterone concentration at baseline (ng/dL) IQR | 0.77 (0.65–0.93) | <0.01 | 0.71 (0.57–0.89) | <0.01 |
| Sex, male | 2.99 (1.72–5.18) | <0.01 | 3.22 (1.55–6.69) | <0.01 |
| Age (years) IQR | 1.29 (0.89–1.87) | 0.18 | 0.92 (0.53–1.58) | 0.76 |
| Duration of hypertension (years) IQR | 1.49 (1.07–2.06) | 0.02 | 1.77 (1.11–2.81) | 0.02 |
| Defined daily dose of antihypertensive medications before adrenalectomy IQR | 0.93 (0.70–1.25) | 0.65 | 0.62 (0.42–0.92) | 0.02 |
| Body mass index (kg/m$^2$) IQR | 1.83 (1.30–2.58) | <0.01 | 1.30 (0.84–2.00) | 0.24 |
| Ever smoker | 2.11 (1.24–3.61) | <0.01 | 1.79 (0.96–3.36) | 0.07 |
| eGFR before adrenalectomy (ml/min/1.73 m$^2$) IQR | 0.67 (0.50–0.90) | <0.01 | 0.81 (0.55–1.18) | 0.27 |

See Table 1 for abbreviations.

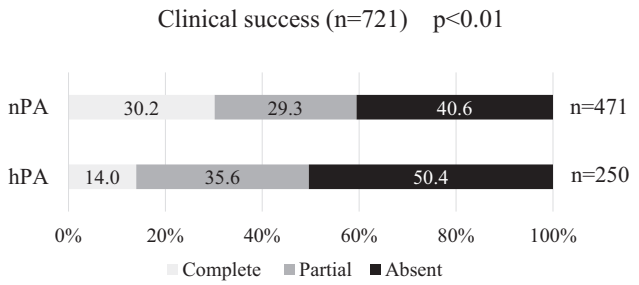


**Figure 3.** Clinical outcomes after treatment with mineralocorticoid receptor antagonists in patients with primary aldosteronism. Clinical outcomes (n = 721) were assessed by the international consensus criteria. *P* values for comparisons of the proportions of the 3 groups (complete, partial, and absent).

Although the original international consensus criteria [16] were designed to assess surgical outcomes in unilateral PA, we adopted clinical success defined by these criteria based on blood pressure plus the use of antihypertensive drugs, excluding MRA for evaluation of the MRA therapeutic outcomes. The rate of complete success was higher and the rate of absent success was lower in the nPA group than in the hPA group (30.2% vs. 14.0%, $P < 0.01$ and 40.6% vs. 50.4%, $P = 0.01$, respectively, Fig. 3). As mentioned above, the MRA equivalent potency total daily dose and DDD excluding MRA was significantly smaller in the nPA group than in the hPA group (Table 3). We also evaluated the independent predictors of absent clinical success after MRA treatment (Table 5). Univariate analysis showed that PAC at baseline, male sex, duration of hypertension, and BMI were significantly associated with absent clinical success after MRA treatment. Logistic regression analysis of the above parameters identified PAC at baseline, male sex, long duration of hypertension, DDD, and BMI as significant independent predictors of absent clinical success after MRA treatment.

We also investigated clinical outcomes in 58 unilateral PA patients treated with MRA who did not undergo ADX. Even in these PA patients, the MRA equivalent potency total daily dose was lower in the nPA group than in the hPA group (50 [50–100] vs. 100 [50–100] mg/day, $P < 0.01$), and the clinical outcome tended to be better with nPA than with hPA (complete + partial 60.9, absent 39.1 vs. complete + partial 40.0%, absent 60.0%, $P = 0.12$).

**Table 5. Results of logistic regression analysis for the factors associated with absent clinical success after treatment with mineralocorticoid receptor antagonists.**

| | Unadjusted Analysis | | Adjusted Analysis | |
|---|---|---|---|---|
| **Variable** | **Odds ratio (95% CI)** | ***P*** | **Odds ratio (95% CI)** | ***P*** |
| Plasma aldosterone concentration at baseline (ng/dL) | 1.02 (1.00–1.04) | <0.01 | 1.03 (1.00–1.05) | 0.02 |
| Plasma aldosterone concentration at baseline (ng/dL) IQR | 1.31 (1.05–1.63) | <0.01 | 1.37 (1.04–1.79) | 0.02 |
| Sex, male | 1.83 (1.36–2.46) | <0.01 | 1.66 (1.16–2.38) | <0.01 |
| Age (years) IQR | 0.89 (0.71–1.13) | 0.35 | 0.93 (0.67–1.28) | 0.66 |
| Duration of hypertension (years) IQR | 1.36 (1.13–1.65) | <0.01 | 1.48 (1.17–1.86) | <0.01 |
| Defined daily dose of antihypertensive medications before MRA IQR | 0.90 (0.74–1.09) | 0.28 | 0.62 (0.48–0.80) | <0.01 |
| Body mass index (kg/m$^2$) IQR | 1.31 (1.07–1.61) | <0.01 | 1.39 (1.09–1.76) | <0.01 |
| Ever smoker | 1.27 (0.91–1.76) | 0.15 | 1.06 (0.73–1.54) | 0.76 |
| eGFR before MRA (ml/min/1.73 m$^2$) IQR | 1.11 (0.92–1.35) | 0.28 | 1.14 (0.89–1.45) | 0.30 |

See Table 1 for abbreviations.

## 3. Discussion

The main findings of the present study suggested that MRA treatment was a better therapeutic choice than ADX in nPA patients. Our study also showed that PAC at baseline was a significant and independent predictor of absent clinical success after both ADX and MRA treatment.

Previous studies reported that the cure rate of hypertension (blood pressure < 140/90 mmHg without medication) in PA after ADX ranged from 37% to 42% [16, 25]. In our study, the cure rate of hypertension in 349 PA patients (including 79 nPA and 270 hPA patients) by ADX was 36.0%. Interestingly, the rate of absent clinical success was significantly higher in nPA patients than in those with hPA. The results demonstrated that it might be difficult for nPA patients to achieve normotension after ADX without medication. Other investigators identified several predictors of the resolution of hypertension in PA patients after ADX. These include shorter duration of hypertension [22, 23, 26], fewer drug classes [22, 23, 26, 27], younger age [24, 26], female sex [22, 26, 27], lower BMI [26, 27], larger tumor size [24], lower eGFR [23], and a negative medical history of diabetes [26]. In the present study, we found that lower PAC was a significant predictor of absent clinical success with the lack of blood pressure normalization after ADX. On the other hand, Zhang et al [28] reported that higher PAC (≥35 ng/dL) was associated with a lower hypertension cure rate after surgery, probably because high PAC may induce irreversible cardiovascular remodeling.

Treatment with MRA (spironolactone and eplerenone) is recommended for PA patients with the bilateral subtype or who are unwilling to undergo surgery [29–31]. Our results suggest that nPA was a mild type of PA because the nPA group included a larger proportion of patients who showed complete clinical success than that of the hPA group, and the MRA equivalent potency total daily dose and DDD excluding MRA was significantly lower in the nPA group than in the hPA group after MRA treatment.

Absent biochemical success after ADX reflects a failure in PA treatment. One of the causes of such a failure is misdiagnosis of the PA subtype by AVS [32]. However, there were no significant differences in AVS results (rate of LR > 4 and CLR < 1) between absent biochemical success and complete + partial biochemical success groups (56.3 vs. 72.6%, $P = 0.17$).

The PA patients with absent biochemical success had higher serum potassium (3.8 [3.5–4.3] vs. 3.4 [3.0–3.7] mEq/L, $P < 0.01$) and smaller DDD (1.0 [0–1.8] vs. 1.3 [1.0–2.3], $P < 0.01$] at baseline than those in the complete + partial biochemical success group. Although the PRA levels at baseline were similar in the nPA and hPA groups, the level was significantly

lower in the nPA group than in the hPA group after ADX. These results suggest that nPA might involve other factors that can suppress PRA rather than PAC excess. For example, a high salt diet, aging [33], drugs known to interfere with the renin-angiotensin-aldosterone system, and a reduction in the nephron population are known factors involved in low-renin essential hypertension [34, 35]. Another reason for this result could be due to asymmetrical bilateral PA that was detected at AVS as unilateral.

The interpretation of the results of this study might be limited by its retrospective design. Adrenal venous sampling with adrenocorticotropic hormone (cosyntropin) stimulation improves AVS, but it hides the lateralization of aldosterone excess in some cases. Further prospective studies are needed to confirm the clinical significance of nPA on therapeutic outcomes, including ADX and MRA treatment.

In conclusion, we have demonstrated in the present study the importance of PAC at baseline as a predictor of clinical and biochemical success as assessed by the international consensus criteria of ADX and MRA treatment. The results also showed that MRA treatment may be a better therapeutic strategy with regards to clinical outcomes than ADX in patients with normal basal PAC.

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## Additional Information

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***Data Availability:*** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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