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Prediction of long-term biochemical cure in patients with unilateral primary hyperaldosteronism treated surgically based on the early post-operative plasma aldosterone value

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Abstract. In 2017, the Primary Aldosteronism Surgical Outcome (PASO) investigators proposed consensus criteria for clinical and biochemical outcomes. However, 6 to 12 months need to pass in order to assess for the outcome in patients who have undergone surgery for the management of primary hyperaldosteronism. This study aims to evaluate the post-operative biochemical and clinical outcomes of primary aldosteronism (PA) on the basis of the laboratory findings obtained within 10 days after surgery. We retrospectively studied 59 consecutive patients with unilateral PA who underwent adrenalectomy and were assessed for plasma aldosterone concentration (PAC) and plasma renin activity both at the initial assessment (1–10 days after surgery) and the final assessment (6–12 months after surgery). When comparing the complete biochemical success group ($n = 51$) and the partial or absent biochemical success group ($n = 8$), the median post-operative PAC at the initial assessment was significantly greater in the partial or absent biochemical success group (12.7 ng/dL; interquartile range [IQR], 10.6–14.5) than that in the complete biochemical success group (6.3 ng/dL; IQR, 5.0–7.9) ($p < 0.001$), while no significant differences were observed in other factors. The receiver operating characteristic curves of post-operative PAC at the initial assessment, which was used to predict biochemical outcomes, indicated that 8.1 ng/dL is the optimal PAC cut-off for biochemical success (sensitivity, 76.5%; specificity, 100%). Low post-operative PAC at the initial assessment may predict the biochemical cure of PA.

Key words: Primary aldosteronism, Aldosterone, Biochemical outcome, Surgical outcome

PRIMARY ALDOSTERONISM (PA) is the most common form of secondary hypertension, accounting for 5% to 10% of all patients with hypertension [1, 2] and 15% to 20% of patients with hypertension who are resistant to treatment [3]. As patients with PA have a higher risk of cardiovascular complications [4, 5] and stroke [5, 6] than patients with essential hypertension, appropriate diagnosis and treatment of PA are important. PA consists of two subgroups: unilateral PA (*e.g.*, aldosterone-producing adenoma) and bilateral PA (*e.g.*, idiopathic hyperaldosteronism). Unilateral PA can be treated with unilateral adrenalectomy, whereas bilateral PA requires lifelong medical treatment [7, 8].

In 2017, the Primary Aldosteronism Surgical Outcome (PASO) investigators proposed criteria for the post-surgical clinical and biochemical outcomes of PA [9]. The PASO study recommends that the final evaluation of clinical and biochemical outcomes should be performed 6 to 12 months after surgery. Therefore, in patients who have undergone surgery for the management of primary hyperaldosteronism, 6 to 12 months need to have passed to assess for outcome according to the PASO evaluation method. Although some studies reported prediction scores for post-operative clinical outcomes using pre-operative clinical data, such as the aldosteronoma resolution score (ARS) [10-12], the utility of clinical data immediately after surgery for the prediction of long-term

clinical and biochemical outcomes is unclear. The preoperative prediction scores for clinical outcomes will help both the physician and patient understand what to expect from surgery, but is not suitable for predicting the post-operative outcomes immediately after surgery. Early intervention with additional treatment based on the evaluation of post-operative outcomes may prevent the development of complications associated with residual PA, while early post-operative prediction may assist the clinician with deciding which patients are unlikely to need follow-up. Therefore, the prediction of long-term outcomes based on immediate post-operative data is worthwhile. We aimed to evaluate biochemical and clinical outcomes on the basis of the clinical data obtained during hospitalization within 10 days of surgery.

Materials and Methods

Study design and subject

We retrospectively studied consecutive patients with PA who underwent adrenalectomy at Kyoto Medical Center between January 2007 and March 2019. We followed up on various inspections on post-operative days 1 to 10 (median = 4.0 days; interquartile range [IQR], 4.0–5.0, initial assessment) during hospitalization and during post-operative months 6 to 12 (median = 9.0 months; IQR, 7.0–11.0, final assessment) to evaluate the post-operative clinical outcomes. This retrospective study was conducted according to the guidelines for clinical studies published by the Ministry of Health and Labor of Japan. Furthermore, this retrospective study was approved by the Institutional Ethics Committee of the National Hospital Organization Kyoto Medical Center.

Diagnosis of PA

All patients with PA were diagnosed according to the guidelines of the Japanese Endocrine Society [8] and the Japanese Society of Hypertension [13]. Screening for PA was performed on the basis of a plasma aldosterone concentration (PAC; ng/dL) to plasma renin activity (PRA; ng/mL/h) ratio of >20, known as the aldosterone to renin ratio (ARR). A diagnosis of PA was established by at least one positive result of confirmatory testing, including the captopril challenge ($n = 58$), saline infusion test ($n = 43$), and furosemide upright test ($n = 15$). In all cases, anti-hypertensive medications were switched to calcium channel blockers and/or α-blockers as appropriate before making a diagnosis. An adrenal nodule was defined as a nodule >6 mm in diameter on abdominal computed tomography. Hypokalemia was considered when serum potassium was <3.5 mEq/L the day before surgery or when an oral potassium supplement was prescribed.

Adrenal venous sampling (AVS) was performed by experienced radiologists. Adrenocorticotropic hormone (cosyntropin) was administered by bolus injection, followed by continuous infusion during AVS, as previously described [14]. Adrenal vein cannulation was considered successful when the ratio of the cortisol concentration in the adrenal vein to the cortisol concentration in the inferior vena cava (selective index) was >5 [15]. We considered unilateral lateralization when the aldosterone to cortisol ratio on the dominant adrenal side was 4-fold higher than that on the non-dominant adrenal side (lateralization index) [15].

Assay methods

The PAC of 53 patients were measured using a radioimmunoassay (SPAC-S Aldosterone Kit, Fujirebio) and the PAC of 6 patients were measured using an automated chemiluminescent enzyme immunoanalyzer (Accuraseed Aldosterone, Fujifilm). The reference range of the PAC was 2.99 ng/dL to 15.9 ng/dL. The PRA was measured using a radioimmunoassay (PRA RIA kit, Yamasa). The reference range of the PRA was 0.2 ng/mL/h to 15.9 ng/mL/h.

Measurements and statistical analysis

Statistical analysis was performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [16]. Categorical variables are expressed as numbers and percentages. Categorical variables were analyzed using χ^2 or Fisher's exact test as appropriate. Continuous variables are expressed as the median and IQR. Continuous variables were analyzed using the Mann–Whitney U-test. Furthermore, EZR was used to draw the receiver operating characteristic (ROC) curves. The optimal cut-off point was set at the closest point on the upper left corner of the ROC curves. All tests were two-tailed, and a p-value <0.05 was considered statistically significant.

To assess the clinical and biochemical characteristics, we used the following post-operative variables at post-operative 1–10 days and 6–12 months: systolic blood pressure (sBP), diastolic blood pressure (dBP), anti-hypertensive medications (defined daily dose [DDD]), and clinical laboratory data (including serum potassium, serum creatinine, estimated glomerular filtration rate [eGFR], PAC, PRA, and ARR). SBP, dBP, and anti-hypertensive medications (DDD) were evaluated from the same day data as the biochemical characteristics. The eGFR was calculated using the following formula: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 in females [17]. Post-operative laboratory data at 1–10 days were evaluated by fasting blood sampling in the early morning during hospitalization.

Complete clinical success was defined normal blood pressure without the aid of anti-hypertensive medicine; partial clinical success was defined as the same blood pressure as before surgery with less anti-hypertensive medication or a reduction in blood pressure with either the same amount or a reduction in anti-hypertensive medication; and absent clinical success was defined as unchanged or increased blood pressure with either the same amount or an increase in anti-hypertensive medication. Complete biochemical success was defined as the correction of hypokalemia and normalization of the ARR; partial biochemical success was defined as the correction of hypokalemia and a raised ARR with a decrease in baseline PAC >50%; and absent biochemical success was defined as persistent hypokalemia or persistent raised ARR. We evaluated the clinical and biochemical outcomes after adrenalectomy for unilateral PA on the basis of the criteria proposed in the PASO study [9]; however, we did not evaluate captopril challenge test or saline infusion test when the ARR was elevated at 6–12 months follow-up. We analyzed the clinical and biochemical characteristics in two groups, namely, the complete biochemical success group and the partial or absent biochemical success group, and the complete clinical success group and the partial or absent clinical success group. Moreover, ROC analysis of PAC 1–10 days after surgery for predicting biochemical outcomes was performed.

Results

Seventy-eight consecutive patients with unilateral PA underwent adrenalectomy between January 2007 and March 2019. Seventeen patients were excluded from this study due to lack of follow-up data at 6–12 months after surgery, as were 2 patients without PAC and PRA measurements on post-operative days 1–10. As a result, a total of 59 patients were included in the study.

Table 1 shows the clinical and biochemical characteristics of patients before adrenalectomy. The median age of the patients was 46.0 years (male to female ratio, 34:25), the median duration of hypertension was 6.0 years (IQR, 2.0–11.0), and the median pre-operative number of anti-hypertension medications (DDD) was 2.3 (IQR, 1.5–3.5). Fifty-one patients were taking mineralo-corticoid receptor antagonist (MRA) before surgery, but all patients stopped taking MRA just after surgery.

Table 2 shows the clinical and biochemical characteristics of patients 1–10 days after adrenalectomy and 6–12 months after adrenalectomy. In terms of the biochemical outcomes, complete biochemical success was achieved in 51 patients (86.4%), while 5 (8.5%) and 3 (5.1%) patients had partial or absent biochemical success,

respectively. For the clinical outcomes, 27 patients (45.8%) had complete clinical success, while 28 (47.5%) and 4 (6.8%) patients had partial or absent clinical success, respectively. The median PAC at 1–10 days after adrenalectomy (7.0 ng/dL [IQR, 5.2–10.0]) was lower than that at 6–12 months after adrenalectomy (12.5 ng/dL [IQR, 8.4–16.0)]), and the median ARR at 1–10 days after adrenalectomy (25.0 ng/dL per ng/mL/h [IQR, 12.2–49.5]) was higher than that at 6–12 months after adrenalectomy (6.7 ng/dL per ng/mL/h [IQR, 4.0–15.5]).

Table 3 shows a comparison of pre-operative clinical and biochemical characteristics with post-operative clinical and biochemical characteristics at post-operative days 1–10 between the complete clinical success group and the partial or absent clinical success group, and between the complete biochemical success group and the partial or absent biochemical success group. In the comparison between the complete clinical success group and the partial or absent clinical success group, there were significant differences in sex (male/female 10/17 vs. 24/8, p = 0.004), age (42.0 [IQR, 37.5–46.0] vs. 54.0 [IQR, 43.8–62.3], p = 0.002), body mass index (23.2 [IQR, 20.1–23.8] vs. 25.3 [IQR, 22.6–28.2], p = 0.002), duration of hypertension (3.0 [IQR, 1.0–4.0] vs. 9.0 [IQR, 6.8–19.3], p < 0.001), hypokalemia (25 [92.6%] vs. 21 [65.6%], p = 0.025), and anti-hypertensive medications (DDD) (1.7 [IQR, 1.1–2.2] vs. 2.7 [IQR, 2.3–4.0], p < 0.001) before surgery. Moreover, anti-hypertensive medications (DDD) (0.0 [IQR, 0.0–0.0] vs. 0.0 [IQR, 0.0–0.8], p = 0.042) and eGFR (80.9 [IQR, 72.1–91.5] vs. 70.0 [IQR, 54.3–78.5], p = 0.032) at post-operative days 1–10 were significantly different. However sBP, dBP, PAC, PRA, serum sodium, and serum potassium at post-operative days 1–10 showed no significant difference. In 43 patients who had not taken anti-hypertensive medications immediately after surgery, 23 patients showed complete clinical success, but 20 patients showed partial or absent clinical success 6–12 months after surgery. In 16 patients who had taken anti-hypertensive medications immediately after surgery, 4 patients had complete clinical success, but 12 patients had partial or absent clinical success 6–12 months after surgery. In the comparison between the complete biochemical success group and the partial or absent biochemical success group, post-operative PAC at the initial assessment was significantly lower in the complete biochemical success group (6.3 ng/dL; IQR, 5.0–7.9) than that in the partial or absent biochemical success group (12.7 ng/dL; IQR, 10.6–14.5) (p < 0.001). No significant difference was observed in any of the remaining factors.

ROC curves were drawn to predict biochemical outcomes. Fig. 1 shows the result of the ROC curve analysis

Table 1   Clinical characteristics of the study population prior to adrenalectomy ($n = 59$)

	Study population ($n = 59$)
Age, years	46.0 (39.5–57.5)
Sex, male	34 (57.6%)
Body mass index	23.3 (20.9–27.1)
Duration of hypertension, years	6.0 (2.0–11.0)
Anti-hypertensive medications (defined daily dose)	2.3 (1.5–3.5)
(MRA/Ca-blocker/α-blocker/β-blocker/ACE or ARB, *n*)	51/53/7/3/13
Serum potassium, mEq/L	3.6 (3.2–4.1)
Serum sodium, mEq/L	142 (140–143)
eGFR, mL/min/1.73 m^2	83.5 (68.1–94.3)
Presence of hypokalemia	46 (78.0%)
Adrenal nodule on CT	56 (94.9%)
Adrenal nodule size on CT, mm	12.0 (9.0–15.0)
ARR, ng/dL per ng/mL/h	94.3 (54.0–187.4)
PAC, ng/dL	34.2 (21.8–49.0)
PRA, ng/mL/h	0.30 (0.20–0.50)
Systolic blood pressure, mmHg	133.0 (126.0–145.5)
Diastolic blood pressure, mmHg	82.0 (75.5–91.0)

The values represent medians with interquartile ranges for continuous variables, and numbers and percentages for categorical variables. *n*, Number of samples; IQR, Interquartile range; MRA, Mineralocorticoid receptor antagonist; ACE, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blockers; eGFR, Estimated glomerular filtration rate; adrenal nodule, Presence of adrenal nodule on adrenal computed tomography (CT) was defined as a nodule >6 mm in diameter; PAC, Plasma aldosterone concentration; PRA, Plasma renin activity; ARR, PAC to PRA ratio.

Table 2   Clinical characteristics of the study population 1–10 days after adrenalectomy and at 6–12 months after adrenalectomy

	1–10 days	6–12 months
Biochemical outcome, complete/partial/absent (*n*)	—	51/5/3
Clinical outcome, complete/partial/absent (*n*)	—	27/28/4
Anti-hypertensive medications (defined daily dose)	0.0 (0.0–0.5)	0.4 (0.0–1.0)
Serum potassium, mEq/L	4.0 (3.8–4.3)	4.4 (4.2–4.6)
Serum sodium, mEq/L	140.0 (139.0–141.0)	140.0 (139.0–141.0)
eGFR, mL/min/1.73 m^2	76.2 (60.1–88.1)	67.4 (53.2–81.0)
ARR, ng/dL per ng/mL/h	25.0 (12.2–49.5)	6.7 (4.0–15.5)
PAC, ng/dL	7.0 (5.2–10.0)	12.5 (8.4–16.0)
PRA, ng/mL/h	0.30 (0.15–0.50)	1.40 (0.85–2.90)
PAC ≥16.0 ng/dL, *n*	2 (3.4%)	15 (25.4%)
ARR ≥20 ng/dL per ng/mL/h, *n*	34 (57.6%)	8 (13.6%)
Systolic blood pressure, mmHg	128.0 (120.5–134.0)	122.0 (115.0–135.0)
Diastolic blood pressure, mmHg	83.5 (76.5–90.0)	80.0 (72.5–86.5)

The values represent medians with interquartile ranges for continuous variables, and numbers and percentages for categorical variables. *n*, Number of samples; IQR, Interquartile range; eGFR, Estimated glomerular filtration rate; PAC, Plasma aldosterone concentration; PRA, Plasma renin activity; ARR, PAC to PRA ratio.

Table 3 Comparison of the clinical characteristics between the complete clinical success group and the partial or absent clinical success group, and between the complete biochemical success group and the partial or absent biochemical success group

	Clinical Outcome			Biochemical Outcomes		
	Complete clinical success (n = 27)	Partial or absent clinical success (n = 32)	p-value	Complete biochemical success (n = 51)	Partial or absent biochemical success (n = 8)	p-value
Sex, male/female, n	10/17	24/8	0.004*	27/24	7/1	0.122
Age, years	42.0 (37.5–46.0)	54.0 (43.8–62.3)	0.002*	46.0 (40.5–58.0)	43.5 (37.0–51.0)	0.364
Body mass index, mean	23.2 (20.1–23.8)	25.3 (22.6–28.2)	0.002*	23.3 (20.8–27.1)	23.1 (21.9–25.7)	0.816
Duration of hypertension, years	3.0 (1.0–4.0)	9.0 (6.8–19.3)	<0.001*	6.0 (2.0–9.5)	5.5 (3.3–17.5)	0.781
Anti-hypertensive medication (DDD) before surgery	1.7 (1.1–2.2)	2.7 (2.3–4.0)	<0.001*	0.4 (0.0–0.7)	1.3 (0.0–2.5)	0.108
Serum potassium before surgery, mEq/L	3.7 (3.3–3.9)	3.7 (3.6–3.9)	0.284	3.7 (3.5–3.9)	3.6 (3.2–4.1)	1.000
Hypokalemia before surgery, n	25 (92.6%)	21 (65.6%)	0.025*	40 (78.4%)	6 (75.0%)	1.000
Adrenal nodule, n	27 (100%)	29 (90.6%)	0.243	48 (94.1%)	8 (100%)	1.000
PAC before surgery, ng/dL	38.5 (24.4–54.9)	27.7 (21.2–41.9)	0.095	34.2 (21.7–51.3)	34.5 (28.9–38.7)	0.921
PRA before surgery, ng/mL/h	0.30 (0.20–0.40)	0.30 (0.20–0.55)	0.244	0.30 (0.20–0.50)	0.30 (0.28–0.40)	0.973
Lateralization index at AVS	16.64 (5.70–32.37)	8.81 (5.08–17.52)	0.169	11.75 (5.46–24.95)	7.54 (5.66–15.23)	0.566
Contralateral ratio at AVS	0.36 (0.15–0.77)	0.42 (0.24–0.80)	0.653	0.40 (0.15–0.80)	0.66 (0.35–0.78)	0.321
Biochemical outcome complete, n	24 (88.9%)	27 (84.4%)	0.715	—	—	—
Clinical outcome complete, n	—	—	—	27 (52.9%)	3 (37.5%)	0.715
Anti-hypertensive medications (DDD) (1–10 d)	0.0 (0.0–0.0)	0.0 (0.0–0.8)	0.042*	0.0 (0.0–0.2)	0.0 (0.0–0.6)	0.506
No anti-hypertensive medications (1–10 d)	23 (85.2%)	20 (62.5%)	0.078	38 (74.5%)	5 (62.5%)	0.670
PAC after surgery (1–10 d), ng/dL	6.3 (5.0–7.9)	7.3 (5.6–11.3)	0.068	6.3 (5.0–7.9)	12.7 (10.6–14.5)	<0.001*
PRA after surgery (1–10 d), ng/mL/h	0.20 (0.10–0.48)	0.40 (0.20–0.63)	0.197	0.3 (0.1–0.6)	0.2 (0.2–0.4)	0.645
Serum sodium after surgery (1–10 d), mEq/L	140.0 (139.0–141.0)	140.0 (139.0–141.3)	0.860	140.0 (139.0–141.5)	140.5 (138.8–141.0)	0.911
Serum potassium after surgery (1–10 d), mEq/L	4.0 (3.8–4.3)	4.0 (3.7–4.2)	0.843	4.0 (3.8–4.3)	4.1 (3.8–4.2)	0.705
eGFR after surgery (1–10 d), mL/min/1.73 m^2	80.9 (72.1–91.5)	70.0 (54.3–78.5)	0.032*	74.3 (59.6–88.1)	77.2 (65.8–82.8)	0.903
Systolic blood pressure after surgery (1–10 d), mmHg	128.0 (119.5–132.5)	129.0 (121.0–140.3)	0.283	127.0 (119.5–134.5)	130.0 (129.3–131.8)	0.499
Diastolic blood pressure after surgery (1–10 d), mmHg	82.0 (76.5–89.5)	84.0 (79.0–90.3)	0.364	83.5 (76.5–90.0)	83.5 (79.0–90.0)	0.901

The values represent medians with interquartile ranges for continuous variables, and number and percentages for categorical variables. n, Number of samples; IQR, Interquartile range; d, Days; DDD, Defined daily dose; adrenal nodule, Presence of adrenal nodule on adrenal CT was defined as a nodule >6 mm in diameter; PAC, Plasma aldosterone concentration; PRA, Plasma renin activity; ARR, PAC to PRA ratio; eGFR, Estimated glomerular filtration rate; *, p-value < 0.05.
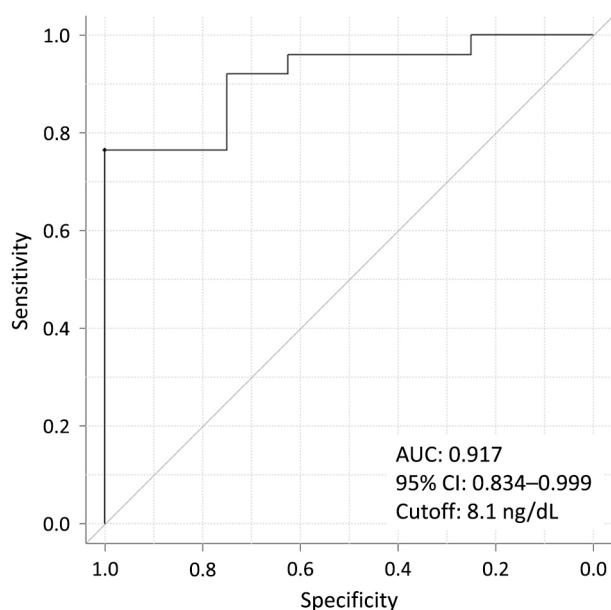
AUC: 0.917
95% CI: 0.834–0.999
Cutoff: 8.1 ng/dL

Fig. 1 Receiver operating characteristic (ROC) curves based on PAC on post-operative days 1–10 to predict biochemical success. The optimal cutoff for post-operative PAC was 8.1 ng/dL (area under the ROC curve [AUC], 0.917; sensitivity, 76.5%; specificity, 100%).

Discussion

Our study suggests that post-operative PAC at the initial assessment is useful for predicting biochemical outcomes. The optimal cut-off of post-operative PAC at initial assessment for biochemical success was 8.1 ng/dL (sensitivity, 76.5%; specificity, 100%; AUC, 0.917). To the best of our knowledge, the prediction scores for post-surgical biochemical outcomes have not been published previously. With regard to clinical outcome, anti-hypertensive medications (DDD) at post-operative days 1–10 were significantly different between the complete clinical success group and the partial or absent clinical success group.

The autonomous production of aldosterone and the resultant relative hypervolemia inhibit the renin-angiotensin system in patients with PA [18], which subsequently lead to increased PAC and decreased PRA. In the early phase after surgery, PRA is normally suppressed; therefore, PAC should also be suppressed if PA is cured. We hypothesized that PAC suppression can predict biochemical outcomes. In our study, the PAC was measured by radioimmunoassay, and the optimal cut-off of post-operative PAC at initial assessment for biochemical success was 8.1 ng/dL. The aldosterone kits and the standard value of PAC differs by institute. In Japan, chemiluminescent enzyme immunoassay (CLEIA) has become the mainstream method for measuring PAC. Our study suggests that low post-operative PAC at the initial assessment may predict the biochemical cure of PA; however, the specific cut-off PAC at the initial assessment should also be investigated in CLEIA and liquid chromatography/mass spectrometry (LC/MS) in the future.

In our study, PAC at the initial assessment after surgery was associated with biochemical success when using the PASO study criteria. Early intervention with medical treatment for PA should be considered if no reduction in PAC is observed immediately after surgery. However, when post-operative PAC was >8.1 ng/dL at the initial assessment, 12 patients showed complete biochemical success in our study. The group with a post-operative PAC of >8.1 ng/dL and complete biochemical success was not significantly different from the group with a PAC of >8.1 ng/dL and partial or absent biochemical success in PAC 6–12 months after surgery, but showed differences in ARR and PRA 6–12 months after surgery. In those patients with a post-operative PAC of >8.1 ng/dL between complete biochemical success and partial or absent biochemical success, no significant differences in clinical and biochemical findings on post-operative days 1–10 were observed. This suggests that the suppression of PRA and biochemical outcome are gradually restored in some cases. Therefore, if

of PAC on post-operative days 1–10 for predicting biochemical success (area under the curve [AUC], 0.917; 95% confidence interval, 0.834–0.999). The optimal PAC cut-off for biochemical success was 8.1 ng/dL (sensitivity, 76.5%; specificity, 100%).

Eight patients had PAC measured within 3 days of surgery and all patients had complete biochemical outcome. Among the 51 patients with complete biochemical success, we compared 8 patients whose PAC was measured within 3 days after surgery with the 43 patients whose PAC was measured 4–10 days after surgery, and found no significant difference in post-operative PAC and PRA at the initial assessment <(PAC 5.4 ng/mL [IQR, 5.1–7.3 ng/mL] *vs.* 6.7 ng/mL [IQR, 5.0–9.0 ng/mL], *p* = 0.33), (PRA 0.3 mg/mL/h [IQR, 0.2–0.5ng/mL/h] *vs.* 0.3 ng/mL/h [IQR, 0.1–0.6 ng/mL/h], *p* = 0.752)>.

In cases with a post-operative PAC >8.1 ng/dL, 12 patients had complete biochemical success, and 8 patients showed partial or absent biochemical success. Table 4 shows a comparison of the clinical and biochemical characteristics between the complete biochemical success group and the partial or absent biochemical success group in those with post-operative PAC >8.1 ng/dL; no significant difference was shown at post-operative days 1–10.

Table 4 Comparison of the clinical characteristics between the complete biochemical success group and the partial or absent biochemical success group in patients with a PAC of >8.1 ng/dL 1–10 days after surgery

	Complete biochemical success (n = 12)	Partial or absent biochemical success (n = 8)	p-value
Sex, male/female, n	9/3	7/1	0.619
Age, years	43.5 (37.0–50.5)	43.5 (37.0–51.0)	0.938
Body mass index, mean	23.6 (22.8–28.4)	23.1 (21.9–25.7)	0.571
Duration of hypertension, years	6.0 (4.5–10.5)	5.5 (3.3–17.5)	0.907
Serum potassium before surgery, mEq/L	3.8 (3.7–3.9)	3.6 (3.2–4.1)	1.000
Hypokalemia before surgery, n	8 (66.7%)	6 (75.0%)	1.000
Adrenal nodule, n	11 (91.7%)	8 (100%)	1.000
Clinical outcome, complete/partial or absent	3/9	3/5	0.642
Anti-hypertensive medication (DDD) after surgery (6–12 m)	0.8 (0.0–1.1)	1.3 (0.0–2.5)	0.451
PAC after surgery (1–10 d), ng/dL	10.7 (10.1–11.8)	12.7 (10.6–14.5)	0.305
PAC after surgery (6–12 m), ng/dL	15.2 (12.8–18.5)	15.9 (13.3–17.5)	0.908
PRA after surgery (1–10 d), ng/mL/h	0.50 (0.20–0.80)	0.20 (0.20–0.43)	0.195
PRA after surgery (6–12 m), ng/mL/h	2.10 (1.28–3.58)	0.50 (0.41–0.70)	<0.001*
ARR after surgery (1–10 d), ng/dL per ng/mL/h	20.9 (14.7–48.4)	50.8 (34.2–62.0)	0.115
ARR after surgery (6–12 m), ng/dL per ng/mL/h	6.7 (41.3–14.7)	29.3 (23.3–39.7)	<0.001*
Serum potassium after surgery (1–10 d), mEq/L	4.2 (3.9–4.3)	4.1 (3.8–4.2)	0.815
eGFR after surgery (1–10 d), mL/min/1.73 m^2	66.9 (54.1–80.2)	77.2 (65.8–82.8)	0.487
Systolic blood pressure after surgery (1–10 d), mmHg	120.5 (110.0–131.0)	130.5 (126.5–132.3)	0.135
Diastolic blood pressure after surgery (1–10 d), mmHg	77.5 (70.8–79.3)	83.0 (77.3–88.0)	0.202

Values represent medians with interquartile ranges for continuous variables and numbers and percentages for categorical variables. n, Number of samples; IQR, Interquartile range; adrenal nodule, Presence of adrenal nodule on adrenal CT was defined as a nodule >6 mm in diameter; DDD, Defined daily dose; d, Days; m, Months; PAC, Plasma aldosterone concentration; PRA, Plasma renin activity; ARR, PAC to PRA ratio; eGFR, Estimated glomerular filtration rate; *, p-value < 0.05.

post-operative PAC is not reduced, a careful follow-up may be required in cases without an increase in PRA.

In our study, anti-hypertensive medications (DDD) at post-operative days 1–10 showed significant differences between the complete clinical success group and the partial or absent clinical success group. The patients who had taken anti-hypertensive medications immediately after surgery tended to have partial or absent clinical success. However, in some cases, anti-hypertensive medications became unnecessary during follow-up after surgery. A high number of immediate post-operative anti-hypertensive medications (DDD) tends to increase the likelihood of partial or absent clinical success, but follow-up to evaluate clinical outcome is still required.

Moreover, in our study, sex, age, body mass index, duration of hypertension, hypokalemia, and anti-hypertensive medications (DDD) before surgery showed a significant difference between the complete clinical success group and the partial or absent clinical success group. Some studies have reported prediction scores for post-operative clinical outcomes using pre-operative clinical data, such as the ARS [10-12]. In these previous studies, age, sex, body mass index, duration of hypertension, and anti-hypertensive medications (DDD) showed significant differences. Our results are in agreement with previous studies in this field.

Limitations

This study has several limitations. The main limitation is its retrospective single center based design. Although we had included consecutive patients, we had to exclude 19 cases because of missing data on follow-up. The only factor contributing to the biochemical outcome was the PAC immediately after surgery, making it difficult to construct a prediction model for biochemical outcomes. A validation study is needed with more patients and a multi-center based approach, and the construction of a

prediction model for biomedical outcomes that includes other factors should also be considered. Secondly, an MRA was taken by many patients prior to surgery, and the PRA on post-operative days 1–10 could be increased. In the present study, 4 patients had a PRA >1.0 ng/mL/h on post-operative days 1–10. The median PAC of these patients on post-operative days 1–10 was 7.0 ng/dL (IQR, 6.7–8.1), and the median PRA on post-operative days 1–10 was 1.20 ng/mL/h (IQR, 1.17–1.25). We believe that the involvement of MRAs was minimal in our study. Thirdly, we had no access to data on the use of heparin, volume expansion with saline solutions, hypokalemia, or use of potassium supplementation during or immediately following surgery. The potential confounding variables for the aldosterone measurement during or immediately following surgery, such as volume expansion with saline solutions, hypokalemia, or use of potassium supplementation might have affected post-operative PAC. However, as there was no significant difference in PAC and PRA between patients measured within 3 days after surgery and those measured 4–10 days after surgery, we expect the effects of saline solutions and surgical invasion to be minimal. Fourthly, in our study, the case in which the ARR was elevated at 6–12 months follow-up failed to evaluate confirmatory test after 6–12 months. Finally, our study was based on the PAC measured using a radioimmunoassay, and the aldosterone kits and the standard value of PAC differs by institute. Therefore, the cut-off PAC at the initial assessment may differ on the basis of the assay used by each institute, and the specific cut-off PAC at the initial assessment should also be investigated in CLEIA and LC/MS.

Conclusion

An improvement in PAC immediately after surgery may predict biochemical cure in a subset of patients with PA. Although follow-up for evaluating clinical outcome is required, in patients with an improvement in PAC after surgery, follow-up by laboratory data for evaluating biochemical outcome may not be necessary.

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Disclosure

The authors have nothing to disclose.

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