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Outcome-Based Decision-Making Algorithm for Treating Patients with Primary Aldosteronism

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Background: Optimal management of primary aldosteronism (PA) is crucial due to the increased risk of cardiovascular and cerebrovascular diseases. Adrenal venous sampling (AVS) is the gold standard method for determining subtype but is technically challenging and invasive. Some PA patients do not benefit clinically from surgery. We sought to develop an algorithm to improve decision-making before engaging in AVS and surgery in clinical practice.

Methods: We conducted the ongoing Korean Primary Aldosteronism Study at two tertiary centers. Study A involved PA patients with successful catheterization and a unilateral nodule on computed tomography and aimed to predict unilateral aldosterone-producing adenoma (n=367). Study B involved similar patients who underwent adrenalectomy and aimed to predict postoperative outcome (n=330). In study A, we implemented important feature selection using the least absolute shrinkage and selection operator regression.

Results: We developed a unilateral PA prediction model using logistic regression analysis: lowest serum potassium level ≤3.4 mEq/L, aldosterone-to-renin ratio ≥150, plasma aldosterone concentration ≥30 ng/mL, and body mass index <25 kg/m^2 (area under the curve, 0.819; 95% confidence interval, 0.774 to 0.865; sensitivity, 97.6%; specificity, 25.5%). In study B, we identified female, hypertension duration <5 years, anti-hypertension medication <2.5 daily defined dose, and the absence of coronary artery disease as predictors of clinical success, using stepwise logistic regression models (sensitivity, 94.2%; specificity, 49.3%). We validated our algorithm in the independent validation dataset (n=53).

Conclusion: We propose this new outcome-driven diagnostic algorithm, simultaneously considering unilateral aldosterone excess and clinical surgical benefits in PA patients.

Keywords: Adrenalectomy; Clinical decision rules; Hyperaldosteronism; Patient selection; Treatment outcome

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INTRODUCTION

Primary aldosteronism (PA) is the most common type of endocrine hypertension (HTN), and affects 5% to 10% of hypertensive subjects [1,2]. Subjects with PA have increased cardiovascular and cerebrovascular risks compared with those with essential HTN [3]. Therefore, PA management aims to reduce the cardiovascular disease risk by improving blood pressure (BP) and normalizing potassium levels, thereby lowering mortality.

However, there are two significant points to consider in this respect. The first is whether adrenal venous sampling (AVS) should be implemented. AVS is the gold standard for subtyping PA but is invasive, technically challenging, and has limited availability [1,4]. Therefore, several researchers have suggested clinical predictors of a unilateral aldosterone excess, such as serum potassium levels, estimated glomerular filtration rate (eGFR), plasma aldosterone concentration (PAC), aldosterone-to-renin ratio (ARR) before/after confirmatory tests, and computed tomography (CT) findings [5-8]. If CT shows normal adrenal glands or bilateral lesions, AVS should be performed in patients who are willing to undergo surgery. However, in cases with a unilateral lesion on CT, AVS may be avoided if the lesion can accurately predict unilateral aldosterone excess. Thus, while previous reports have included CT findings as predictors, we have reconsidered whether AVS needs to be performed when unilateral adrenal nodules were already observed on CT.

Second, it needs to be considered whether surgery improves a clinical outcome in all patients with unilateral aldosterone excess. Although surgery is the mainstay treatment in patients with unilateral aldosterone excess, complete clinical success in terms of clinical outcome occurs only in 37% of patients with unilateral aldosterone excess [9]. Thus, confirmation of unilateral aldosterone excess does not guarantee surgical remission. Zarnegar et al. [10] developed the aldosterone resolution score (ARS), which is based on female sex, shorter HTN duration, lower number of antihypertensive medications, and low body mass index (BMI). The ARS was validated in several studies but was not useful in a French cohort [11-13]. Recently, the Primary Aldosteronism Surgical Outcome (PASO) score was developed by an international group, which additionally includes adrenal nodule size and target organ damage [14]. A Japanese group also suggested using the absence of diabetes mellitus (DM) as another predictor of clinical benefit [15]. However, the definition of surgical outcome was not consistent across studies.

Hitherto, no algorithm has considered both unilateral aldosterone excess and surgical benefit for deciding on surgery in PA patients. Moreover, a single algorithm is not sufficient to decide on surgical intervention. Herein, we sought to combine predictors of unilateral aldosterone excess with the clinical benefits of surgery in PA patients into an algorithm that can improve decision-making before embarking on invasive procedures and surgery in clinical practice.

METHODS

Study population

The Korean Primary Aldosteronism Study is an ongoing cohort study of PA. In this retrospective cohort study, 676 PA patients were enrolled from Seoul National University Hospital from 2000 to 2018 (SNUH, n=363) and Asan Medical Center from 2007 to 2016 (AMC, n=313). Among 676 PA patients from the two centers, Study A was conducted in PA patients with successful catheterization and a unilateral adrenal nodule on CT (n=367) (Fig. 1). The study A cohort was randomly divided into a training dataset (n=257), to develop a lateralization predictive model, and a test dataset (n=110), to validate the model. Patients in Study B were also recruited from the original population of 676 PA patients. Study B was performed in PA patients who underwent adrenalectomy, completed a 3-month postoperative follow-up, and had postoperative clinical outcomes (n=330) (Fig. 1). Among a total of 676 PA patients, 239 patients were included in both Study A and B. The final algorithm was applied to the independent validation dataset derived from Seoul National University Bundang Hospital (n=53). The validation set consisted of PA patients with a unilateral adrenal nodule who underwent adrenalectomy and followed-up after surgery at 3 months from 2010 to 2020 at Seoul National University Bundang Hospital.

Data collection

We collected the following data from electronic medical records: age, sex, BMI, BP, family history of HTN, diagnosis and duration of HTN, number of antihypertensive medications, DM, dyslipidemia, coronary artery disease (CAD), atrial fibrillation, cerebrovascular disease (CVD), obstructive sleep apnea (OSA), and hypertensive retinopathy.

HTN was defined as systolic blood pressure (SBP) ≥140 and/or diastolic blood pressure (DBP) ≥90 mm Hg, or current use of antihypertensive medication. Antihypertensive medications were shown as a defined daily dose (DDD), which is the assumed average maintenance dose per day, according to the World Health Organization anatomical therapeutic chemical

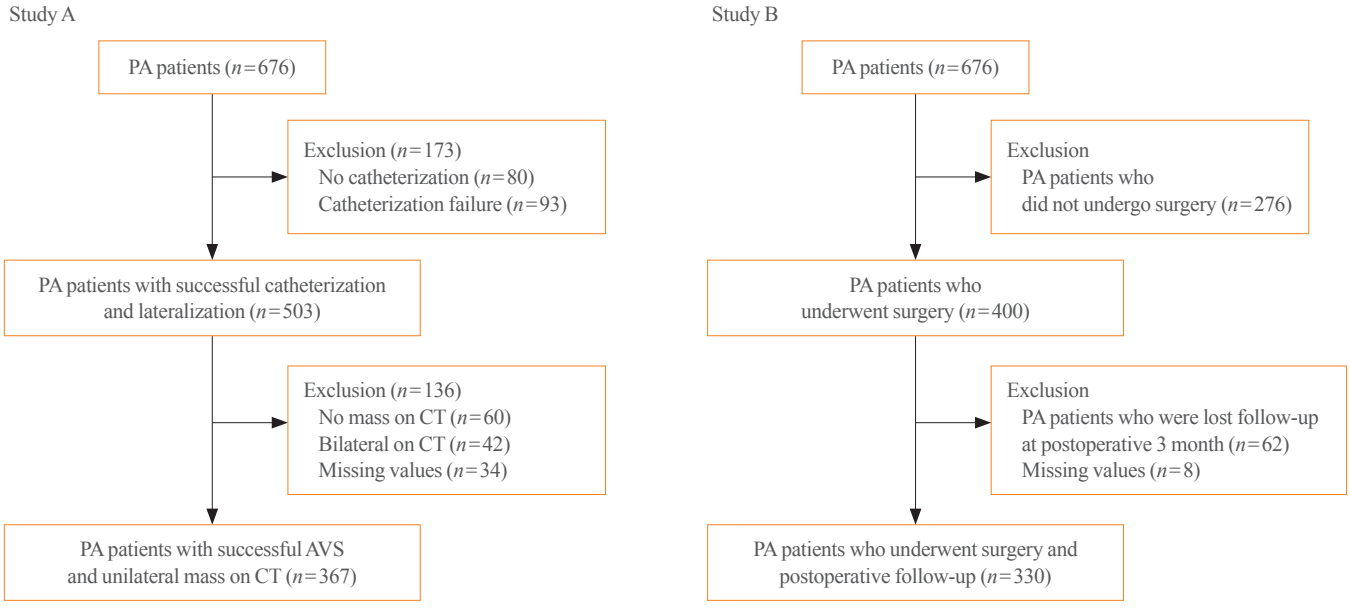


Fig. 1. Flow diagram of study subjects. PA, primary aldosteronism; CT, computed tomography; AVS, adrenal venous sampling.

(ATC)/DDD index 2019. DM was defined by fasting plasma glucose level ≥7.0 mmol/L (126 mg/dL), glycated hemoglobin ≥6.5%, or current use of oral antidiabetic drugs or insulin. Patients taking lipid-lowering agents or with an abnormal lipid panel (total cholesterol ≥240 mg/dL, low-density lipoprotein cholesterol ≥160 mg/dL, triglyceride ≥200 mg/dL, and high-density lipoprotein cholesterol <40 mg/dL) were considered to have dyslipidemia.

CAD was defined as a history of percutaneous coronary intervention, coronary artery bypass surgery, or unstable angina noted on their medical records. CVDs were indicated by doctor-diagnosed ischemic or hemorrhage stroke. The presence of atrial fibrillation, OSA, and hypertensive retinopathy was retrieved from the medical records.

Laboratory measurements

PAC was measured by radioimmunoassay (RIA) using the SPAC-S Aldosterone kit (TFB Inc., Tokyo, Japan). Plasma renin activity (PRA) was measured by RIA using Renin RIA beads (TFB Inc., at SNUH before 2011) or a PRA RIA kit (TFB Inc., at SNUH after 2011 and at AMC). Intra- and inter-assay coefficients of variation for each assay were 10% and 5%, respectively. PAC and PRA measured at baseline were used as variables. Serum potassium levels, creatinine levels, and eGFR (calculated using the Modification of Diet in Renal Disease equation) were also retrieved from the medical records.

Diagnosis of PA

PA was confirmed using a saline infusion test (SIT) in patients with an ARR of ≥20 and a PAC of >15 ng/dL [1]. PAC >10 ng/dL SIT confirmed the diagnosis of PA, whereas PAC after SIT <5 ng/dL excluded the diagnosis PA [1]. The SIT was repeated if PAC of 5 to 10 ng/dL after SIT. We discontinued diuretics and mineralocorticoid receptor antagonists for ≥6 weeks and beta-adrenergic receptor blockers for ≥2 weeks before confirmatory testing. Calcium channel or alpha-adrenergic receptor blockers were preferred for BP control; however, if BP was persistently elevated more than 140/90 mm Hg, angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors were added.

CT and AVS

A unilateral adrenal nodule on CT was defined as a nodule measuring ≥7 mm in diameter, and a normal contralateral adrenal gland [16]. Thin-slice (1 to 3-mm-thick) CT was performed for all patients, and findings were evaluated by radiologists. AVS was performed sequentially under adrenocorticotropic hormone stimulation [1,4]. Successful catheterization was defined as a selectivity index (the ratio of cortisol levels in the adrenal vein to those in the inferior vena cava) of ≥3. The lateralization index (LI) was calculated by dividing the aldosterone-to-cortisol ratio of the dominant adrenal vein by that of the non-dominant vein. Unilateral aldosterone excess was defined as an LI of >4, while bilateral aldosterone excess was defined as an LI of <3.

Concordance between the side of the adrenal nodule on CT imaging and the side of aldosterone excess on AVS was evaluated.

Definition of clinical outcomes

We assessed postoperative outcomes at 3 months post-surgery, according to the BP outcome published by the PASO study group [9]. Complete clinical success was defined as SBP <140 and DBP <90 mm Hg without antihypertensive medication. Partial clinical success was defined by a decrease in the number of antihypertensive medications, an SBP of >20 mm Hg, or a DBP of >10 mm Hg, with the same dose of antihypertensive medications. Alternatively, clinical success was considered absent.

Statistical analyses

Categorical variables are expressed as numbers (%) and were compared using the chi-square test. Continuous variables were compared using the Mann-Whitney *U* test for non-normally distributed variables or Student's *t* test for normally distributed variables, and are expressed as medians (interquartile ranges).

All statistical analyses were performed using R version 3.6.2 (Foundation for Statistical Computing, Vienna, Austria), and the criteria for statistical significance was $P<0.05$ for two-tailed tests.

For variable selection, we applied the L1 penalized, least absolute shrinkage and selection operator (LASSO) regression to minimize potential collinearity and over-fitting of variables. We augmented 10-fold cross-validation and selected the value of the penalty parameter (λ) as 1 standard error estimate to show the highest accuracy. The R package "glmnet" was used for LASSO regression. Subsequently, the selected variables were incorporated into stepwise logistic regression models. The area under the curve (AUC), with a 95% confidence interval (CI) and cutoff points, of selected variables were analyzed using the R package "OptimalCutpoints."

Ethical considerations

The studies involving human participants were reviewed and approved by the Institutional Review Board of SNUH (no. H-1801-010-911) and AMC (no. 2016-0254). The need for obtaining informed consent was waived due to the retrospective study design.

RESULTS

Study A: development of the Primary Aldosteronism Predicting Subtype score

Among 367 PA patients with a unilateral adrenal nodule on CT, 243 (66.2%) revealed concordant unilateral excess and 19 (5.2%) revealed discordant unilateral excess in AVS (Table 1, Study A cohort). The concordant group was younger ($P=0.005$), had lower BMI ($P<0.001$), and higher DBP ($P=0.041$) than the discordant group. The prevalence and duration of HTN, and the dose of anti-hypertensive medications were similar, and there were no differences in the prevalence of comorbidities, including DM, CAD, atrial fibrillation, CVD, OSA, and retinopathy, between the two groups. Serum creatinine level and eGFR was also similar. The concordant group displayed lower serum potassium levels ($P<0.001$) and PRA ($P<0.001$), but higher PAC ($P<0.001$) and ARR ($P<0.001$) than the discordant group. The concordant group had a larger tumor size than the discordant group ($P=0.010$). In the discordant group, contralateral lateralization on AVS was present in 15.3% (19/124).

We selected all variables in the training set to predict the concordance on AVS using the LASSO regression models ($n=257$) (Fig. 2). The final values used for the model were cost=0.5, and epsilon=0.001. Accuracy was used to select the optimal model, using the largest value. The confusion matrix for the training, test, and combined sets is shown in Fig. 2A. In the training set ($n=257$), 206 patients (accuracy, 80.1%) were correctly classified, with a sensitivity and specificity of 61.0% and 89.1%, respectively. To circumvent overfitting bias and assess generalizability, the LASSO model was validated by a 10-fold cross-validation algorithm, and the accuracy was 75.9%. In the test set, 90 of 110 patients were correctly classified (accuracy, 81.8%) (Fig. 2B). Based on the feature importance, the lowest serum potassium level, ARR, PAC, and BMI were incorporated into the final model (Fig. 2C). The cutoff point of each variable was identified in the training set, and lowest serum potassium level ≤3.4 mEq/L, ARR ≥150, PAC ≥30 ng/mL, and BMI <25 kg/m^2 were identified as significant predictors of aldosterone-producing adenoma on CT.

We performed logistic regression analysis using the above-mentioned four variables in the combined set ($n=367$). The odds ratios in the multivariate logistic regression models were 4.38 for lowest serum potassium level ≤3.4 mEq/L, 2.94 for ARR ≥150, 2.42 for PAC ≥30 ng/mL, and 1.89 for BMI <25 kg/m^2. Accordingly, a point was assigned for each variable, and the scoring system with a total score of 10 points (the Primary Aldosteronism Predicting Subtype [PAPS] score) was developed (Table 2).

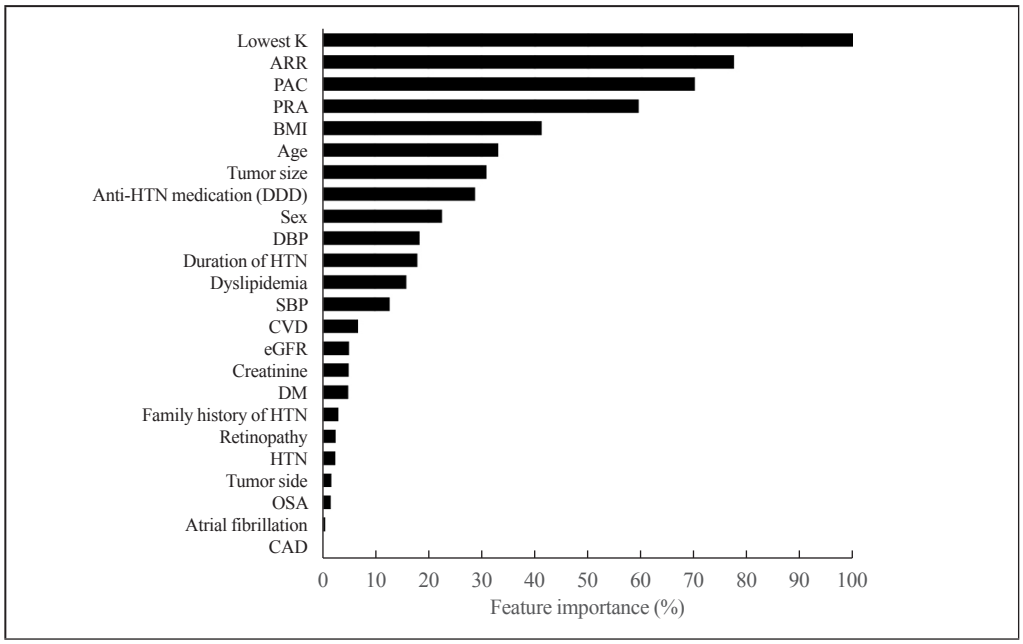
The developed PAPS score in the training set was validated in the test set. Receiver operating characteristic (ROC) curve analysis yielded an AUC of 0.819 (95% CI, 0.774 to 0.865) (Fig.

Table 1. Clinical Characteristics of Primary Aldosteronism Patients with Unilateral Adrenal Nodules on CT According to Concordance between CT and AVS (n=367[a])

Variable	Concordance (n=243)	Discordance (n=124)	Total (n=367)	P value
Age, yr	49.0 (42.0–57.0)	53.0 (46.0–60.0)	51.0 (44.0–59.0)	0.005
Female sex	131 (53.9)	54 (43.5)	185 (50.4)	0.077
Height, cm	163.2 (157.2–169.0)	163.6 (157.7–170.3)	163.2 (157.4–169.8)	0.411
Weight, kg	65.2 (56.3–73.8)	70.9 (62.5–80.1)	67.1 (57.2–76.2)	<0.001
BMI, kg/m^2	24.3 (22.2–26.7)	26.3 (23.6–28.8)	25.2 (22.6–27.2)	<0.001
SBP, mm Hg	144.0 (131.0–157.0)	140.0 (132.0–152.5)	142.0 (132.0–155.0)	0.265
DBP, mm Hg	90.0 (82.0–99.0)	88.0 (81.0–94.0)	90.0 (81.0–97.0)	0.041
Family history of HTN	128 (52.7)	63 (50.8)	191 (52.0)	0.349
HTN	236 (97.1)	120 (96.8)	356 (97.0)	>0.999
Duration of HTN	6.0 (2.0–10.0)	8.0 (2.0–12.0)	6.0 (2.0–10.0)	0.121
Anti-HTN medication (DDD)	2.0 (1.0–3.5)	2.0 (0.7–3.0)	2.0 (1.0–3.3)	0.060
DM	31 (12.8)	20 (16.1)	51 (13.9)	0.469
Dyslipidemia	42 (17.3)	37 (29.8)	79 (21.5)	0.008
CAD	25 (10.3)	13 (10.5)	38 (10.4)	>0.999
Atrial fibrillation	3 (1.2)	1 (0.8)	4 (1.1)	>0.999
CVD	16 (6.6)	14 (11.3)	30 (8.2)	0.175
OSA	2 (0.8)	0	2 (0.5)	0.792
Retinopathy	6 (2.5)	3 (2.4)	9 (2.5)	>0.999
Serum creatinine, mg/dL	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.826
eGFR, mL/min/1.73 m^2	85.5 (73.0–101.2)	87.0 (75.1–96.1)	86.5 (73.8–100.3)	0.859
Lowest serum potassium, mEq/L	3.1 (2.8–3.5)	3.9 (3.5–4.1)	3.3 (2.9–3.9)	<0.001
PAC, ng/dL	37.2 (28.0–55.5)	26.1 (20.9–31.9)	31.4 (24.3–47.2)	<0.001
PRA, ng/mL/hr	0.20 (0.10–0.28)	0.28 (0.20–0.51)	0.20 (0.10–0.38)	<0.001
ARR	233.0 (118.6–397.4)	85.2 (51.0–156.9)	162.5 (76.2–315.8)	<0.001
Tumor location in CT				0.431
Left	147 (60.5)	81 (65.3)	228 (62.1)	
Right	96 (39.5)	43 (34.7)	139 (37.9)	
Tumor size on CT, cm	1.5 (1.2–1.9)	1.3 (1.0–1.8)	1.5 (1.1–1.8)	0.010
Lateralization on AVS				<0.001
Bilateral	0	105 (84.7)	105 (28.2)	
Unilateral	243 (100.0)	19 (15.3)	262 (71.8)	

Values are expressed as median (interquartile ranges) or number (%). Data with non-normal distribution were analyzed using the Mann–Whitney U test.
CT, computed tomography; AVS, adrenal venous sampling; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; DDD, daily defined dose; DM, diabetes mellitus; CAD, coronary artery disease; CVD, cerebrovascular disease; OSA, obstructive sleep apnea; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio.
[a]Five subjects among 372 primary aldosteronism patients with unilateral adrenal nodule on CT were excluded due to the missing variable values.

3A). The cutoff point of PAPS score with the highest sensitivity was 10, which could avoid misclassified adrenalectomy. In the test set, a PAPS score 10 identified concordance between CT imaging and AVS findings in 20 of 23 (sensitivity, 92.9%) with an accuracy of 61.1% (Fig. 3B). A PAPS score 10 identified concordance between CT imaging and AVS findings in 62 of 65 (sensitivity, 97.6%) with an accuracy of 61.6% in the combined set. In the combined set, a PAPS score 0 identified discordance between CT imaging and AVS findings in 38 of 48 (79.2%).



A

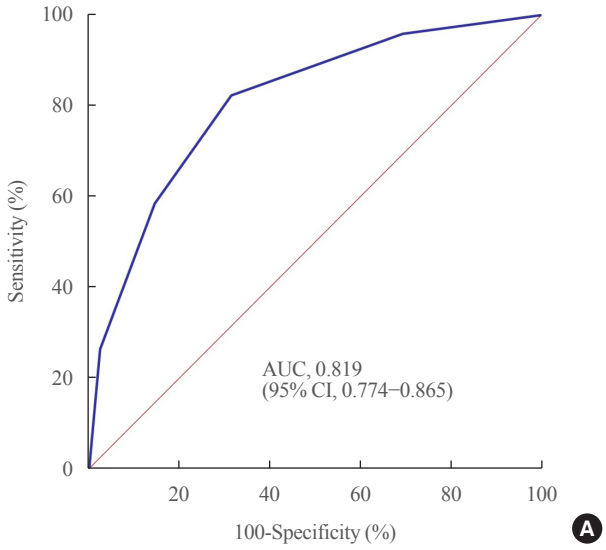
		Predicted concordance state		Performance	
Real concordance state	Training set (n=257)	Concordant (n=188)	Discordant (n=69)	Accuracy	80.1%
	Concordant	156 (83.0%)	19 (27.5%)	Sensitivity	61.0%
	Discordant	32 (17.0%)	50 (72.5%)	Specificity	89.1%
	Test set (n=110)	Concordant (n=80)	Discordant (n=30)	Accuracy	81.8%
	Concordant	64 (80.0%)	4 (13.3%)	Sensitivity	61.9%
	Discordant	16 (20.0%)	26 (86.7%)	Specificity	94.1%
	Combined set (n=367)	Concordant (n=268)	Discordant (n=99)	Accuracy	80.7%
	Concordant	220 (82.1%)	23 (23.2%)	Sensitivity	61.3%
	Discordant	48 (17.9%)	76 (76.8%)	Specificity	90.5%
	10-Fold cross validation	75.9%			

B

Variables	Regression coefficient	AUC (95% CI)	Cutoff point
Lowest serum K (mEq/L)	−0.515	0.798 (0.739–0.857)	≤3.4
ARR	0.262	0.743 (0.690–0.795)	≥150
PAC (ng/dL)	0.304	0.741 (0.679–0.804)	≥30
BMI (kg/m^2)	−0.198	0.649 (0.577–0.722)	<25

C

Fig. 2. Variable selection using the least absolute shrinkage and selection operator (LASSO) regression model in the training set to predict concordance between computed tomography imaging and adrenal venous sampling findings (n=257). Tuning parameter (λ) selection in the LASSO model used 10-fold cross-validation via 1 standard error estimates. The final values used for the model were cost=0.5, and epsilon=0.001. Accuracy was used to select the optimal model using the largest value. (A) Plot of the importance coefficient for each variable in the LASSO model. (B) Confusion matrix showing real and predicted clinical outcomes, the accuracy, sensitivity, specificity, and 10-fold cross-validation of the LASSO model. (C) Area under the curve (AUC) and cutoff point of four selected variables using the R package "OptimalCutpoints." ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity; BMI, body mass index; HTN, hypertension; DDD, daily defined dose; DBP, diastolic blood pressure; SBP, systolic blood pressure; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; OSA, obstructive sleep apnea; CAD, coronary artery disease.



	PAPS score=10	Predicted concordance state		Performance	
Real concordance state	Training set (n=257)	Concordant (n=42)	Discordant (n=215)	Accuracy	62.0%
	Concordant	42 (100.0%)	133 (61.9%)	Sensitivity	100%
	Discordant	0 (0.0%)	82 (38.1%)	Specificity	24.0%
	Test set (n=110)	Concordant (n=23)	Discordant (n=87)	Accuracy	61.1%
	Concordant	20 (87.0%)	48 (55.2%)	Sensitivity	92.9%
	Discordant	3 (13.0%)	39 (44.8%)	Specificity	29.4%
	Combined set (n=367)	Concordant (n=65)	Discordant (n=302)	Accuracy	61.6%
	Concordant	62 (95.4%)	181 (59.9%)	Sensitivity	97.6%
	Discordant	3 (4.6%)	121 (40.1%)	Specificity	25.5%

B

Fig. 3. The discrimination ability of Primary Aldosteronism Predicting Subtype (PAPS) score to detection of concordance between computed tomography imaging and adrenal venous sampling findings. (A) Receiver operating characteristic (ROC) curve for assessing the area under the curve (AUC) and the best cutoff point for the maximal sensitivity for unilateral excess in the training set. (B) Confusion matrix showing real and predicted clinical outcomes, the accuracy, sensitivity, and specificity for the training, test, and combined sets. CI, confidence interval.

Table 2. Logistic Regression Analysis and the Score of Each Variable Identified by LASSO Regression for Unilateral Excess in the Combined Set (n=367)

Variable	Point	Univariate OR (95% CI)	Multivariate OR (95% CI)
Lowest serum potassium ≤3.4 mEq/L	4	7.27 (4.49–12.03)	4.38 (2.59–7.53)
ARR ≥150	3	5.86 (3.65–9.60)	2.94 (1.70–5.15)
PAC ≥30 ng/dL	2	4.79 (3.02–7.70)	2.42 (1.40–4.19)
BMI <25 kg/m^2	1	2.28 (1.46–3.59)	1.89 (1.12–3.20)
Total points	10		

LASSO, least absolute shrinkage and selection operator; OR, odds ratio; CI, confidence interval; ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration; BMI, body mass index.

Study B: development of the Primary Aldosteronism Predicting Surgical Outcome score

Another decision-making point revolves around whether adrenalectomy can improve the clinical outcome of unilateral PA patients. To address this, we investigated predictors for clinical success in adrenalectomized PA patients (Study B). In PA patients with unilateral adrenalectomy (n=400), 330 patients were followed-up at 3-month postoperatively. Among them, complete and partial clinical success was achieved in 191 and 103 patients (57.8% and 31.2%, respectively). Table 3 demonstrates the clinical characteristics of PA patients according to clinical success after adrenalectomy. Patients with complete clinical success were younger (P<0.001), more frequently female (P<0.001), and had lower BMI (P<0.001). Patients with complete

Table 3. Clinical Characteristics of Primary Aldosteronism Patients According to the Clinical Success after Adrenalectomy (n=330)

Variable	Complete (n=191)	Partial+Absent (n=139)	Total (n=330)	P value
Age, yr	47.0 (39.5–56.0)	53.0 (46.0–59.0)	50.5 (42.0–58.0)	<0.001
Female sex	124 (64.9)	56 (40.3)	180 (54.5)	<0.001
Height, cm	161.7 (156.6–168.2)	164.0 (157.8–170.0)	163.0 (156.8–169.5)	0.086
Weight, kg	63.9 (55.8–71.5)	69.4 (62.2–78.0)	66.0 (56.5–74.0)	<0.001
BMI, kg/m^2	24.1 (21.7–26.2)	25.8 (23.3–27.9)	24.7 (22.5–26.9)	<0.001
SBP, mm Hg	141.0 (128.0–155.0)	147.0 (138.0–158.0)	144.0 (131.0–157.0)	0.006
DBP, mm Hg	90.0 (80.5–98.0)	90.0 (83.0–98.5)	90.0 (81.0–98.0)	0.366
Family history of HTN	104 (54.5)	71 (51.1)	175 (53.0)	0.568
HTN	187 (97.9)	139 (100.0)	326 (98.8)	0.141
Duration of HTN	3.0 (1.0–8.0)	9.0 (5.0–11.0)	5.0 (2.0–10.0)	<0.001
Anti-HTN medication (DDD)	1.5 (1.0–2.7)	3.0 (2.0–4.3)	2.0 (1.0–3.5)	<0.001
DM	21 (11.0)	39 (28.1)	60 (18.2)	<0.001
Dyslipidemia	28 (14.7)	46 (33.1)	74 (22.4)	<0.001
CAD	11 (5.8)	23 (16.5)	34 (10.3)	0.003
Atrial fibrillation	4 (2.1)	2 (1.4)	6 (1.8)	>0.999
CVD	11 (5.8)	13 (9.4)	24 (7.3)	0.305
OSA	1 (0.5)	1 (0.7)	2 (0.6)	>0.999
Retinopathy	6 (3.1)	2 (1.4)	8 (2.4)	0.475
Cr, mg/dL	0.80 (0.68–0.97)	0.90 (0.71–1.10)	0.83 (0.69–1.00)	<0.001
eGFR, mL/min/1.73 m^2	85.0 (74.7–101.6)	79.2 (64.8–96.5)	83.0 (70.7–99.6)	0.008
Lowest serum potassium, mEq/L	3.2 (2.9–3.7)	3.1 (2.8–3.5)	3.1 (2.8–3.6)	0.080
PAC, ng/dL	36.1 (25.6–52.5)	39.5 (27.9–53.3)	36.5 (26.6–53.0)	0.287
PRA, ng/mL/hr	0.20 (0.10–0.31)	0.20 (0.10–0.42)	0.20 (0.10–0.34)	0.660
ARR	190.9 (96.3–376.8)	209.0 (85.7–399.9)	203.3 (93.5–387.1)	0.863
Tumor location in CT				0.012
No lesion	3 (1.6)	3 (2.2)	6 (1.8)	
Left	65 (34.0)	57 (41.0)	122 (37.0)	
Right	114 (59.7)	62 (44.6)	176 (53.3)	
Bilateral	9 (4.7)	17 (12.2)	26 (7.9)	
Tumor size on CT, cm	1.5 (1.2–2.0)	1.6 (1.2–2.0)	1.5 (1.2–2.0)	0.294

Values are expressed as median (interquartile ranges) or number (%). Data with non-normal distribution were analyzed using the Mann–Whitney U test.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; DDD, daily defined dose; DM, diabetes mellitus; CAD, coronary artery disease; CVD, cerebrovascular disease; OSA, obstructive sleep apnea; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio; CT, computed tomography.

clinical success exhibited milder HTN than those with partial or absent clinical success: lower SBP (P=0.006), shorter duration of HTN (P<0.001), and used a lower dose of antihypertensive medications (P<0.001). Moreover, the prevalence of DM, dyslipidemia, and CAD was lower in patients with complete clinical success (P=0.003). Patients with complete clinical success had lower serum creatinine levels (P=0.008), with glomerular hyperfiltration. However, there was no difference in serum potassium level, PAC, or ARR.

We constructed stepwise logistic regression models in the training set (n=227) using all variables (Tables 4-6). In the multivariate models, four variables remained as significant predictors of complete clinical success after adrenalectomy. In the final model, female sex, HTN duration, antihypertensive medications, and CAD were included (Table 4). Next, we identified the cutoff point of continuous variables as duration of HTN <5

Table 4. Variable Selection for Predicting the Complete Clinical Success in Primary Aldosteronism Patients: Variables Selected Using the Stepwise Logistic Regression Model in the Training set (n=227)

Variable	Univariate model		Multivariate model	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Female sex	2.74 (1.75–4.32)	<0.001	1.78 (1.04–3.04)	0.036
Duration of HTN, yr	0.89 (0.85–0.93)	<0.001	0.95 (0.90–1.00)	0.048
Anti-HTN medication (DDD)	0.58 (0.50–0.68)	<0.001	0.64 (0.53–0.77)	<0.001
Coronary artery disease	0.31 (0.14–0.64)	0.002	0.36 (0.14–0.90)	0.032

OR, odds ratio; CI, confidence interval; HTN, hypertension; DDD, defined daily dose.

Table 5. Representation of Cutoffs and Assigned Points of Selected Four Selected Variables of the PAPSO Score for Predicting the Complete Clinical Success in Primary Aldosteronism Patients

Variable	Point	Univariate model OR (95% CI)	Multivariate model OR (95% CI)
Female sex	2	2.74 (1.75–4.32)	2.11 (1.27–3.52)
Duration of HTN <5 years	3	5.26 (3.23–8.79)	3.57 (2.10–6.18)
Anti-HTN medication (DDD) <2.5	3	4.87 (3.06–7.86)	3.26 (1.95–5.48)
Coronary artery disease (absence)	2	3.24 (1.53–7.15)	2.68 (1.16–6.52)
Total points	10		

The cutoff point of each variable was developed using the R package "OptimalCutpoints." Univariate and multivariate logistic regression models were generated.
PAPSO score, Primary Aldosteronism Predicting Surgical Outcome score; OR, odds ratio; CI, confidence interval; HTN, hypertension; DDD, defined daily dose.

Table 6. Validation of the PAPSO Score for Predicting the Complete Clinical Success in Primary Aldosteronism Patients: Confusion Matrix Representing Real and Predicted Outcomes, According to the Cutoffs of the Total Score in the Combined Set (n=330)

Real complete clinical success	Predicted complete clinical success		Performance	
	Presence	Absence	Variable	Value, %
PAPSO score=10			Accuracy	56.7
Presence	56 (87.5)	135 (50.8)	Sensitivity	94.2
Absence	8 (12.5)	131 (49.2)	Specificity	49.3
PAPSO score <4			Accuracy	70.6
Presence	176 (68.2)	15 (19.5)	Sensitivity	41.0
Absence	82 (31.8)	62 (80.5)	Specificity	92.2

Values are expressed as number (%).
PAPSO Score, Primary Aldosteronism Predicting Surgical Outcome Score.

years and anti-HTN medication <2.5 DDD. Accordingly, a point was assigned for each variable, and a scoring system with a total score of 10 points (the Primary Aldosteronism Predicting Surgical Outcome [PAPSO] score) was developed (Table 5). In the confusion matrix using the combined set (n=370), a PAPSO score 10 identified complete clinical success in 56 of 64 (sensitivity, 94.9%) with an accuracy of 56.7% (Table 6), whereas a PAPSO score <4 identified absence of complete clinical success in 62 of 77 (specificity, 92.2%) with an accuracy of 70.6% (Table 6).

Clinical decision-making algorithm for PA patients with a unilateral adrenal nodule

Collectively, we suggested a clinical decision-making algorithm for PA patients with a unilateral adrenal nodule on CT (Fig. 4). First, if PA patients with PAPS score of 10 have a lowest serum

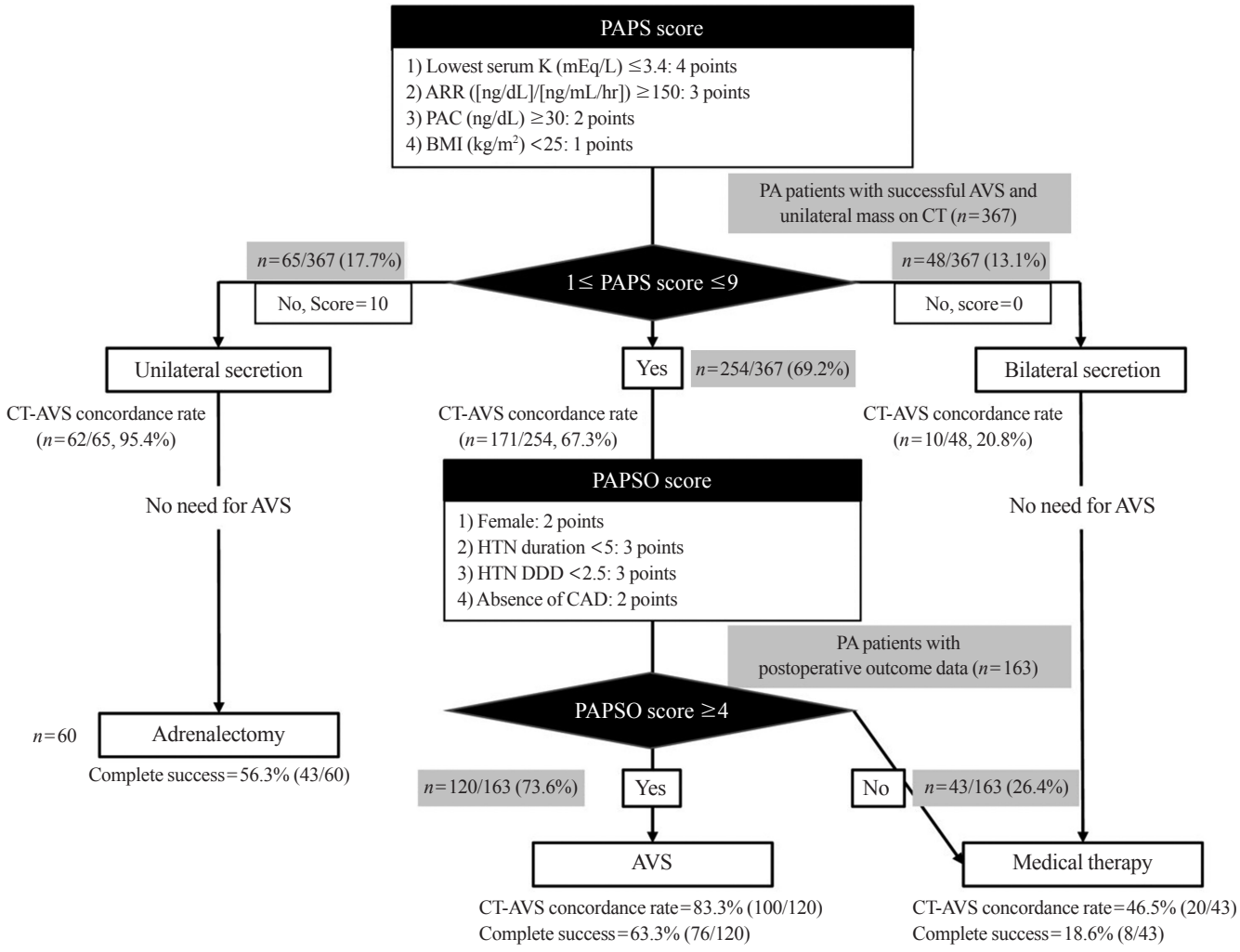


Fig. 4. Clinical decision-making algorithm for primary aldosteronism (PA) patients with unilateral adrenal nodules on computed tomography (CT). PAPS, Primary Aldosteronism Predicting Subtype; ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration; BMI, body mass index; AVS, adrenal venous sampling; PAPSO, Primary Aldosteronism Predicting Surgical Outcome score; HTN, hypertension; DDD, daily defined dose; CAD, coronary artery disease.

potassium level ≤3.4 mEq/L, ARR ≥150, PAC ≥30 ng/mL, and BMI <25 kg/m^2, AVS can be avoided, and adrenalectomy can be performed directly (17.7% in our cohort). On the other hand, if the PA patients with PAPS score of 0 do not satisfy any of the above four criteria, the probability for bilateral secretion was very high, and medical therapy can commence (13.1% in our cohort). Second, those with PAPS score 1 to 9 who satisfied any of the four criteria can be reassessed based on female sex, HTN duration <5 years, antihypertensive medications <2.5 DDD, and the absence of CAD. If they satisfied the criteria with PAPSO scores <4, postoperative clinical improvement was less likely (complete success rate, 18.6%), and medical therapy can be recommended, without AVS. However, if they meet the criteria with PAPSO scores ≥4, AVS may be required for surgery.

Validation of our clinical decision-making algorithms in the independent validation set

We further validated our algorithm in the independent validation set (*n*=53). Clinical characteristics of study subjects in the validation dataset were shown in Table 7. Compared with PA patients who satisfied the inclusion criteria of both Study A and B as the development set (*n*=239), clinical characteristics except ARR were not different between the validation set and development set. A PAPS score 10 identified concordances between CT imaging and AVS findings in 12 of 12 (sensitivity, 100.0%), whereas a PAPS score 0 identified discordance be-

Table 7. Comparison of Clinical Characteristics between the Development and the Validation Set

Variable	Validation set (*n*=53)	Development set (*n*=239)	*P* value
Age, yr	51.0 (39.0–58.0)	49.0 (43.0–57.0)	0.886
Female sex	26 (49.1)	108 (45.2)	0.720
Height, cm	164.4 (160.0–170.5)	162.1 (157.4–169.0)	0.173
Weight, kg	67.5 (57.0–75.2)	65.2 (56.5–74.1)	0.422
BMI, kg/m^2	24.6 (22.2–27.4)	24.5 (22.1–26.8)	0.741
Duration of HTN	7.0 (2.0–10.0)	6.0 (2.0–10.0)	0.636
Anti-HTN medication (DDD)	2.5 (1.3–3.4)	2.0 (1.0–3.5)	0.520
CAD	5 (9.4)	22 (9.2)	>0.999
Lowest serum potassium, mEq/L	3.0 (2.5–3.5)	3.1 (2.8–3.5)	0.173
PAC, ng/dL	42.4 (30.0–59.7)	36.5 (27.8–53.0)	0.093
PRA, ng/mL/hr	0.16 (0.10–0.30)	0.20 (0.10–0.40)	0.148
ARR	299.0 (153.0–599.0)	205.0 (98.8–383.9)	0.022
Clinical success			0.168
Complete	27 (50.9)	137 (57.3)	
Partial	24 (45.3)	80 (33.5)	
Absent	2 (3.8)	22 (9.2)	

Values are expressed as median (interquartile ranges) or number (%).
BMI, body mass index; HTN, hypertension; DDD, daily defined dose; CAD, coronary artery disease; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio.

tween CT imaging and AVS findings in 1 of 2 (50.0%) (Table 8). In PA patients with PAPS scores ranging from 1 to 9 points (*n*=35, 66.0%), a PAPSO score <4 identified absence of complete clinical success in 9 of 11 (specificity, 81.8%).

Table 8. Validation of the Clinical Decision-Making Algorithm in the Independent Cohort (*n*=53)

Score	Value	Concordance	Complete clinical success
PAPS score=10 points	16 (30.2)	12 of 12[a] (100)	11 of 16 (68.8)
PAPS score=0 points	2 (3.8)	1 of 2 (50.0)	0 of 2 (0)
PAPS score=1–9 points	35 (66.0)		16 of 35 (45.7)
PAPSO score ≥4 points	24 (45.3)		14 of 24 (58.3)
PAPSO score <4 points	11 (20.7)		2 of 11 (18.2)
Total	53 (100.0)		27 of 53 (50.9)

Values are expressed as number (%).
PAPS, Primary Aldosteronism Predicting Subtype; PAPSO, Primary Aldosteronism Predicting Surgical Outcome.
[a]Among 16 patients, adrenal venous sampling was failed in 1 patient and not done in 3 patients.

DISCUSSION

In the present study, we developed a new outcome-driven diagnostic algorithm for AVS and surgery in PA patients that incorporated which patients would benefit from the surgery. We predicted that surgery without AVS can be performed in non-obese patients with a unilateral adrenal nodule, hypokalemia, ARR ≥ 150, and PAC ≥30 ng/mL, with a sensitivity of 97.6%. For the remaining patients, the algorithm indicates that female patients with an HTN duration <5 years, antihypertensive medications <2.5 DDD, and without CAD may benefit from adrenalectomy, with a sensitivity of 94.2%.

Previous reports have suggested clinical prediction scores for circumventing invasive AVS in unilateral aldosterone excess [5-7,14,17]. Firstly, Kupers et al. [5] developed a clinical prediction score, including typical Conn's adenoma (≥8 mm on CT), hypokalemia, and glomerular hyperfiltration (eGFR >100 mL/min/1.73 m^2). This scoring system exhibited a specificity of 100%, and 30% of PA patients could undergo surgery without AVS directly. However, this score showed very low sensitivity (46% to 64%) and specificity (53% to 85%) in other validated studies [7,18,19]. Therefore, Kuper's prediction score was considered as a complementary tool for AVS. Subsequently, to improve the accuracy of clinical prediction scores, the extent of aldosterone excess, as indicated by PAC and the ARR, was incor-

porated into the scoring system in other studies [6,8,17,20,21]. However, those studies were limited by the small number of enrolled patients, data from confirmation testing, and lack of internal and external validation. The scoring system suggested by Kamemura et al. [22] was developed based on 200 patients but only applied to patients with no adrenal nodule on CT. Kobayashi et al. [23] also developed a score for bilateral PA based on 1,290 patients, which was validated in 646 patients, and reported a positive-predictive value of 93.5%. However, their scoring system can be applied to few patients, because they assumed no adrenal nodule on CT. Recently, Burrello et al. [8] combined PAC at screening and after a SIT, serum potassium level, the presence of an adrenal nodule, the largest nodule size, and unilateral adrenal nodule as predictive variables using a machine learning algorithm and an external validation set. However, PAC at screening and after SIT were collinear, and the three imaging variables were redundant. In our study, we incorporated PAC at screening instead of post-SIT PAC. We assumed a unilateral adrenal nodule because CT imaging is easily performed, and the lack of tumor or bilateral lesions on CT require AVS to decide on surgery. Furthermore, in the present study, nodule size was not a strong predictor among the 32 variables, although the nodule size differed between the two groups.

In our cohort, 57.8% (191/330) of subjects achieved HTN resolution, and 31.2% achieved HTN improvement after surgery. In previous studies, the proportion of patients with complete clinical success was 16% to 72% [10,24-27]. The discrepancy in clinical success rate can be attributed to different outcomes and study populations. In 2017, the PASO study group was defined, and the clinical outcome was standardized. They reported that 37% (range, 17 to 62) and 47% (range, 35 to 66) of patients achieved complete and partial clinical success, respectively [9]. We also followed the PASO criteria, and the clinical success rate was comparable to the PASO results.

Several potential predictors of complete clinical success have been reported. First, the ARS included the number of antihypertensive medications, HTN duration, BMI, and female sex [10]. The ARS was validated in several studies, with an AUC of 0.71 to 0.84 [11-13]. Other groups also included these variables as outcome predictors [14,15]. The number of antihypertensive medications and the duration of HTN may reflect the absence of essential HTN or vascular damage caused by long-term aldosterone excess. These variables also remained strong predictors in our final models.

Female sex was also a significant prognostic factor in our study. Although the mechanism was uncertain, estrogen may have a vasoprotective effect on salt-sensitive HTN as well as on heart and kidney diseases [28-30]. Barrett Mueller et al. [31] also demonstrated that estrogens suppress renin–angiotensin–aldosterone system activity, which attenuates the complication of aldosterone excess. High BMI may be associated with essential HTN as well as persistent HTN after adrenalectomy [32]. However, in our final model, the inclusion of the female sex abolished the effect of low BMI because female individuals may have a relatively lower BMI than male individuals.

Morisaki et al. [15] newly identified DM as a predictive factor of the postoperative outcome. The presence of DM is strongly associated with the progression of essential HTN [33]. The prevalence of DM was also significantly higher in the partial/absent clinical success group in the present study. Nonetheless, DM was not selected as a significant variable in multivariate analysis. Instead, we identified the presence of CAD as a new predictor, which implicates target organ complications of long-term aldosterone excess. In this regard, Burrello et al. [14] also included left ventricular hypertrophy and microalbuminuria as target organ damage in the PASO score. However, they did not evaluate hypertensive retinopathy, chronic kidney disease, and peripheral artery disease as possible factors.

There are several strengths in the present study. In real practice, subjects with a unilateral nodule are cases who require decision-making, including whether to perform AVS and surgery. In contrast to previous reports, we included subjects with unilateral nodules. For these patients, the question arises whether they should undergo AVS to ascertain whether they require surgery. We used a moderate sample size from two different centers. We included the ARR, without confirmatory data, which expands the usefulness of our algorithm. We emphasized the clinical decision algorithm instead of a simple scoring system. We simultaneously included the unilateral aldosterone excess and postoperative benefit for deciding on surgery in PA patients with a unilateral adrenal nodule. In terms of methodology, the machine learning algorithm, such as linear discriminant analysis or random forest analysis, was introduced in the PASO score [14]. Rather, we selected representative variables using the LASSO method, which shrinks the estimates of weaker factors toward zero and allows the strongest predictors alone to remain in the model. Additionally, we calculated the standardized potency of antihypertensive agents, expressed as DDD, instead of simply using the number of antihypertensive medications.

The study had some limitations. It was a long-term retrospective cohort study, which may increase the risk of ascertainment bias. We did not assess biochemical success because biochemi-

cal data were not available for a considerable number of patients at the postoperative follow-up visit (144 of 330, 43.6%). Clinical outcome was assessed at the 3-month postoperative follow-up; thus, complete remission can be underestimated because the resolution of HTN may take up to 6 months after surgery. Unfortunately, our algorithm was not validated in another independent cohort. To compensate for these shortcomings, we conducted the study in subjects from two centers and randomly split these into the training and testing sets, and validated the algorithm's accuracy in the testing set.

Recent research reported on the expanding spectrum of PA [34]. A considerable number of patients present with bilateral, but asymmetrical aldosterone excess. Thus, simple dichotomization into unilateral and bilateral PA does not reflect the complexity of PA. Given the clinical spectrum of PA, we envisioned an outcome-based algorithm instead of dichotomized treatment. Our algorithm may help clinicians to decide to perform AVS or to undergo surgery in clinical practice.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: J.H.K., S.H.L. Acquisition, analysis, or interpretation of data: J.H.K., C.H.A., S.J.K., K.E.L., J.W.K., H.K.Y., Y.M.L., T.Y.S., S.W.K., C.S.S., J.M.K., S.H.L. Drafting the work or revising: J.H.K. Final approval of the manuscript: J.H.K., C.H.A., S.J.K., K.E.L., J.W.K., H.K.Y., Y.M.L., T.Y.S., S.W.K., C.S.S., J.M.K., S.H.L.

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