Predictors of Clinical Success After Surgery for Primary Aldosteronism in the Japanese Nationwide Cohort

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Context: Aldosterone-producing adenomas are a curable subtype of primary aldosteronism (PA); however, hypertension persists in some patients after adrenalectomy.

Objective: To identify factors associated with, and develop prediction models for, blood pressure (BP) normalization or improvement after adrenalectomy.

Design: Retrospective analysis of patients treated between 2006 and 2018, with a 6-month follow-up.

Setting: A nationwide, 29-center Japanese registry encompassing 15 university hospitals and 14 city hospitals.

Patients: We categorized 574 participants in the Japan Primary Aldosteronism Study, who were diagnosed with PA and underwent adrenalectomy, as BP normalized or improved, on the basis of their presentations at 6 months postsurgery.

Main Outcome Measure: The rate of complete, partial, and absent clinical success. Predictive factors related to BP outcomes after PA surgery were also evaluated.

Abbreviations: APA, aldosterone-producing adenoma; AVS, adrenal vein sampling; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; JPAS, Japan Primary Aldosteronism Study; LR, lateralized ratio; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PASO, Primary Aldosteronism Surgical Outcome; ROC, receiver operating characteristic; SBP, systolic blood pressure.

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Results: Complete clinical success was achieved in 32.6% and partial clinical success was achieved in 53.0% of the patients at 6 months postsurgery. The following five variables were independent predictors for BP normalization: ≤7 years of hypertension, body mass index ≤25 kg/m^2, no more than one antihypertensive medication, absence of medical history of diabetes, and female sex. The area under the receiver operator characteristic curve was 0.797 in the BP normalization model.

Conclusion: We established models that predicted postoperative BP normalization in patients with PA. These should be useful for shared decision-making regarding adrenalectomy for PA.

Freeform/Key Words: primary aldosteronism, surgery, hypertension, predictive model, cure, improvement

Primary aldosteronism (PA) afflicts 6% to 15% of all hypertensive patients [1–5] and is the most common cause of secondary hypertension. Owing to this PA epidemic, we recently established the Japan Primary Aldosteronism Study (JPAS), which includes a nationwide, multicenter PA registry as a research tool [6–13], and is dedicated to improving the clinical management of patients with PA.

Aldosterone-producing adenomas (APAs) and bilateral (idiopathic) adrenal hyperplasia are the major subtypes of PA. APAs can be cured by unilateral adrenalectomy [14, 15]; nevertheless, approximately half of patients with APA experience persistent hypertension after surgery [16, 17]. In a recent meta-analysis [18], the overall rate of hypertension resolution after PA surgery was 52%, although the rates varied from 24% to 86%. The Primary Aldosteronism Surgical Outcome (PASO) study [19] also found that 37% of subjects achieved resolution of their hypertension and an additional 47% had improved blood pressure (BP) based on consensus definitions of clinical outcomes among participating countries. The rate of hypertension resolution after PA surgery is not sufficiently high; therefore, it is critical for clinicians and patients to be aware of markers that predict more favorable clinical outcomes.

Previous studies have proposed several models for predicting the resolution of hypertension after PA surgery. Zarnegar *et al.* [20] devised the Aldosteronoma Resolution Score, which is a scoring system encompassing four predictive factors: fewer antihypertensive medications (no more than two), lower body mass index (BMI; ≤25 kg/m^2), fewer years of hypertension (no more than 6 years), and female sex. This model was established on the basis of analyzing a database of patients with PA in the United States and subsequently proved useful for Japanese patients with PA as well [21, 22]. Moreover, Utsumi *et al.* [23] proposed a novel nomogram comprising four independent predictors: duration of hypertension, number of antihypertensive drug classes, age, and sex. This scoring model was established on the basis of data from a single-center study of Japanese patients with PA.

In our study, we first aimed to develop a prediction model for postoperative hypertension resolution by using nationwide cohort data of Japanese patients with PA. Importantly, although several prediction models for the postoperative cure of hypertension have been reported, these sometimes mislead patients into foregoing surgery if the BP is not predicted to be resolved. However, even if the hypertension resolution prediction score is low, most patients who undergo surgery may still benefit from an improvement in their hypertension, even if normalization is not achieved. Therefore, we also aimed to identify predictive factors for absence of hypertension improvement after surgery for PA.

1. Methods

A. Study Design and Patients

This investigation was conducted as a part of the JPAS. A nationwide, 29-center PA registry was established in Japan that encompassed 15 university hospitals and 14 city hospitals. The

JPAS included patients >20 years of age who were diagnosed with PA between January 2006 and October 2018 and who underwent adrenal vein sampling (AVS). Patients who were diagnosed with PA after adrenalectomy were also enrolled even if they did not undergo AVS. The number of patients with PA who skipped AVS was only 10 (1.7%) of the total number of patients in this study.

Patients eligible for the current study were those who were diagnosed with unilateral PA, underwent adrenalectomy, and were followed at 6 months postsurgery. The baseline clinical characteristics, biochemical findings, results of confirmatory testing, AVS results, surgical findings, postoperative outcomes, and related follow-up data were electronically collected using the WEB registry system. System construction, data security, and maintenance of the registered data were outsourced to EPS Corporation (Tokyo, Japan). The study protocol was approved by the ethics committee of each participating center.

B. Diagnosis of PA

All patients were diagnosed with PA according to the guidelines of the Japan Endocrine Society [24] and the Japan Society of Hypertension [25]. PA was diagnosed on the basis of a ratio of plasma aldosterone concentration (PAC; measured in picograms per milliliter) to plasma renin activity (PRA; measured in nanograms per milliliter per hour) of >200, or on a PAC-to-active renin concentration (measured in picograms per milliliter) ratio of >40, and at least one positive result from a confirmatory test such as the captopril challenge, saline infusion, furosemide upright, or oral salt-loading test. Antihypertensive medications were usually changed to calcium channel blockers or α-adrenergic blockers, as appropriate, until the final diagnosis was made. Hypokalemia was considered present if the serum potassium level was ≤3.5 mEq/L or when a patient was taking a potassium supplement. Oral potassium was administered if hypokalemia was present.

The diagnosis of the PA subtype was determined based on AVS results with ACTH (cosyntropin) stimulation, the procedures for which were previously described [26]. Adrenal vein cannulation was considered successful if the selectivity index was >5 [27]; the selectivity index was defined as the ratio of cortisol concentration in the adrenal vein to that in the inferior vena cava. Unilateral hyperaldosteronism on AVS was defined as a lateralized ratio (LR) >4 [27]. The LR was calculated by dividing the aldosterone-to-cortisol ratio on the dominant side by that on the opposite side. AVS data after ACTH stimulation were used for analysis in the current study.

C. Definition of Clinical Outcomes

After adrenalectomy, patients were categorized as having achieved complete clinical success if their systolic BP (SBP) was <140 mm Hg and diastolic BP (DBP) was <90 mm Hg with no antihypertensive medications at 6 months postsurgery. Patients were categorized as having achieved partial clinical success if the number or dose, which was evaluated by Defined Daily Dose, of antihypertensive medications was reduced after surgery, or if their SBP decreased by ≥20 mm Hg or their DBP decreased by ≥10 mm Hg at 6 months postsurgery with no change in the number of antihypertensive medications. The rest of clinical outcome was categorized as absent clinical success. These BP outcomes were defined according to the previously described worldwide consensus used in the PASO study [19].

D. Data Collection

We collected the following data: age, sex, family history of hypertension, history of diabetes mellitus and dyslipidemia, smoking habits, drinking habits, SBP, DBP, cardiothoracic ratio, echocardiography of the left ventricular hypertrophy (Cornell product), duration of hypertension, number of antihypertensive medications, BMI, and proteinuria. Furthermore, blood test results were collected that included levels of Na^+, K^+, CL^-, serum creatinine, uric acid, triglycerides, and high- and low-density lipoprotein cholesterol; estimated glomerular filtration rate (eGFR); HbA1c, based on the National Glycohemoglobin Standardization Program; PAC; PRA; aldosterone-to-renin ratio; LR after ACTH stimulation on AVS; and contralateral ratio after ACTH stimulation on AVS. PAC was measured by commercial RIA kits (SPAC-S Aldosterone kit; Fuji Rebio, Tokyo, Japan) in all centers. PRA was measured by commercial RIA kits (FR RIA kit, Fuji Rebio; PRA RIA kit, Yamasa, Choshi, Japan) or enzyme immunoassay (PRA EIA kit, Yamasa). Plasma active renin concentration was measured by immunoradiometric assay (Renin IRMA-FR; Fuji Rebio). The active renin concentration value was used for analysis by converting to PRA. The eGFR was measured using an abbreviated equation, as follows:

$$\text{eGFR}\left(\text{mL} \times \text{min}^{-1} \times 1.73\text{m}^{-2}\right) = 186 \times (\text{creatinine})^{-1.094} \times (\text{age})^{-0.287} \times (0.742 \text{ for women})$$

E. Statistical Analyses

We retrospectively surveyed the clinical variables associated with postoperative resolution and improvement of hypertension. SPSS software, version 25 (IBM, Armonk, NY) was used for each analysis. One-way ANOVA with *post hoc* Tukey analysis was used for quantitative normally distributed variables. Kruskal-Wallis or Mann-Whitney-U test was used for quantitative nonnormally distributed variables, and the χ^2 test or Fisher exact test was used for categorical variables.

Next, we subjected variables that were linked to postoperative BP normalization on univariate analysis to multivariate logistic regression analysis. Variables independently associated with resolution of hypertension ($P < 0.05$) were then ranked according to the magnitudes of their ORs. Only factors that were easily accessible at clinical presentation were chosen to create a highly versatile model. Next, we assigned these predictors appropriate scores on the basis of the β values and ORs, and generated receiver operating characteristic (ROC) curves to assess the accuracy of the model. The univariate analysis results are described as median (range) or mean $\pm$ SD, as appropriate. Statistical significance was defined at the level of $P < 0.05$.

2. Results

Among a total of 919 patients who underwent adrenalectomy for unilateral PA, 574 patients were eligible for this study. BP was postoperatively normalized in 187 patients (32.6%) and improved in 304 patients (53.0%; Table 1) at 6 months postsurgery.

We considered the correction of hypokalemia and normalization of aldosterone-to-renin ratio as postoperative biochemical cure, on the basis of the recent international PASO consensus [19]. Complete biochemical cure was achieved in 88.2% of the patients at the 6-month time point. Normokalemia was achieved in 99.1% of the patients, and ARR normalization was achieved in 89.0%.

Table 1 lists the results of preoperative variables that were candidates for being associated with postoperative resolution and improvement of hypertension. The following variables were significantly different among three groups of postoperative clinical outcomes and were potentially linked to BP normalization: sex, medical history of diabetes and dyslipidemia, drinking, smoking, age, duration of hypertension, the number of antihypertensive medications, BMI, preoperative SBP under antihypertensive medications, cardiothoracic ratio on chest radiography, proteinuria, creatinine, eGFR, uric acid, serum sodium levels, HbA1c (National Glycohemoglobin Standardization Program), triglyceride levels, high-density lipoprotein cholesterol level, and lateralized ratio and contralateral ratio of AVS without ACTH administration. On the contrary, the following variables were potentially associated with absent clinical success: the number of antihypertensive medications, preoperative SBP under antihypertensive medications, low-density lipoprotein cholesterol level, preoperative PAC, and lateralized ratio and contralateral ratio of AVS with and without ACTH administration.

The variables that were associated with postoperative BP outcomes were subjected to multivariate logistic regression analysis. Continuous variables were dichotomized and

Table 1. Univariate Analyses of Candidate Predictor Variables in the JPAS Database

		Clinical Success				Pairwise Comparison *P* Value		
Variable[a]	Total Cohort	Complete	Partial	Absent	Overall *P* Value	C vs P	C vs A	P vs A
Clinical outcome, no. (%)	574 (100)	187 (32.6)	304 (53.0)	83 (14.5)	NA	NA	NA	NA
Sex, female/male	291/283	130/57	121/183	40/43	<0.001	<0.001	0.001	0.169
Family history of hypertension, Y/N (n = 523)	334/189	105/69	188/88	41/32	0.144	NA	NA	NA
Diabetes mellitus, Y/N	86/488	9/178	65/239	12/71	<0.001	<0.001	0.006	0.161
Dyslipidemia, Y/N	145/429	24/163	97/207	24/59	<0.001	<0.001	0.001	0.602
Current or past drinking, Y/N (n = 530)	293/237	79/95	174/108	40/34	0.010	0.003	0.260	0.248
Current or past smoking, Y/N (n = 535)	202/333	48/130	128/155	26/48	0.001	<0.001	0.082	0.131
Potassium supplementation, Y/N (n = 572)	333/239	113/74	179/123	41/42	0.205	NA	NA	NA
Age, mean ± SD, y (n = 573)	51.4 ± 11.7	46.3 ± 11.3	53.7 ± 11.2	54.6 ± 11.1	<0.001	<0.001	<0.001	0.513
Duration of hypertension, median (IQR), y (n = 536)	8.0 (3.0–15.0)	4.0 (1.0–8.0)	10.0 (6.0–19.3)	8.5 (4.0–15.3)	<0.001	<0.001	<0.001	0.073
Preoperative no. of antihypertensive medications, median (IQR)	1.42 (0–5)	1.01 (0–2)	1.80 (0–5)	0.96 (0–3)	<0.001	<0.001	0.456	<0.001
BMI, mean ± SD, kg/m^2 (n = 573)	24.1 ± 4.1	22.6 ± 3.3	24.9 ± 4.4	24.8 ± 3.9	<0.001	<0.001	<0.001	0.803
SBP, mean ± SD, mm Hg (n = 568)	142.5 ± 19.1	136.7 ± 17.9	146.3 ± 19.6	141.4 ± 17.0	<0.001	<0.001	0.044	0.040
DBP, mean ± SD, mm Hg (n = 568)	87.8 ± 12.6	86.8 ± 11.5	88.7 ± 13.0	86.7 ± 13.4	0.216	NA	NA	NA
CTR, mean ± SD, % (n = 519)	48.1 ± 4.9	46.4 ± 4.9	49.0 ± 4.6	48.3 ± 5.2	<0.001	<0.001	0.007	0.199
LVH, mean ± SD, Cornell product (n = 302)	2056.7 ± 844.2	1912.2 ± 829.8	2133.8 ± 854.8	2089.8 ± 815.2	0.121	NA	NA	NA
Proteinuria (1–5),[b] median (IQR) (n = 529)	1.67 (1–5)	1.40 (1–5)	1.84 (1–5)	1.62 (1–5)	<0.001	<0.001	0.054	0.211
Creatinine, mean ± SD, mg/dL (n = 569)	0.78 ± 0.42	0.66 ± 0.17	0.86 ± 0.53	0.77 ± 0.20	<0.001	<0.001	<0.001	0.119
eGFR, mean ± SD, mL/min/1.73m^2 (n = 569)	79.5 ± 23.5	88.8 ± 23.2	74.8 ± 23.4	76.1 ± 18.0	<0.001	<0.001	<0.001	0.576
Uric acid, mean ± SD, mg/dL (n = 529)	5.33 ± 1.60	4.75 ± 1.70	5.56 ± 1.49	5.71 ± 1.42	<0.001	<0.001	<0.001	0.441
Na^+, mean ± SD, mEq/L (n = 571)	142.8 ± 2.2	142.4 ± 2.2	143.0 ± 2.3	143.3 ± 2.1	0.003	0.004	0.003	0.337
K^+, mean ± SD, mEq/L (n = 431)	2.84 ± 0.45	2.86 ± 0.45	2.81 ± 0.45	2.92 ± 0.41	0.173	NA	NA	NA
Cl^+, mean ± SD, mEq/L (n = 569)	103.9 ± 7.9	103.9 ± 7.9	104.0 ± 6.6	103.7 ± 11.4	0.954	NA	NA	NA
HbA1c (NGSP), mean ± SD, % (n = 468)	5.54 ± 0.77	5.34 ± 0.65	5.65 ± 0.81	5.52 ± 0.74	0.001	<0.001	0.084	0.222
TG, mean ± SD, mg/dL (n = 512)	113.2 ± 68.7	89.1 ± 48.7	122.1 ± 70.5	132.4 ± 84.2	<0.001	<0.001	<0.001	0.287
HDL, mean ± SD, mg/dL (n = 511)	57.5 ± 16.7	62.4 ± 17.2	55.3 ± 16.6	54.5 ± 13.3	<0.001	<0.001	<0.001	0.651
LDL, mg/dL (n = 516)	112.1 ± 28.0	110.7 ± 24.4	110.3 ± 28.6	121.9 ± 31.4	0.005	0.877	0.007	0.003
PAC, median (IQR), pg/mL (n = 571)	310.0 (196.0–464.5)	310.0 (201.5–452.3)	325.0 (201.0–493.0)	250.0 (159.0–399.0)	0.025	0.584	0.024	0.008
PRA, median (IQR), ng/mL/h (n = 565)	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.2 (0.2–0.4)	0.732	NA	NA	NA
ARR, median (IQR), PRA pg/mL per ng/mL/h (n = 565)	1140.0 (600.0–2330.0)	1323.3 (650.8–2313.8)	1117.5 (565.1–2499.4)	760.0 (475.7–2193.3)	0.084	NA	NA	NA
LR, median (IQR) (n = 455)	13.3 (4.4–32.3)	18.7 (6.7–39.1)	12.7 (4.4–29.0)	5.8 (2.2–31.1)	0.003	0.036	0.001	0.038
CR, median (IQR) (n = 465)	0.5 (0.3–0.9)	0.4 (0.3–0.7)	0.5 (0.3–0.9)	0.7 (0.3–1.5)	0.001	0.014	0.001	0.035
LR after ACTH, median (IQR) (n = 522)	10.6 (4.7–24.2)	11.4 (4.5–29.6)	11.7 (5.0–24.3)	6.1 (3.5–13.2)	0.003	0.569	0.003	0.001
CR after ACTH, median (IQR) (n = 525)	0.4 (0.2–0.7)	0.3 (0.2–0.7)	0.3 (0.2–0.7)	0.5 (0.3–1.2)	0.005	0.999	0.004	0.002

Abbreviations: ARR, aldosterone to renin ratio; CR, contralateral ratio; CTR, cardiothoracic ratio; HDL, high-density lipoprotein cholesterol; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NA, not applicable; NGSP, National Glycohemoglobin Standardization Program; TG, triglycerides.

[a]Where the number of patients on which the data were calculated was less than the total cohort, the number is indicated in parentheses.

[b]Proteinuria: 1: negative; 2: ±; 3, +; 4, ++;, 5, +++.

optimum cutoffs for dichotomization were selected by analyzing the ROC curve for each variable. The following five variables were found to be independent predictors of hypertension resolution: duration of hypertension ≤7 years, BMI ≤25 kg/m^2, no more than one antihypertensive medication, absence of diabetes mellitus, and female sex (Table 2). We assigned these variables graded scores on the basis of their β values and developed prediction models for postoperative outcomes (Table 3), and we subsequently generated ROC curves for these models with calculated areas under the curve to assess the accuracy of their predictive scores. The area under the curve value was 0.797 (95% CI, 0.759 to 0.836) in the hypertension resolution model (Fig. 1). The ratio of patients with BP normalization was none of 12 patients (0%) in the group with a hypertension resolution score of 0, and 64 of 90 patients (71.1%) in the group with a hypertension resolution score of 6. The proportion of patients who achieved hypertension resolution increased as the score increased [Fig. 2(A) and 2(B)].

3. Discussion

Although unilateral PA can be cured by adrenalectomy, BP outcomes, including hypertension resolution and hypertension improvement, are sometimes dissociated from the biochemical outcomes of PA surgery. In our JPAS cohort, 32.6% of the patients achieved hypertension resolution and 53.0% achieved improvement; the rate of complete clinical success was lower than that of biochemical cure after surgery. The dissociation of biochemical and clinical outcomes sometimes discourages patients from opting for surgical treatment of PA; therefore, a prediction model for postoperative BP outcomes is clinically valuable, and several such models have been developed and reported.

Zarneger *et al.* [20] established the Aldosteronoma Resolution Score to predict the resolution of hypertension after adrenalectomy, and Utsumi *et al.* [23] developed a nomogram for the same reason. Both models consider a short hypertension duration, fewer antihypertensive medications, and female sex as important predictors for favorable outcomes. Notably, our own predictive model is most similar to that of Zarneger *et al.* model, because it also found that the duration of hypertension, BMI, number of antihypertensive medications, and female sex are the prevailing predictive factors related to curing hypertension after adrenalectomy for PA. On the other hand, we found that the absence of diabetes mellitus is a predictive factor related to BP normalization. Additional studies should be performed to determine whether diabetes mellitus is a factor that is specific to Japanese/Asian people or has wider applicability.

In the meantime, fewer studies have investigated the factors that predict the absence of BP improvement after adrenalectomy. Williams *et al.* [19] reported that male sex, preoperative SBP and DBP, and the number of antihypertensive medications were determinants of absent clinical success. Some predictors are also similar to ours as related to absent clinical success. The reproducibility of these data across multiple studies strongly supports their reliability.

Previous studies have found that the presence of essential hypertension affects the persistence of such hypertension after adrenalectomy [20, 28]. Metabolic abnormalities such as high BMI [29] and the presence of diabetes [30–32] are strongly associated with progression of essential hypertension; as such, our findings that low BMI and the absence of

Table 2. Results of Multivariate Logistic Regression Analysis of the Major Predictors of BP Normalization

Major Predictor of BP Normalization	β	OR	*P* Value	95% CI
Years of hypertension ≤7	1.507	4.513	<0.001	2.924 to 6.966
Absence of diabetes mellitus	1.041	2.832	0.013	1.249 to 6.421
≤1 Antihypertensive medication	1.027	2.793	<0.001	1.706 to 4.574
Female sex	0.781	2.184	<0.001	1.407 to 3.389
BMI ≤25 kg/m^2	0.768	2.156	0.002	1.327 to 3.502

Table 3. Prediction Model: BP Normalization

Major Predictor of BP Normalization	Points	
	Present	Absent
Years of hypertension ≤7	2	0
Absence of diabetes mellitus	1	0
≤1 Antihypertensive medication	1	0
Female sex	1	0
BMI ≤ 25 kg/m^2	1	0

diabetes are significant predictors of hypertension resolution are consistent with these notions. Female sex has proven to be relevant to hypertension resolution and improvement, although the underlying mechanism for this association remains unclear. Previous studies *in vivo*, including human clinical studies, showed that female sex hormones have a protective effect on salt-sensitive BP [33] as well as on cardiac [34, 35] and renal disease [36] outcomes. Other *in vitro* studies revealed that estrogens are potentially vasoprotective, because they suppress renin-angiotensin-aldosterone system activity [37, 38].

Our study has some limitations. This is a long-term retrospective cohort study, which could increase the risk of bias. The Japanese PA guideline was issued in 2009 and has not been revised until now; therefore, most of the study period was covered under the same guideline. Because advanced medical institutions tend to accept patients with intractable conditions, the rates of hypertension resolution and improvement might be underestimated in this study. Moreover, most participants in our study were Japanese, and our models were not validated for populations of other races. In addition, subtle difference of PA guideline between in Japan and in the United States might potentially affect the results of this study. Hence, the quality of our model should be additionally validated in future studies.

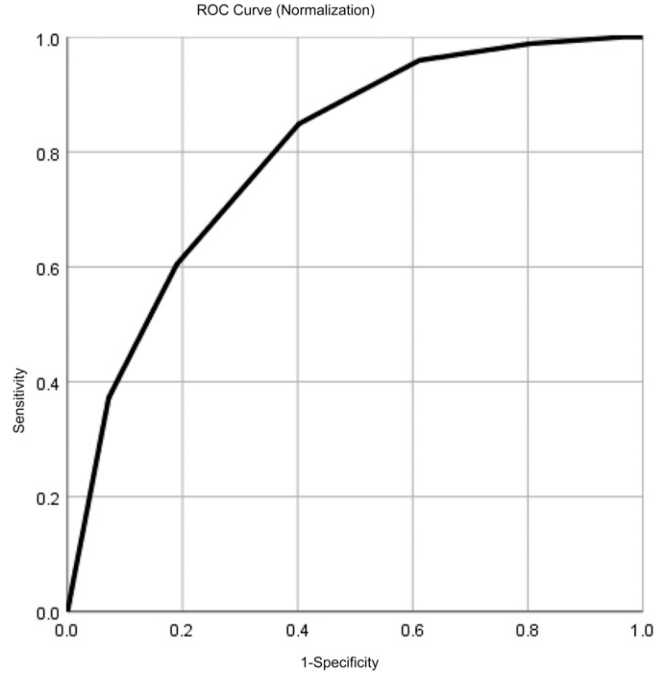

Figure 1. The ROC curve of the variables correlated with BP normalization (duration of hypertension ≤7 y, BMI ≤ 25 kg/m^2, no more than one antihypertensive medication, absence of diabetes mellitus, and female sex). The values of the area under the curve is 0.797 (95% CI, 0.759 to 0.836).

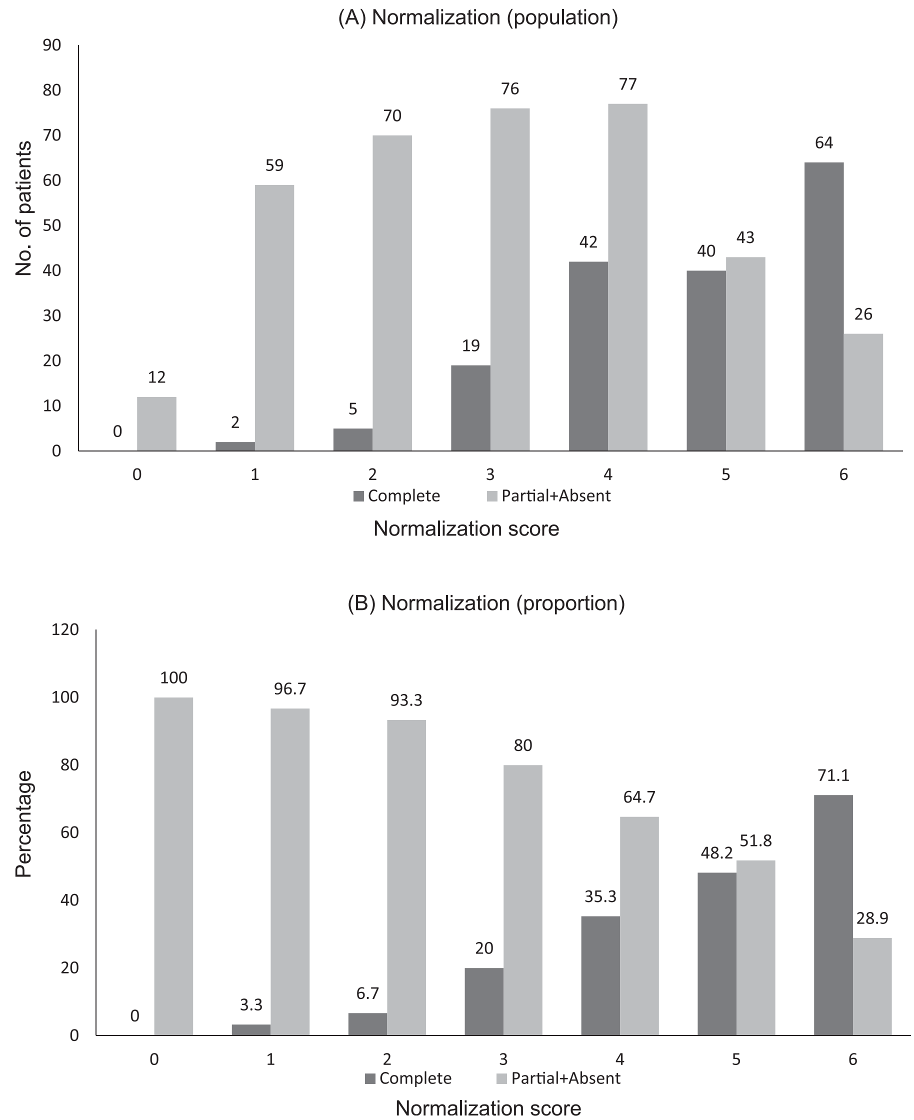

Figure 2. Performance of the normalization scores as indicated by the (A) number of patients and (B) ratio of patients. The populations of patients with normalization are represented for each score; the proportions of patients experiencing normalization increased with greater predictive scores.

In contrast, our prediction models had a number of advantages. They were developed on the basis of a larger patient database than in past studies of this kind. Moreover, our prediction models are practical because they are based on easily obtained clinical variables. As such, they have the potential to help patients diagnosed with unilateral PA with their decision-making regarding surgical intervention and pursuing their optimal treatment options.

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