ORIGINAL ARTICLE

Body mass index and contralateral ratio predict outcome following unilateral adrenalectomy in primary aldosteronism

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The effect of unilateral adrenalectomy on blood pressure (BP) outcome in primary aldosteronism (PA) is diverse. Therefore, we sought to investigate the preoperative factors contributing to postoperative BP outcome. Data for 96 PA patients who underwent unilateral adrenalectomy at our institution from January 2000 to February 2015 were retrospectively collected. Based on postoperative BP after a 12-month follow-up period, the patients were categorized into two groups: cured (C) ($< 140/90$ mm Hg with no antihypertensive drug) and not cured (NC) (if not normotensive). Patient demographics, blood and urine data, data of loading tests and adrenal vein sampling were evaluated. In all, 46 patients were categorized as C and 50 patients as NC. There were significantly more males in the NC group. Age, body mass index (BMI), number of antihypertensive drugs prescribed, serum uric acid concentration and contralateral ratio (CR) after adrenocorticotropic hormone stimulation were significantly higher in the NC group. In the multivariate model, BMI and CR significantly correlated with resolution outcome. The optimal cutoff values were 23.3 kg m^{-2} for BMI and 0.5 for CR, and when both parameters were used as predictors, the most optimal cutoff values for BMI and CR were 25.2 kg m^{-2} and 0.1, respectively. BMI and CR significantly correlated with BP outcome after adrenalectomy. To our knowledge, this is the first report to show that in addition to BMI, CR is a factor in postoperative BP outcome and to determine the optimal cutoff values of BMI and CR and calculate their sensitivities and specificities.
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INTRODUCTION

Primary aldosteronism (PA) is a state in which inappropriate secretion of the mineralocorticoid aldosterone occurs from one or both adrenal glands. Although the true prevalence of PA is difficult to determine, it is a common form of secondary hypertension and has been reported to account for 1 to 10% of hypertensive patients.[1,2] It is associated with cardiovascular,[3–5] renal[6–8] and metabolic[9–11] complications, independent of the organ damage caused by an increase in blood pressure (BP).

Therapeutic options for PA are medical management and surgery. Medical treatment is preferred when the disease is determined as bilateral or when surgery is contraindicated. In cases of unilateral disease, unilateral adrenalectomy is now recognized as the standard therapy. However, the effect of unilateral adrenalectomy on BP outcome in PA is thought to be diverse.[12] To predict the postoperative resolution of hypertension, several studies have evaluated the preoperative characteristics of PA patients.[13,14] Factors that have been associated with BP outcome include age, sex, body weight, hypokalemia, duration of hypertension, number of antihypertensive drugs, preoperative response to aldosterone and TT genotype of the aldosterone synthase gene.[15–20] Aldosteronoma Resolution Score,

which includes (1) $\leqslant 2$ antihypertensive medications, (2) body mass index (BMI) $\leqslant 25$ kg m^{-2}, (3) duration of hypertension $\leqslant 6$ years and (4) female sex, has been reported to accurately identify individuals at high likelihood of cure in terms of BP reduction after adrenalectomy.[13,21] However, varying measures of disease cure are included in the primary outcomes of these studies.

It has also been reported that treatment with a mineralocorticoid receptor blocker has an effect equivalent to that of surgical treatment in patients with unilateral disease. Prospective studies indicate that mineralocorticoid receptor blockers have therapeutic values comparable to adrenalectomy in terms of correcting metabolic abnormalities[22,23] and reducing the risk of cardiovascular diseases[3,4] and renal disease[22–24] progression. This evidence makes it difficult to select appropriate treatment in PA patients with unilateral disease. However, there is no doubt that the discontinuation of antihypertensive drugs for a lifetime will significantly improve one's quality of life.

The aim of this study was to retrospectively investigate the preoperative factors contributing to postoperative BP outcome and to determine specific cutoff values for each continuous variable. To our knowledge, this is the first report to show that in addition to BMI, contralateral ratio (CR) is a factor in postoperative BP outcome by

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analyzing the data from adrenal vein sampling (AVS) and to determine the optimal cutoff values of BMI and CR and calculate their sensitivities and specificities.

METHODS

Study population and design
This study is a retrospective review of prospectively collected data from 96 patients with PA who had undergone laparoscopic unilateral adrenalectomy at Tokyo Women's Medical University Hospital from January 2000 to February 2015. Adrenalectomy was recommended when the lateralized ratio (LR) after adrenocorticotropic hormone (ACTH) stimulation was over 2.6. The study was approved by the ethical review committee of Tokyo Women's Medical University Hospital.

Patient characteristics were obtained from medical records. Information including age, gender, BMI, presence of complications of diabetes mellitus and dyslipidemia, past history of cerebrovascular disease, smoking and drinking habits, family history of hypertension, number and type of prescribed antihypertensive agents and presence of K^+ supplementation was obtained at their first visit. Serum K^+, creatinine, uric acid (UA), plasma aldosterone concentration (PAC) and plasma renin activity from venous blood samples were measured with the patient in a sitting position (for at least 15 min) at their first admission, after they had been under antihypertensive treatment with only calcium channel blockers and an α-blocker for >3 weeks. The estimated glomerular filtration rate (eGFR) and aldosterone/renin ratio were calculated. Urinary aldosterone excretion and Na^+/K^+ ratio were evaluated in overnight urine samples during admission. The necessity for mineralocorticoid receptor blocker medication (after diagnosis) until the operation was also evaluated. Information regarding tumor diameter (maximum diameter on computed tomography), pathologic diagnosis and postoperative medications and BP was collected.

Loading tests
Three loading tests for the diagnosis of PA—the captopril challenge test, the furosemide upright test and the saline loading test—were performed. The aldosterone/renin ratio during the captopril challenge test, peak plasma renin activity level during the furosemide upright test and trough PAC during the saline loading test were evaluated. To detect the presence of the autonomous secretion of cortisol along with aldosterone, we also performed an overnight 1 mg dexamethasone suppression test.

Adrenal vein sampling
AVS was performed as described previously.[25] Only calcium channel blockers and an α-blocker were used as antihypertensive medications. Successful cannulation of the adrenal vein was confirmed by adequate adrenal vein to peripheral vein cortisol ratios (>5.0 after ACTH stimulation). Aldosterone to cortisol (A/F) ratios were then calculated to correct PACs for dilution from nonadrenal blood. We also evaluated LR ($A/F_{dominant}$:$A/F_{nondominant}$) and CR ($A/F_{nondominant}$:$A/F_{peripheral}$) both before and after ACTH stimulation. The result was considered to demonstrate contralateral suppression (CS) if CR after ACTH stimulation was <1.0.

Outcomes
Office BP was obtained at regular postoperative follow-up with the patient in a sitting position after resting for at least 5 min. The first reading was used in this study. Hypertension was defined as 'cured (C)' if patients remained normotensive (BP <140/90 mm Hg) without taking any antihypertensive agents and as 'not cured (NC)' if not normotensive after a 12-month follow-up period.

Statistics
All statistical analyses were performed with JMP Pro 12.1.0 software (SAS Institute, Cary, NC, USA). Patient characteristics of each group were compared and analyzed using Student's t-test for continuous data, and Pearson's χ^2 test was used for categorical data. A P-value of <0.05 was considered statistically significant. Multivariate logistic regression modeling was performed on variables demonstrating statistical significance in the univariate modeling.

To review the sensitivity and specificity of preoperative variables that showed statistical significance in the multivariate modeling, we constructed receiver operating characteristic (ROC) analyses.

RESULTS
From January 2000 to February 2015, a total of 96 PA patients underwent laparoscopic unilateral adrenalectomies at our institution. All of the patients underwent successful AVS. LR was over 2.6 in 83 patients. Although 13 patients did not meet this criterion, 8 of them underwent adrenalectomy because their AVS results revealed contralateral suppression (CR <1). The remaining 5 patients met neither criterion, but the patients desired to have surgery (tumor resection). Tables 1 and 2 show the age, gender distribution, BMI, number of type of prescribed antihypertensive medications, serum K^+, UA, eGFR, PAC, plasma renin activity and aldosterone/renin ratio at rest, the results of the loading tests and the AVS data for the entire population.

Patient characteristics by cured vs. not cured
In all, 46 patients were categorized as C and 50 as NC, according to the method mentioned above (Table 1). Autonomous cortisol secretion was observed in 5 patients, all of them in the NC group. Histopathological diagnoses were cortical adenoma, nodular hyperplasia or cortical adenoma with hyperplasia. There were no cases of microadenoma. A significant difference was seen in age at surgery between the two groups (47 ± 12 vs. 55 ± 10 years old, $P = 0.0009$). There were significantly more males in the NC group than in the C group. BMI was significantly higher in the NC group (21.8 ± 3.4 (30.3–16.4) vs. 24.6 ± 3.0 (32.2–18.6) kg m^{-2}, $P < 0.0001$). More types of antihypertensive drugs were prescribed in the NC group before surgery (1.1 ± 0.7 vs. 1.5 ± 1.0, $P = 0.0338$). Preoperative UA also significantly differed between the two groups (4.4 ± 1.1 vs. 5.5 ± 1.4 mg dl^{-1}, $P < 0.0001$). We constructed a multivariate logistic regression model that included gender and UA as the only variables and revealed that UA ($\beta = -0.609$, $P = 0.0034$) was an independent predictive factor, but gender ($\beta = -0.370$, $P = 0.1360$) was not.

Patients' diagnostic characteristics by cured and not cured
Diagnostic measures are compared in Table 2. All patients met the diagnostic criteria for three loading tests in the C group, whereas in the NC group two patients did not meet the diagnostic criteria for the captopril challenge test, another patient did not meet the criteria for the captopril challenge test and another patient did not meet the criteria for the saline loading test. The results of the three loading tests did not differ between the two groups. In the AVS results, there were no significant differences in PAC levels for the affected side, LR or CR, before ACTH stimulation. However, after ACTH stimulation, CR was significantly lower (0.4 ± 0.2 (1.1–0.1) vs. 0.7 ± 0.6 (2.6–0.1), $P = 0.0003$), and the percentage of patients with CS was higher (97.6 vs. 76.2%, $P = 0.0041$) in the C group. There was no significant difference in LR after ACTH stimulation between the two groups (13.5 ± 12.1 (56.1–1.2) vs. 12.9 ± 13.8 (71.6–1.1), $P = 0.8576$).

Results of multivariate logistic regression analysis
We constructed a multivariate logistic regression model including all preoperative variables that demonstrated statistical significance between the C and NC groups for the BP outcome following unilateral adrenalectomy (Table 3). BMI ($P = 0.0473$) and CR ($P = 0.0199$) significantly correlated with resolution outcome; however, gender, age, numbers of types of preoperatively prescribed antihypertensive medications and UA did not.

ROC characteristic analysis of BMI and CR

Using BMI and CR, we constructed ROC curves to evaluate their utility as predictors of postoperative outcome (Figure 1). When BMI was used as a predictor, the area under the ROC curve was 73.4% and the highest combination of sensitivity and specificity was obtained at a BMI of 23.2 kg m^{-2} (sensitivity, 67.4%; specificity, 74.0%). When CR was evaluated, the area under the ROC curve was 64.7% and the highest combination of sensitivity and specificity was obtained at a CR of 0.5 (sensitivity, 82.9%; specificity, 42.9%). The area under the ROC curve reached up to 79.4% when both BMI and CR were used as predictors, and the optimal cutoff values for BMI and CR were 25.2 kg m^{-2} and 0.1, respectively (sensitivity, 73.2%; specificity, 76.2%).

DISCUSSION

The present study showed that in the univariate model, age, BMI, number of antihypertensive drugs prescribed, uric acid and CR after adrenocorticotropic hormone stimulation were significantly higher in the NC group. BMI and CR significantly correlated with BP outcome in the multivariate model. The optimal cutoff values were 23.2 kg m^{-2} for BMI and 0.5 for CR and when both parameters were used as predictors, the optimal cutoff values for BMI and CR were 25.2 kg m^{-2} and 0.1, respectively.

Characteristics such as older age,[18,26–32] male sex,[26,33] presence of family history of hypertension,[27,30] longer duration of hypertension[27,30,34] and renal dysfunction[35] have previously been reported to correlate with BP outcome following unilateral adrenalectomy in PA patients. We found no association between the presence of a family history of hypertension and BP outcome, probably because of the high prevalence of hypertension in Japanese populations. In addition, eGFR was independent of operative outcome in this study, in contrast to previous reports, possibly because the renal function of our study population was relatively preserved (mean eGFR was 78.2±20.8). The mean eGFR of the NC group tended to be lower than that of the C group, although the difference was not significant. In the present study, age and male sex were associated with BP outcome in the univariate but not in the multivariate analysis. Data regarding the duration of hypertension could not be collected in our study because of its retrospective nature.

Low serum UA levels predicted the postoperative resolution of hypertension in a single regression model. It seemed that the high proportion of males affected the results for UA in the NC group, and hence we constructed a multivariate logistic regression model that included gender and UA as the only variables. This revealed that UA was an independent predictive factor, but gender was not, indicating that a high UA level affected the gender distribution in the NC group.

Table 1 Patient characteristics by cured and not cured

	All (n = 96)	Cured (n = 46)	Not cured (n = 50)	P-value (cured vs. not cured)
Age at surgery, years	51±11	47±12	55±10	**0.0009**
Male, n (%)	40 (41.7)	13 (28.3)	27 (54.0)	**0.0106**
BMI, kg m^{-2}	23.3±3.5	21.8±3.4	24.6±3.0	**<0.0001**
Complication of DM, n (%)	4 (4.2)	2 (4.4)	2 (4.0)	0.9321
Complication of DL, n (%)	18 (18.8)	5 (10.9)	13 (26.0)	0.0587
Past history of CVD, n (%)	5 (5.2)	2 (4.4)	3 (6.0)	0.7159
Smoking, n (%)	32 (33.7)	12 (26.1)	20 (40.8)	0.129
Alcohol, n (%)	32 (33.7)	15 (32.6)	17 (34.7)	0.8298
Family history of HTN, n (%)	67 (69.8)	33 (71.7)	34 (68.0)	0.6902
Preoperative systolic BP, mm Hg	140±17	138±13	142±21	0.3419
Preoperative diastolic BP, mm Hg	85±12	84±11	86±13	0.5771
Number of antihypertensive medications	1.3±0.9	1.1±0.7	1.5±1.0	**0.0338**
K$^+$ supplementation, n (%)	47 (49.0)	25 (54.4)	22 (44.0)	0.311
MRB medication, n (%)	65 (67.7)	29 (63.0)	36 (72.0)	0.3485
K$^+$, mEq l^{-1}	3.2±0.5	3.2±0.4	3.2±0.6	0.5027
UA, mg dl^{-1}	4.9±1.4	4.4±1.1	5.5±1.4	**<0.0001**
eGFR, ml min^{-1} per 1.73 m^2	78.2±20.8	81.7±16.0	75.0±24.1	0.1172
PAC, pg ml^{-1}	362±269	338±179	384±332	0.3999
PRA, ng ml^{-1} h^{-1}	0.3±0.4	0.3±0.2	0.3±0.5	0.3729
ARR	2545±4331	2727.3±5522.6	2374.7±2843.2	0.6939
Urinary aldosterone excretion, µg per day	24.4±15.2	25±16	23±14	0.6102
Urinary Na$^+$/K$^+$ excretion	3.0±1.5	2.9±1.6	3.1±1.3	0.4891
Tumor diameter, mm	14.6±5.4	14.3±4.6	15.0±6.2	0.5019
Pathologic diagnosis				
Cortical adenoma, n (%)	76 (79)	37 (80.4)	38 (79.8)	0.8784
Nodular hyperplasia, n (%)	4 (4)	0 (0)	4 (8.3)	**0.0454**
Cortical adenoma + hyperplasia, n (%)	16 (17)	9 (19.6)	6 (12.5)	0.3498
Postoperative systolic BP, mm Hg	125±12	122±13	127±11	**0.0375**
Postoperative diastolic BP, mm Hg	79±8	78±9	79±8	0.7381
Postoperative antihypertensive medications	0.7±0.8	0.0±0.0	1.3±0.6	**<0.0001**

Abbreviations: ARR, aldosterone/renin ratio; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; DL, dyslipidemia; eGFR, estimated glomerular filtration ratio; HTN, hypertension; MRB, mineralocorticoid receptor; PAC, plasma aldosterone concentration; PRA, plasma renin activity; UA, uric acid.
Data are mean ± s.d. for continuous variables, and number (percent) for categorical variables. Bold values are those found to be significant; P-value <0.05.

Table 2 Patient diagnostic characteristics by cured and not cured

	All (n = 96)	Cured (n = 46)	Not cured (n = 50)	P-value (cured vs. not cured)
ARR after captopril challenge test	1977 ± 2162	2127 ± 1567	1831 ± 2630	0.5565
PRA after furosemide upright test, ng ml^{-1} h^{-1}	0.7 ± 1.8	0.4 ± 0.3	0.9 ± 2.5	0.2063
PAC after saline loading test, pg ml^{-1}	331 ± 263	376 ± 258	283 ± 265	0.1853
AVS before ACTH stimulation				
PAC$_{dominat}$, pg ml^{-1}	13 385 ± 16 907	13 784 ± 18 225	13 031 ± 15 844	0.839
LR	21.7 ± 26.5	24.7 ± 28.5	18.9 ± 24.5	0.3216
CR	1.0 ± 1.4	0.8 ± 1.0	1.2 ± 1.7	0.2216
AVS after ACTH stimulation				
PAC$_{dominant}$, pg ml^{-1}	69 503 ± 68 686	77 697 ± 79 009	61 689 ± 57 009	0.2884
LR	13.2 ± 12.9	13.5 ± 12.1	12.9 ± 13.8	0.8576
CR	0.5 ± 0.5	0.4 ± 0.2	0.7 ± 0.6	**0.0033**
CS, n (%)	72 (87)	40 (97.6)	32 (76.2)	**0.0041**

Abbreviations: ACTH, adrenocorticotropic hormone; ARR, aldosterone/renin ratio; AVS, adrenal venous sampling; CR, contralateral ratio; CS, contralateral suppression; LR, lateralized ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity.
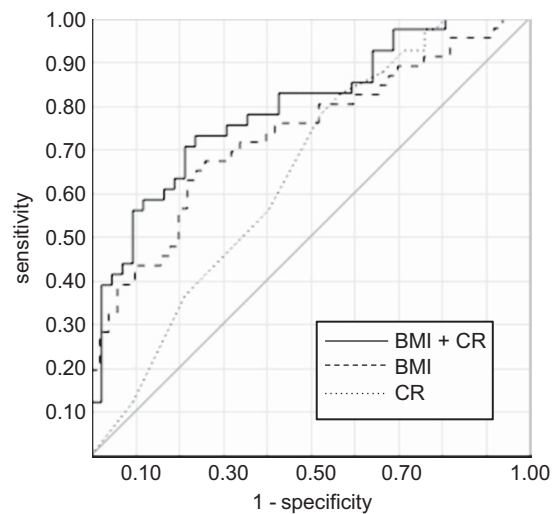Data are mean ± s.d. for continuous variables. Bold values are those found to be significant; P-value <0.05.

Table 3 Results of multivariate logistic regression analysis

	β	P-value
Male	− 0.382	0.24
Age	− 0.036	0.213
BMI	− 0.209	**0.0473**
Antihypertensive medications	− 0.466	0.2324
UA	− 0.366	0.148
CR (after ACTH)	− 2.06	**0.0199**

Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; CR, contralateral ratio; UA, uric acid.
Bold values are those found to be significant; P-value <0.05.

Figure 1 Comparison of the predictive factors of the cured patients. The receiver operating characteristic (ROC) curve shows the predictability of three parameters. The area under the ROC curve was 0.7938 (body mass index (BMI) and contralateral ratio (CR)), 0.7335 (BMI) + 0.6469 (CR).

Hyperuricemia is highly prevalent among hypertensive patients, including essential hypertension, renal parenchymal hypertension and renovascular hypertension, but not in PA. UA transport is said to be closely related to sodium transport in the renal tubules, particularly at the proximal site, and could also lead to the conclusion that the lower serum UA in PA resulted from the suppression of reabsorption and/or an enhancement of the secretion of UA in the proximal tubule, related to the so-called escape phenomenon.[36] Preoperative low serum UA levels may indicate that the rise in BP is due solely to hyperaldosteronism and that hypertension will resolve after adrenalectomy.

Obesity independently alters cardiovascular hemodynamics and impairs cardiac performance.[37] It has also been recognized as a predictor of cure following adrenalectomy in PA patients.[19,20] The present study also supports this finding. In a univariate and multivariate regression analysis, BMI was significantly higher in the C group. The association between adipose mass and hyperaldosteronism has been suspected in diverse populations.[38] Increased adiposity has been linked to alterations in adrenal function, with increased aldosterone production and mineralocorticoid receptor activity via 'adipose-adrenal crosstalk'.[39,40] In addition to aldosterone, adipokines such as leptin, adiponectin and osteopontin are also independently linked to hypertension. Hyperinsulinemia is also associated with the development of hypertension because of activation of the sympathetic nervous system.[41] Lifestyle factors often observed in overweight patients, including sedentary behavior, excess sodium intake and low potassium intake, also lead to an increase in BP. Hypertension may persist in obese patients even after adrenalectomy, through these diverse mechanisms of the residual obesity.

In PA, AVS is well established as the most reliable method for localization of excess aldosterone production. The present study revealed that patients with CS and lower CR values had better BP outcomes in both a single model and a multivariate regression model. Wolley et al.[25] previously assessed 80 patients who underwent unilateral adrenalectomy after successful AVS and found that those with CS had lower postoperative BP and a greater proportion showed cure or improvement of hypertension as well as biochemical cure of PA on fludrocortisone suppression testing. It can be interpreted that abnormal reaction of the contralateral adrenal gland and normal to increased aldosterone production under suppressed renin activity indicate autonomous excretion of aldosterone from the contralateral side, predicting residual hyperaldosteronism after resection of the

dominant side. In a previous multicenter study that evaluated 234 patients who underwent AVS procedures before unilateral adrenalectomy, the presence or absence of CS did not correlate with BP outcome.[42] However, because eight separate centers were included in this study, protocols to diagnose PA and unilateral disease were not standardized and there was heterogeneity in the patients' background characteristics.

We also assessed the results to determine the most reliable values for predicting the postoperative BP outcome and found that a BMI of 23.2 and a CR of 0.5 gave the most acceptable sensitivity and specificity. When these two variables were combined, a BMI of 25.2 and a CR of 0.1 were the optimal values, and the area under the ROC curve reached up to 0.7938, increasing the accuracy of prediction of the postsurgery BP outcome.

One of the limitations of our study is that it was based on retrospective data. Although prospective validation would be ideal as all the variables evaluated were objective clinical information and we had a high rate of complete data collection, it is unlikely that the results would be very different if analyzed prospectively. Another weakness of the present study is that the outcome measure of cure was not confirmed biochemically, and whether it represented a true cure is unknown. The strength of the present study is that although AVS is an invasive and difficult technique, a large number of patients in this study underwent AVS and were examined before and after administration of ACTH, making it possible to evaluate various indicators.

In conclusion, BMI and the presence of CS and CR values independently predicted BP outcome after unilateral adrenalectomy in PA patients. Referring to BMI and CR preoperatively may be helpful to determine the appropriate treatment—surgical or medical—for PA patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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