The implication of aortic calcification on persistent hypertension after laparoscopic adrenalectomy in patients with primary aldosteronism

（原発性アルドステロン症に対する腹腔鏡下副腎摘除術抵抗性高血圧のリスク因子として大動脈石灰化が重要である）

申請者　　弘前大学大学院医学研究科
腫瘍制御科学領域泌尿器腫瘍学教育研究分野

氏　名　　藤田 尚紀

指導教授　　大山 力

Abstract:

Objectives: To identify risk factors, including aortic calcification, for persistent hypertension in primary aldosteronism (PA) patients who underwent laparoscopic adrenalectomies.

Methods: Between October 2000 and October 2015, we performed consecutive 101 laparoscopic adrenalectomies for unilateral PA patients. Of those, 95 patients who had at least one year follow-up periods were included. The patients were divided into two groups based on whether they had normal blood pressure without antihypertensive medications (resolved group) or still required medications (unresolved group) at one year after surgery. Variables included age, gender, body mass index, history of hypertension, dosage of antihypertensive medication score, presence of type 2 diabetes, subclinical Cushing syndrome, preoperative renal function, aldosteronoma resolution score (ARS), and abdominal calcification index (ACI). Univariate and multivariate logistic regression analyses were used to assess independent risk factors for persistent hypertension one year after surgery.

Results: The complete resolution of hypertension without antihypertensive medication one year after adrenalectomy was 36/95 (38%). Preoperative antihypertensive medication score, systolic blood pressure, ACI were significantly higher, and ARS were significantly lower in the unresolved group than in the resolved group. Using multivariate logistic regression analysis, independent risk factors significantly correlating with persistent hypertension one year after surgery were ARS and ACI.

Conclusions: Adrenalectomy improved blood pressure and the need for antihypertensive medications, whereas ARS and ACI were potential independent risk factors for persistent hypertension one year after adrenalectomy.

Keywords: primary aldosteronism, aortic calcification, persistent hypertension, laparoscopic adrenalectomy, aldosteronoma resolution score

Introduction

Primary aldosteronism (PA) is considered a common cause of secondary hypertension, accounting for 5–20% of patients with hypertension.[1-4] Adrenalectomy is known to be the best management of a unilateral aldosterone-producing adenoma.[5] Despite postoperative normalization of the biochemical abnormalities in an aldosterone-producing adenoma after adrenalectomy, complete resolution rates of hypertension without the need for antihypertensive medications are only 30–60%.[6-10] Previous studies have identified potential factors affecting complete resolution of hypertension, including plasma aldosterone levels, longer duration of hypertension, preoperative blood pressure level, need for >3 antihypertensive agents, and *CYP11B2* gene polymorphism.[8-11] In addition, a predictive model for the complete postoperative resolution of hypertension was defined as the aldosteronoma resolution score (ARS) that includes four preoperative parameters: (A) ≤2 antihypertensive medications; (B) body mass index 25 kg/m^2 or less; (C) duration of hypertension <6 years; and (D) female sex.[12] The accuracy of ARS was validated in Japanese PA patients.[13] However, available data is limited, and not all confounders are well investigated.

Aortic degradation complicated with arterial stiffness and atherosclerosis may cause persistent hypertension in PA patients after adrenalectomy. It is reported that over-production of aldosterone leads to endothelial dysfunction, increased arterial stiffness, and atherosclerosis.[14-16] Arterial stiffness and atherosclerosis are related to aortic calcification, which is a risk factor for cardiovascular disease (CVD).[17, 18] PA patients have a greater risk of developing CVD than essential patients with hypertension.[19] Aortic calcification can be quantitatively measured by abdominal computed tomography (CT) on the aortic calcification index (ACI). ACI is widely used[20-23] and defines 12 levels of calcification as a percentage. We previously reported the clinical significance of ACI among hemodialysis patients and renal transplant recipients.[22, 23] However, no study addresses the relationship between ACI and postoperative hypertension after adrenalectomy.

In the present study, we hypothesized that preexisting aortic calcification may play a

crucial role in persistent hypertension after adrenalectomy. The aim of the present study was to identify risk factors, including aortic calcification, for persistent hypertension in PA patients who underwent adrenalectomies.

Methods

Between October 2000 and October 2015, we performed 101 consecutive laparoscopic adrenalectomies for unilateral PA. Patients for whom inadequate data was available or those followed up within a year after the surgery were excluded. The remaining 95 patients were enrolled in this retrospective study. We analyzed the resolution of hypertension one year after laparoscopic adrenalectomy for aldosterone-producing adenoma. This study was performed in accordance with the ethical standards of the Declaration of Helsinki.

A preoperative diagnosis of PA was defined as a plasma aldosterone concentration: plasma renin activity ratio ≥ 20, with a plasma aldosterone concentration of ≥12 ng/dL and plasma renin activity suppressed to ≤1 ng/mL per hour. Hypokalemia was defined as having a serum potassium level < 3.5 mmol/L. CT scans, magnetic resonance imaging, and adrenal venous sampling (AVS) were performed in all patients to localize the side of the tumor. Diagnosis of lateralization was defined based on guidelines for PA from Japanese Endocrine Society.[24] The following clinical information was obtained from the medical records of patients: age, gender, body mass index, hypertension history (years), blood pressure (systolic and diastolic), number and dosage of antihypertensive medications taken, comorbidities, and laboratory data. Blood pressure was measured on the day before (at three different times), one month after, and one year after adrenalectomy. World Health Organization 1999 guidelines defined blood pressure < 140/90 mmHg as normal. The number of antihypertensive medications was scored according to amount and kind of the agent (standard initial dose of antihypertensive agent = score 1) during pre- and post-surgery periods. After surgery, all patients were carefully followed up by their primary care physicians. One year after adrenalectomy, patients were divided into two categories: 1) the resolved group: normotensive with no antihypertensive medications and 2) the unresolved group: normotensive or hypertensive with antihypertensive medications.

Aortic calcification was quantitatively measured by preoperative abdominal CT images (TSX-021B, Toshiba Medical systems Corp, Ohtawara, Japan) focusing around the

left renal artery and scanned 10 times at 10-mm intervals, as previously described.[22, 23] When calcified intimas of the section 1 (i = 1) were five-twelfths, calcification of section 1 will be scored 5/12 = 41.7% (Figure 1A). The average value of section 1 - 10 is ACI (%).

Statistical analysis

Statistical analyses of the clinical data were performed using SPSS ver. 19.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA). Categorical variables reported as percentages and compared using the Fisher's exact test. Quantitative data were expressed as medians with quartile 1 and 3 (Q1, Q3). Differences between the groups were statistically compared using the Student's *t*-test for normal distribution or the Mann–Whitney *U*-test for non-normal distribution. *P* values < 0.05 were considered statistically significant. Risk factors for unresolved hypertension were identified using univariate and multivariate analyses with the logistic regression model, and odds ratios (ORs) with 95% confidence intervals were calculated after concurrently controlling for potential confounders. Variables included in the models were age, gender, body mass index, history of hypertension, type 2 diabetes, subclinical Cushing syndrome, antihypertensive medication score, renal function (estimated glomerular filtration rate: eGFR), ACI, and ARS. Moreover, we evaluated the predictive accuracy of ARS and selected variables in our dataset using the area under the curve (AUC) derived from the receiver operator characteristics (ROC) curve.

Results

Thirty-five males and 60 females (median age, 55 years) were included in the study. Postoperative serum potassium levels, plasma aldosterone concentrations, plasma renin activity, and aldosterone: renin ratios were normal in 99% of patients. Postoperative median blood pressure was significantly improved for both systolic (before, 136 mmHg; after, 125 mmHg; $P < 0.001$) and diastolic (before, 82; after, 78 mmHg; $P = 0.007$) readings. Median antihypertensive medication score was significantly reduced from 2.5 to 1.0 points ($P < 0.001$) one year after adrenalectomy (Fig.1B). One year after adrenalectomy, improvements in blood pressure and complete resolution of hypertension without any antihypertensive medication was observed in 36/95 (38%) patients. The remaining 62% of patients required antihypertensive medication (Fig.1C), of which 9 (9.5%) required an increase in antihypertensive medication dosage (Fig.1D). Table 1 summarizes patients' details. Preoperative hypertensive medication scores, systolic blood pressures, ACI were significantly higher, and ARS were significantly lower in the unresolved group. The resolved group required fewer antihypertensive medications (2.1 vs. 3.0 points; $P = 0.002$), had a lower ACI (0.0 vs. 3.3; $P = 0.002$), and a higher ARS (3.0 vs. 2.0; $P = 0.002$) than the unresolved group. Although blood pressure was significantly improved in the both groups (Fig.2A), improvements in post-adrenalectomy antihypertensive medication scores were significantly lower in the unresolved group (Fig. 2B, $P < 0.001$)

In univariate analysis, the preoperative antihypertensive medication scores, ACI, and ARS were significantly correlated with no resolution of the requirement for antihypertensive medication(s) one year after adrenalectomy (Table 2). Because ARS scores include 4 parameters (gender, body mass index, duration of hypertension, and antihypertensive medication), we did not include these in multivariate analysis to avoid covariate effects. We included age, renal dysfunction, type 2 diabetes, and subclinical Cushing syndrome in multivariate analysis because age, renal function decline and diabetes status are strong factors for aortic degradation, and previous study identified diabetes

mellitus was significant potential factor affecting complete resolution of hypertension. [13] In multivariate analysis, ACI and ARS were selected as significant risk factors for no resolution of the requirement for antihypertensive medication(s) one year after adrenalectomy (Table 2).

To evaluate the predictive accuracy of ACI and ARS, ROC curves were generated and AUC was calculated. The AUC values in ARS and ARS + ACI (ARS low = 1 point, + ACI < 1 = 1 point) were 0.69 (*P* = *0.02*, 95%CI, 0.58–0.80) and 0.72 [*P* < *0.01,* 95%CI, 0.61–0.83 (Fig.2D)].

Discussion

In the present study, we identified that 38% of patients obtained resolution of hypertension without the need of any antihypertensive medications, this was concurrent with the range reported by previous studies.[8-10] Significant factors favorably influencing complete hypertension resolution were reported including younger age, female sex, lower body mass index, shorter duration of hypertension, lower plasma aldosterone levels, lower baseline systolic blood pressure, lesser antihypertensive medications, no medical history of diabetes, normal renal function, and the CYP11B2 (344C/T).[8-10, 12, 13] Of these, ARS is the most useful parameter to predict complete postoperative resolution of hypertension. [12] It consists of four preoperative parameters that include <2 antihypertensive medications, body mass index $\leq$ 25 kg/m, duration of hypertension < 6 years, and female sex. Based on the resulting four parameters of ARS, three possible levels for complete resolution were identified: low (0–1); medium (2–3); and high (4–5), with predictive accuracies of 27%, 46%, and 75%, respectively.[12] In the present study, the accuracy of ARS was 20% in the low, 35% in the medium, and 61% in the high group, which was lesser than that mentioned in the original report. The AUC value of ARS was significant (0.69, *P = 0.002*) but not more than that reported in the previous validation study (AUC = 0.81).[13] This may be due to population differences within Japan. For example, this cohort included a higher fraction of patients with type 2 diabetes (48%) than did the previous validation study (10%). Therefore, additional large scale investigations are necessary to identify optimal factors predicting the postoperative resolution of hypertension for Japanese PA patients.

The findings of the present study suggested that the preoperative condition of aortic calcification has a significant impact on postoperative blood pressure. To our knowledge, this is the first report demonstrating a correlation between ACI and hypertensive status after unilateral adrenalectomy in patients with aldosterone-producing adenomas.

We chose ACI measurement by CT imaging in the present study. There are 2 established methods to measure aortic calcification. ACI measurement using CT imaging is well-verified and reliable method to evaluate aortic calcification. Another is lateral lumbar

radiography methods. [24] The presence and severity of calcification were calculated as a validated semi-quantitative scoring system. Therefore, we used ACI measurement by CT imaging because of superiority of detection power for calcification.

Several reasons may explain persistent hypertension, even after unilateral PA patients have undergone adrenalectomies. One of the major hypothesis is that prolonged hyperaldosteronism could induce harmful and irreversible changes to cardiovascular systems, such as atherosclerosis. Atherosclerosis may be a trigger for the onset of essential hypertension which cannot be resolved by adrenalectomy. Therefore, we hypothesized that aortic calcification, which is one of the markers of arterial degradation, may play an important role in persistent hypertension after adrenalectomy. As we expected, the univariate analysis showed that antihypertensive medication scores, ACI, and ARS are indicated as potential risk factors for persistent hypertension one year after surgery. The multivariate logistic regression confirmed that ACI and ARS have a comparable predictive potential, and on combining them, the predictive accuracy of AUC values from ROC curve increased from 0.69 (ARS alone) to 0.72 (ARS + ACI).

It is well known that progression of aortic calcification is closely associated with age, hypertension, history of CVD, and chronic kidney disease.[25, 26] In addition, we have previously described several aspects of aortic calcification as follows: (A) burden of aortic calcification has a negative effect on postoperative renal function in renal transplant patients;[22] (B) ACI progression correlates with the occurrence of postoperative cardiovascular events in renal transplant patients;[22] and (C) ACI progression is closely associated with the occurrence of cardiovascular events in hemodialysis patients.[23] Therefore, aortic calcification is a useful indicator to quantify arterial degradation, and ACI should be selected as a potential predictor for persistent hypertension after adrenalectomy. More recently, Lina et al. demonstrated that adrenalectomy improves carotid intima-media thickness, arterial stiffness, and pulse wave velocity in patients with aldosterone-producing adenoma.[27] Further studies are needed to confirm whether aortic calcification improves after adrenalectomy in unilateral PA patients.

In conclusion, adrenalectomy improved blood pressure and the demand for antihypertensive medications. However, a considerable number of patients showed no discontinuation of antihypertensive medication one year after adrenalectomy. Our results showed ARS and ACI to be the risk factors for persistent hypertension one year after adrenalectomy. Although our study was small and retrospective, ACI may help to evaluate PA patients requiring surgery and to identify patients with persistent hypertension after adrenalectomy.

Limitations of the present study are small sample size and a retrospective analysis. Therefore, we could not control for selection bias and other unmeasurable confounding factors. In addition, we could not include metabolic parameters, including dyslipidemia, contributing to cardiometabolic syndrome and resistant hypertension development. We have no data about change of ACI and left ventricular hypertrophy after adrenalectomy. Our future study should address these issues. Despite these limitations, this study was the first report to assess the implication of aortic calcification on persistent hypertension one year after adrenalectomy.

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Conflicts of interests: All authors have declared no conflicts of interests.

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Figure legends

Figure 1. Measurement of aortic calcification index and antihypertensive medication score before and one year after laparoscopic adrenalectomy

Aortic calcification was quantitatively measured by preoperative abdominal CT images focusing around the left renal artery and scanned 10 times at 10-mm intervals. The calcification profile (CP) was calculated as the sum of calcification areas of 12 fractions in a single slice, and divided by 12. The sum of CP from 10 slices was divided by 10, and multiplied by 100 to get a percentage (A). Antihypertensive medication scores in all patients were significantly improved (*, $P < 0.001$, compared with those before adrenalectomy [B]). Antihypertensive medication scores improved in 38% of patients after adrenalectomy, whereas the remaining 62% required antihypertensive medication (C). Nine patients (9.5%) experienced refractory hypertension one year after adrenalectomy (D).

Figure 2. Comparison of blood pressure, antihypertensive medication score, ACI between the resolved and the not resolved groups.

Preoperative and postoperative blood pressures were compared between the groups. Significant improvement of systolic blood pressures were obtained in both groups but was not seen in diastolic blood pressures in the unresolved group (A, *, $P < 0.001$). Preoperative and postoperative antihypertensive medication scores were significantly different between the groups, and its differences were increased after adrenalectomy (B, *, $P < 0.001$, **, $P = 0.002$). Abdominal calcification index (ACI) was significantly higher in the unresolved group (C). The area under the curve (AUC) value was improved when aldosteronoma resolution score (ARS) was combined with ACI. The AUC values improved from 0.69 (ARS alone) to 0.72 (ARS + ACI) (D)

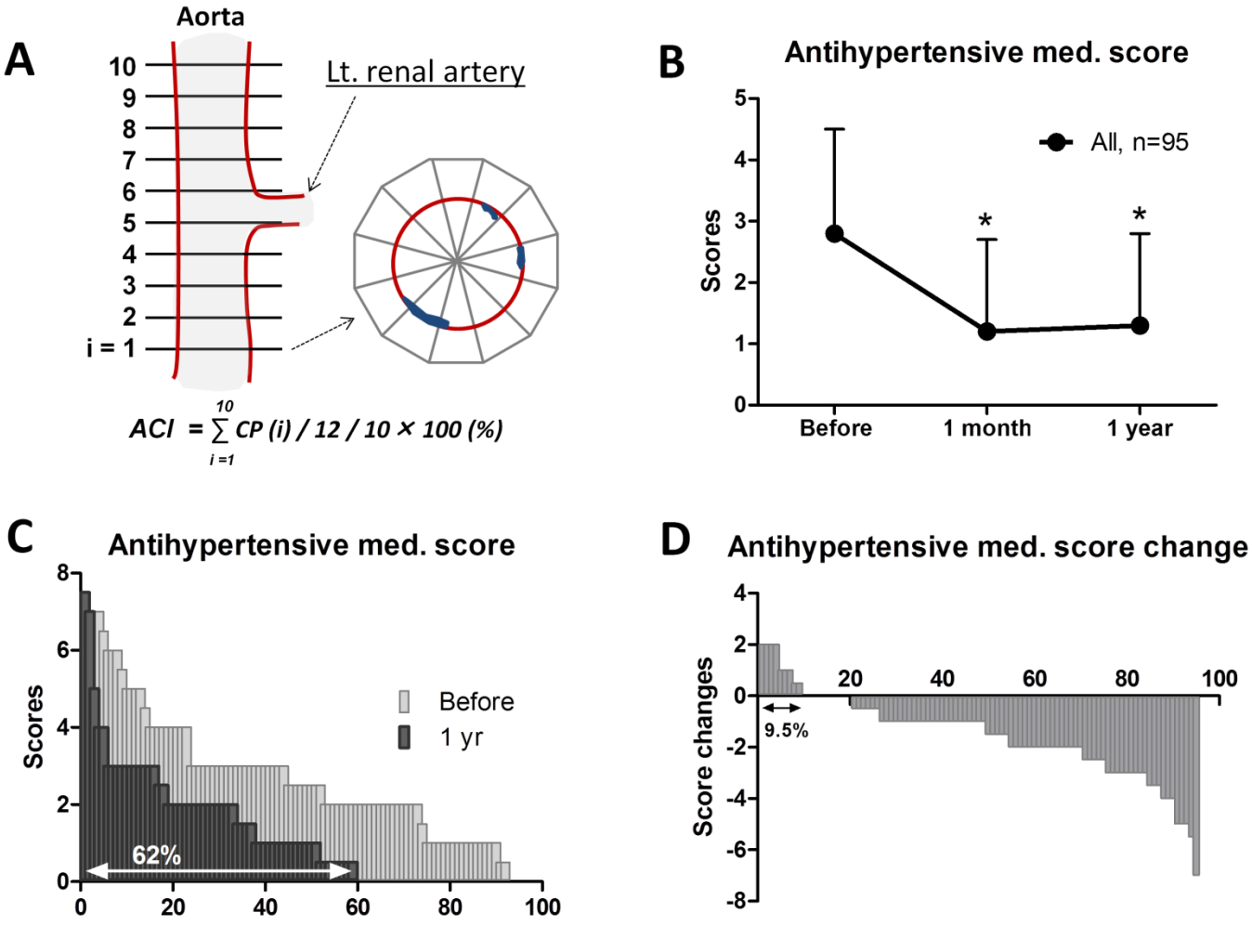
Table 1, Summary of patient's characteristics. Median and interquartile range (Q1, Q3) was used for consecutive variables.

	All n=95	Unresolved n=59	Resolved n=36	*P values*
Age, years	55 (48, 62)	56 (51, 62)	53 (43, 61)	*0.079*
Sex, female	63%	58%	72%	*0.197*
Body mass index, kg/m^2	24.6 (22.2, 27.5)	25.1 (23.0, 28.2)	23.2 (21.4, 26.5)	*0.067*
Duration of hypertension, years	10 (4.0, 17)	12 (4.5, 18.0)	8.0 (3.8, 13.0)	*0.111*
Preoperative antihypertensive medication score	2.5 (2.0. 3.0)	3.0 (2.0, 4.0)	2.1 (1.0, 3.0)	*0.002*
Diabetes mellitus	48%	54%	39%	*0.204*
Subclinical Cushing syndrome	24%	27%	19%	*0.465*
Systolic blood pressure, mmHg	137 (127, 147)	139 (128, 148)	119 (109, 124)	*0.046*
Diastolic blood pressure, mmHg	82 (76, 87)	83 (75, 89)	75 (69, 80)	*0.544*
Initial clinical laboratory values				
Hypokalemia	75%	71%	81%	*0.342*
Plasma aldosterone concentration (PAC), ng/dL	23.9 (16.2, 35.3)	21.8 (16.6, 34.7)	30.0 (814.4, 35.4)	*0.867*
Plasma renin activity (PRA), ng/mL/h	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	0.2 (0.1, 0.3)	*0.093*
Aldosterone - renin ratio (ARR), ng/dL per ng/mL/h	87.5 (48.2, 245)	83.0 (47.1, 238)	124 (55.4, 310)	*0.216*
Estimated glomerular filtration rate (eGFR), mL/min/1.73m^2	77.0 (65.0, 88.4)	67.2 (53.5, 75.4)	79.6 (73.4, 96.4)	*0.041*
Aortic Calcification Index	0.8 (0.0, 11)	3.3 (0.0, 13.3)	0.0 (0.0, 1.5)	*0.002*
Aldosteronoma resolution score (ARS)	3.0 (1.0, 4.0)	2.0 (1.0, 3.0)	3.0 (2.0, 4.0)	*0.002*

Table 2, Univariate and multivariate analysis for risk factors for no resolution of antihypertensive medication at 1 year after adrenalectomy.

Univariate	Risk factors	*P value*	OR	95%CI
Age	Older than 55 years old	*0.179*	1.78	0.77-4.11
Gender	Female	*0.155*	0.52	0.21-1.28
Body mass index	Greater than 25 kg/m^2	*0.164*	1.83	0.78-4.28
History of hypertension	Greater than 6 years	*0.352*	1.50	0.64-3.55
Renal dysfunction (eGFR)	Lower than 60 ml/min/1.73m^2	*0.439*	1.63	0.47-5.65
Diabetes mellitus	Positive	*0.148*	1.86	0.80-4.21
Subclinical Cushing syndrome	Positive	*0.399*	1.54	0.56-2.84
Antihypertensive medication score	Greater than 2 points	*0.034*	2.54	1.07-6.02
Aortic calcification index (ACI)	Greater than 1%	*0.003*	4.08	1.64-10.2
Aldosteronoma resolution score (ARS)	Low (0 or 1)	*0.018*	3.43	1.24-9.50
Multivariate				
Age	Older than 55 years old	*0.472*	0.67	0.22-2.00
Renal dysfunction (eGFR)	Lower than 60 ml/min/1.73m^2	*0.877*	0.89	0.21-3.76
Diabetes mellitus	Positive	*0.389*	1.52	0.58-3.98
Subclinical Cushing syndrome	Positive	*0.137*	2.40	0.76-7.61
Aortic calcification index (ACI)	Greater than 1%	*0.006*	4.59	1.34-13.7
Aldosteronoma resolution score (ARS)	Low (0 or 1)	*0.021*	3.73	1.22-11.4

Fig. 1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$ACI = \sum_{i=1}^{10} CP(i) / 12 / 10 \times 100\ (\%)$
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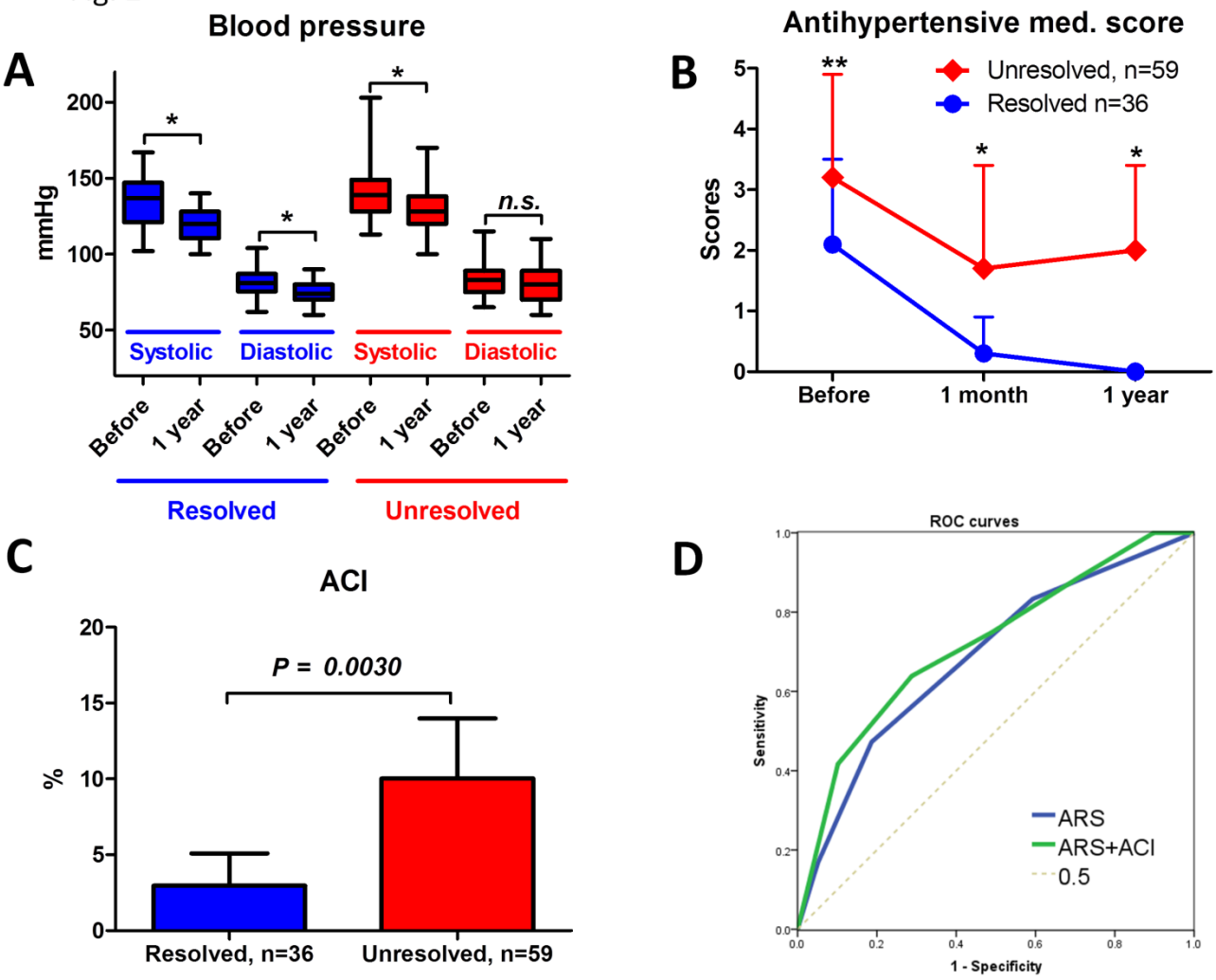
Fig. 2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