

Primary aldosteronism subtyping in the setting of partially successful adrenal vein sampling

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Abstract

Background and aims: Frequent failure of adrenal vein (AV) cannulation is a major obstacle to the universal use of adrenal vein sampling (AVS) for subtyping primary aldosteronism (PA). This study aimed to confirm and modify the value of a previously reported AVS parameter for PA subtyping in the case of cannulation failure on one side.

Methods: Successfully catheterized AVS studies in 157 patients (121 patients as a derivation cohort and 36 patients as a validation cohort) from two tertiary hospitals were retrospectively reviewed. The AV/inferior vena cava (IVC) index was defined by dividing the aldosterone/cortisol ratio (ACR) of AV by the ACR of the IVC. Cutoff values for lateralized PA were obtained from two methods: scatterplots and the values corresponding to Youden's index in receiver operating characteristic (ROC) curves, on the assumption of catheterization failure on one side.

Results: Due to multiple samplings in a single AVS procedure, 252 left AV/IVC ratios (LIRs) and 272 right AV/IVC ratios (RIRs) were calculated. Scatterplot cutoffs of $LIR > 5.4$ or < 0.5 predicted unilateral PA with a sensitivity of 42.1% and a specificity of 98.6%. Scatterplot cutoffs of $RIR < 0.5$ or > 7.0 showed a sensitivity of 55.1% and a specificity of 98.6%. ROC curve cutoffs of $LIR \leq 0.8$ or > 3.1 predicted unilateral PA with a sensitivity of 82.5% and a specificity of 69.6%. ROC curve cutoffs of $RIR \leq 0.8$ or > 3.9 resulted in 87.4% sensitivity and 80.7% specificity.

Conclusion: In the case of unilateral AVS failure, the AV/IVC index may help in diagnosing PA subtype.

Keywords: adrenal vein sampling, lateralization index, primary aldosteronism, subclinical hypercortisolism

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Introduction

Determining the lateralization of primary aldosteronism (PA) is an essential step in deciding the method of treatment since unilateral PA can be cured with adrenalectomy of the affected side, while bilateral hyperaldosteronism (BHA) is an indication for medical treatment. Adrenal vein sampling (AVS) is generally accepted as the gold standard test for the lateralization of PA by the lateralization index (LI), which is derived from the side-to-side ratio of the aldosterone/cortisol ratio (ACR) of each adrenal vein (AV). Therefore,

the success of AV catheterization on both sides is mandatory for an accurate interpretation of AVS. The success rate of catheterization is mainly dependent on the interventionist's skill and the anatomy of the adrenal vasculature. This has caused inconsistency in the reported success rate, ranging from 30% to 96%.¹⁻⁴ Out of concern for cannulation failure and its invasiveness, several studies have suggested clinical diagnostic criteria or computed tomography (CT) images that can conclude laterality of PA before surgical treatment.⁴⁻⁸ Others have proposed the use of C-arm

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CT or intraoperative measurement of cortisol levels to improve cannulation selectivity.^{9,10} However, these methods are time-consuming and require high-cost devices. Those indices are also neither reproducible nor reliable methods for PA subgrouping, and sufficient evidence for new methods should be established.

Attempts have been made to draw results from an incomplete dataset in the setting of failed catheterization of one side. In the context of right side cannulation failure, Pasternak *et al.* suggested that the ACR of the left AV (LAV) to the inferior vena cava (IVC) (ACR of LAV/ACR of IVC ratio; LIR) can accurately discriminate between unilateral and bilateral disease; LIR ≥ 5.5 for ipsilateral disease and ≤ 0.5 for contralateral disease.¹¹ These cutoffs were validated in subsequent studies by other groups.^{12,13} However, they analyzed a relatively small number of PA cases in only LIR with the assumption of failure of the right cannulation or suggested the inadequacy of LIR ≥ 5.5 to diagnose unilateral ipsilateral disease.¹³ In addition, the Endocrine Society published the clinical practice guidelines for PA in 2016¹⁴ with the recommendation to distinguish lateralized PA using the concept of contralateral suppression.¹⁵

The purpose of this study was to find new cutoff values from the ACR of AV to IVC (AV/IVC index) from each side for PA subtyping, assuming the failure of cannulation of one side. We also validated the diagnostic power of new cutoffs and compared them with previously proposed diagnostic criteria.

Methods

Study design and population

Researchers from Asan Medical Center (AMC) and Samsung Medical Center (SMC), the tertiary-care university hospitals in Seoul, Republic of Korea, conducted a retrospective cohort study. To derive the cutoff values for PA lateralization, the clinical data of patients who underwent AVS for PA between 1 May 2007 and 31 March 2017 at AMC were extracted and retrospectively reviewed using ABLE (Asan Biomedical research Environment), the de-identified clinical research data warehouse at AMC.¹⁶ Medical records of patients who underwent AVS for PA from 1 September 2008 to 31 March 2017 at SMC were collected to validate the cutoff values.

Patients older than 18 years and suspicious and screened for PA by aldosterone/renin ratio were included. Patients with subclinical hypercortisolism were excluded since excessive cortisol levels could interfere with AVS interpretation. We excluded patients with subclinical hypercortisolism using the diagnostic criteria as described previously:¹⁷ (1) cortisol level after 1 mg overnight dexamethasone suppression test (DST) $\geq 5 \mu\text{g/mL}$ or (2) cortisol level after 1 mg DST $> 2.2 \mu\text{g/dL}$ with the presence of low levels of either adrenocorticotropic hormone (ACTH; $< 10 \text{ pg/mL}$) or dehydroepiandrosterone-sulfate (DHEA-S; $< 80 \mu\text{g/dL}$ in males or $< 35 \mu\text{g/dL}$ in females). After a saline infusion test confirmed PA, AVS was performed with cosyntropin (ACTH) infusion for PA subtyping. Interventionists did multiple catheterizations in each AV in some cases. These multiple catheterizations were all included for analysis as independent cases. Only cases of successful bilateral catheterization were adopted for the final analysis set. Measurement of serum hormone concentrations are described in Supplemental Material file 1 online.

Definition

There are several diagnostic criteria reported for PA confirmation and AVS interpretation.¹⁸ We adopted the widely used diagnostic criteria from clinical guidelines¹⁴ as follows: (1) PA confirmation: post-saline infusion plasma aldosterone concentration (PAC) $> 5 \text{ ng/dL}$, (2) successful AV cannulation during AVS with cosyntropin stimulation by selectivity index (SI), the cortisol ratio of each AV to the IVC ($C_{\text{AV}}/C_{\text{IVC}} \geq 5$), (3) PA lateralization subtyping by LI, the side-to-side ratio of ACR > 4 for unilateral, < 3 for bilateral, and 3–4 for indeterminate cases. LIR [=ACR of LAV (ACR_{LAV})/ACR of IVC (ACR_{IVC})] and RIR [=ACR of right AV (RAV; ACR_{RAV})/ACR_{IVC}] were used to establish new cutoffs for ipsilateral or contralateral disease.

Data analysis

Categorical variables are presented as number (%) and continuous variables as mean \pm standard deviation or median (interquartile range) depending on the distribution. Patient characteristics from the two hospitals were compared by Student's *t*-test, Mann–Whitney test, and chi-square test. The hospital that had a larger number of cases was assigned as a derivation cohort and

the other as a validation cohort. After the acquisition of cutoffs from the former, they were tested in the latter, and the predictive utility of the tool was evaluated. Statistical analyses were performed using STATA SE 14 (StataCorp LLC, College Station, Texas, USA).

LIR values of all cases of the derivation cohort were plotted and grouped by PA lateralization based on LI criteria. The maximum and minimum LIR values of the BHA group were defined as an upper and a lower reference for PA lateralization, respectively, with the assumption of right-side cannulation failure. This cutoff value based on scatterplot hypothetically predicts unilateral PA with 100% specificity. The same method was used for the right side to establish the RIR cutoff value. These were defined as *Scatterplot cutoffs*.

In addition to the scatterplot method, the ability of LIR or RIR to predict PA subtype was quantified using the area under the receiver operating characteristic (ROC) curve (AUC). The best cutoff values which corresponded to Youden's index¹⁹ were calculated. The cutoffs derived from ROC curves were defined as *ROC curve cutoffs*. The ROC curve analysis was done using MedCalc Version 19.0.5 (MedCalc Software, Ostend, Belgium).

We compared the diagnostic power of *Scatterplot cutoffs* and *ROC curve cutoffs* to predict unilateral PA with those of *Pasternak's cutoffs* (AV/IVC index ≥ 5.5 or ≤ 0.5), which were suggested by Pasternak *et al.*,¹¹ and those of *Funder's cutoffs* (AV/IVC index > 2.5 or < 1.0), which were suggested by Stowasser *et al.*^{15,20} and presented explicitly in the recent clinical practice guidelines.¹⁴

Additional analyses were conducted for (1) inappropriate adrenalectomy (defined as either removing an unaffected gland in a patient with unilateral disease or performing a unilateral adrenalectomy in a patient with bilateral disease), and (2) failed lateralization (defined as failure to recognize a patient with unilateral disease who would benefit from surgery), which were described in an earlier study.¹³

Ethics

The study protocol was approved by the Institutional Review Board (IRB) of SMC in conjunction with AMC, according to the Declaration

	AMC	SMC	Total
Suspicious/screened for PA (+)	278	106	384
Subclinical hypercortisolism (-) ^a	243	99	342
Saline infusion test (+) ^b	181	69	250
Successful catheterizations in both sides ^c	121	36	157

Figure 1. Study population (patient number).

^aSubclinical hypercortisolism is defined by the following: (1) cortisol level after 1 mg DST ≥ 5 $\mu\text{g}/\text{mL}$ or (2) cortisol level after 1 mg DST > 2.2 $\mu\text{g}/\text{dL}$ with the presence of either low levels of adrenocorticotropic hormone (< 10 pg/mL) or dehydroepiandrosterone-sulfate (< 80 $\mu\text{g}/\text{dL}$ in males or < 35 $\mu\text{g}/\text{dL}$ in females).

^bConfirmed primary aldosteronism from saline infusion test when post-saline infusion plasma aldosterone concentration > 5 ng/dL .

^cSuccessful catheterization in both sides is defined by the cortisol ratio of each adrenal vein to inferior vena cava ≥ 5 .

1 mg DST = 1 mg overnight dexamethasone suppression test.

AMC, Asan Medical Center; PA, primary aldosteronism; SMC, Samsung Medical Center.

of Helsinki. The IRB exempted the informed consent requirement for this study because the database access was for analysis purposes only and personal information was not included in the database. The IRB approval IDs for both hospitals are 2016-0254 (derivation cohort) and SMC 2018-02-055 (validation cohort), respectively.

Results

The data of 278 patients from AMC and 106 from SMC were initially screened. With the selection of participants without subclinical hypercortisolism, confirmed PA with saline infusion test, and successful bilateral adrenal vein catheterization, 121 and 36 patients were finally included for the analysis, respectively (Figure 1). The AMC cohort was assigned as the derivation cohort and the SMC as the validation cohort.

Most of the derivation cohort patients were tested for PA because of adrenal incidentaloma. Conversely, the reasons for conducting the test for PA in the validation cohort were as follows: uncontrolled hypertension (27.8%), hypokalemia (25.0%), uncontrolled hypertension with hypokalemia (25.0%), adrenal incidentaloma (16.7%), and adrenal incidentaloma with hypokalemia (5.5%).

Table 1 shows the baseline characteristics of the study populations. The mean age was 52.4 years

Table 1. Baseline characteristics of study population.

	AMC	SMC	<i>p</i> value	Total
	Derivation cohort	Validation cohort		
<i>n</i>	121	36		157
Age, years	53.2 ± 10.3	49.8 ± 13.1	0.098	52.4 ± 11.1
Male	64 (52.9%)	25 (69.4%)	0.078	89 (56.7%)
BMI, kg/m ²	25.9 ± 3.7	25.4 ± 3.3	0.410	25.8 ± 3.6
SBP, mmHg	141.8 ± 17.2	144.4 ± 18.8	0.436	142.4 ± 17.5
DBP, mmHg	86.9 ± 11.4	86.8 ± 11.8	0.961	86.9 ± 11.4
PAC, ng/dL	25.4 (20.1–31.3)	25.6 (13.0–41.0)	0.859	25.4 (19.8–32.0)
PRA, ng/ml per h	0.2 (0.2–0.5)	0.2 (0.1–0.5)	0.170	0.2 (0.2–0.5)
ARR	102.5 (54.3–170.0)	85.2 (44.6–256.0)	0.959	100.0 (53.3–186.9)
K, mmol/L	3.9 ± 0.5	3.6 ± 0.4	0.001	3.8 ± 0.5
K supplement	36 (29.8%)	25 (69.4%)	<0.001	61
DDD	1.5 (0.8–2.8)	3.0 (2.0–4.0)	0.001	2.0 (1.0–3.0)
Size, cm	1.5 ± 0.7	1.6 ± 0.5	0.670	1.5 ± 0.6
Lateralization			<0.001	
Right	19 (15.7%)	13 (36.1%)		32 (20.4%)
Left	31 (25.6%)	11 (30.6%)		42 (26.8%)
Bilateral	70 (57.9%)	9 (25.0%)		79 (50.3%)
Indeterminate	1 (0.8%)	3 (8.3%)		4 (2.5%)
Adrenalectomy	59 (48.8%)	23 (63.9%)	0.111	82 (52.2%)
Pathology			0.685	
Adenoma	53 (89.8%)	22 (95.7%)		75 (91.5%)
Hyperplasia	5 (8.5%)	1 (4.3%)		6 (7.3%)
Both	1 (1.7%)	0 (0.0%)		1 (1.2%)

Categorical variables are presented as number (%), continuous variables as mean ± SD or median (interquartile range) according to distribution.

Lateralization of primary aldosteronism is determined by lateralization index, side-to-side ratio of aldosterone to cortisol ratio.

AMC, Asan Medical Center; ARR, aldosterone to renin activity ratio; BMI, body mass index; DBP, diastolic blood pressure; DDD, daily defined dose; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure; SMC, Samsung Medical Center.

in the total cohort. Median PAC and plasma renin activity were 25.4 ng/dL and 0.2 ng/mL per h, respectively. Serum potassium level was significantly lower, and more unilateral adrenalectomies

were performed in the validation cohort compared with the derivation cohort. The median daily defined dose (DDD) of anti-hypertensive medications was 1.5 in the derivation and 3 in

Table 2. LIR and RIR according to lateralization.

	Lateralization	Derivation cohort	Validation cohort	Total
LIR	<i>n</i> pairs	218	34	252
	Right	33 0.5 (0.3–0.6)	13 0.2 (0.2–0.5)	46 0.4 (0.2–0.6)
	Left	58 4.1 (3.1–5.8)	10 6.8 (2.5–9.3)	68 4.2 (2.8–6.9)
	Bilateral	126 2.5 (1.6–3.0)	8 2.1 (1.3–4.1)	134 2.5 (1.6–3.0)
	Indeterminate	1 3.8	3 2.0 (0.3–3.5)	4 2.7 (1.1–3.6)
RIR	<i>n</i> pairs	228	44	272
	Right	38 4.7 (4.0–6.5)	15 5.6 (2.8–11.2)	53 5.0 (3.9–7.0)
	Left	59 0.2 (0.2–0.4)	15 0.3 (0.1–0.6)	74 0.2 (0.2–0.5)
	Bilateral	130 2.5 (1.7–3.2)	10 2.4 (1.4–2.7)	140 2.5 (1.7–3.2)
	Indeterminate	1 1.2	4 0.7 (0.6–0.9)	5 0.8 (0.6–0.9)

Values are presented as median (interquartile range).
There is no significant difference in comparison of LIR or RIR between both groups (Mann–Whitney test). There is no significant difference in cortisol level at each site of inferior vena cava (IVC), left adrenal vein (LAV), and right adrenal vein (RAV) between LIR and RIR (data not shown). Lateralization is determined by lateralization index (LI) as follows: LI >4, right or left; LI <3, bilateral; LI 3–4 indeterminate. LIR is aldosterone/cortisol ratio (ACR) of LAV to IVC (ACR of LAV/ACR of IVC ratio) and RIR is ACR of RAV to IVC (ACR of RAV/ACR of IVC ratio).

the validation cohorts ($p=0.001$). Interestingly, bilateral aldosterone excess was the most common subtype in the derivation cohort (57.9%), while right PA was the most common subtype in the validation cohort (36.1%), as determined by the LI method. In histopathology, adrenocortical adenoma was found most often, followed by adrenocortical hyperplasia at both centers ($p=0.685$).

There were numerous cases of multiple AV cannulations performed in one AVS procedure. Mainly, interventionists from the derivation cohort performed more multiple catheterizations compared with the validation cohort (81.2% and 43.5%, respectively, $p<0.0001$). In both cohorts, the success rate was higher in multiple catheterizations than in single catheterizations. In the total cohort, the success rates of single AV cannulation were 64.4% and 90.4% for RAV and LAV, respectively. The rates increased to 81.9% and 92.7% for each side when multiple samplings were done ($p=0.0025$, Supplemental file 2). We used all data from multiple sets of cannulations for the analysis. The numbers of LIRs and RIRs used for final analysis were 252 and 272, respectively (Table 2). LIRs and RIRs were compared

between cohorts, specifically according to PA subtype by LI. The median value for LIR or RIR was higher in the case of ipsilateral PA determined by LI and lower in the contralateral PA. There was no institution-specific statistical difference of LIR or RIR by PA subtype.

Figure 2 presented logarithmic-scale scatterplots of LIR and RIR values for PA subtype by LI, both in the derivation and validation cohorts as well as in the combined cohort. The highest and lowest LIR values of bilateral disease in the derivation cohort were 5.4 and 0.5, respectively (Figure 2A). Those of RIR were 7.0 and 0.5 (Figure 2B). Values beyond these cutoffs did not result in false-positive unilateral PA. Assuming right catheterization failure, LIR by *Scatterplot cutoff* >5.4 or <0.5 in derivation, validation, and total cohort predicted unilateral cases with a sensitivity of 36.3%, 65.2%, and 42.1% and a specificity of 100%, 81.8%, and 98.6%, respectively. Likewise, RIR by *Scatterplot cutoff* >7.0 or <0.5 showed a sensitivity of 55.7%, 53.3%, and 55.1% and a specificity of 100%, 85.7%, and 98.6% in each cohort and the combination in the same order (Table 3A).

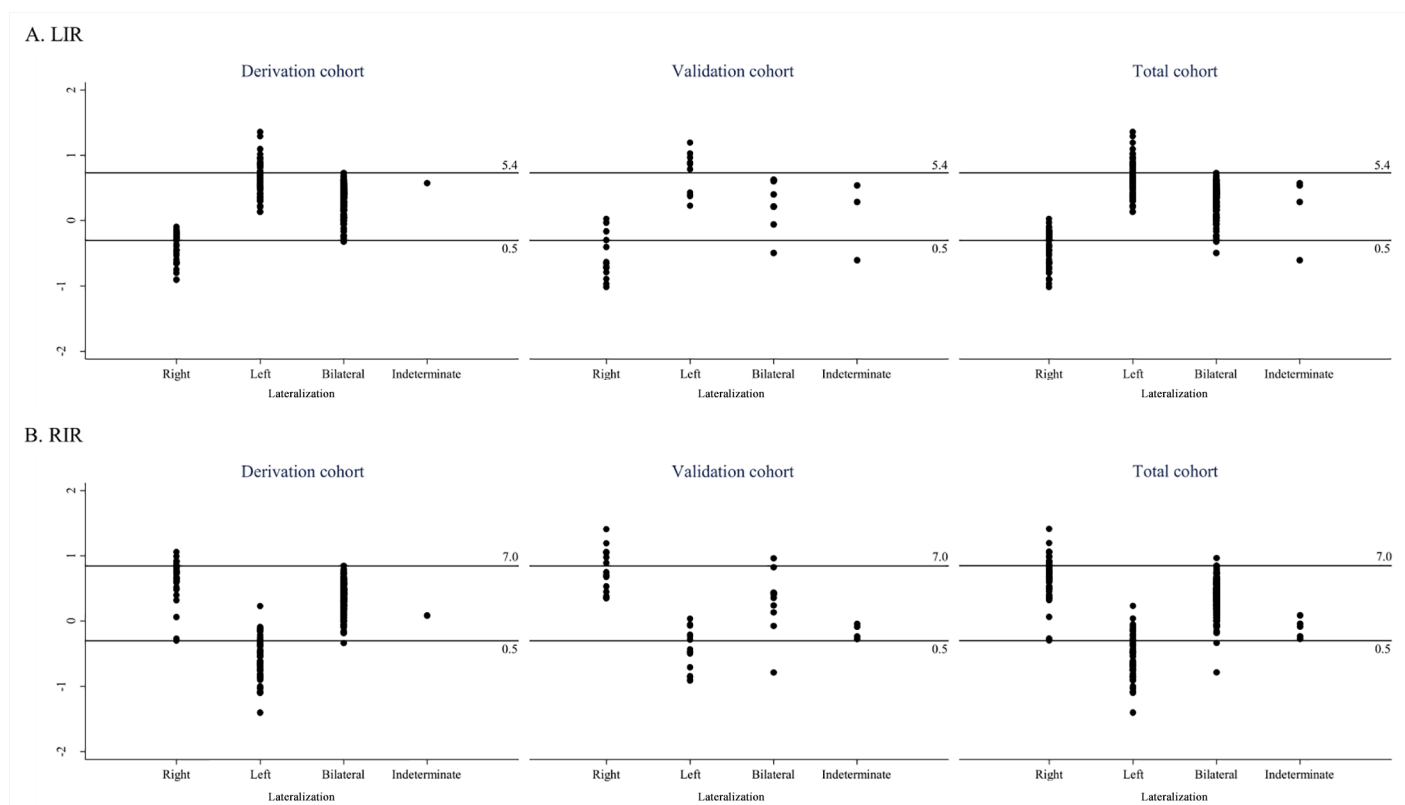


Figure 2. Logarithmic plotting of LIR and RIR with respect to lateralization. Numbers above and below lines present cutoff values of LIR and RIR, respectively. LIR cutoff for lateralization: >5.4 or <0.5 ; RIR cutoff for lateralization: >7.0 or <0.5 . LIR is aldosterone/cortisol ratio [ACR] of left adrenal vein (LAV) to inferior vena cava (IVC) [ACR of LAV/ACR of IVC ratio] and RIR is ACR of right adrenal vein (RAV) to IVC [ACR of RAV/ACR of IVC ratio].

LIR by *Pasternak's cutoffs* ≤ 0.5 or ≥ 5.5 predicted unilateral PA with a sensitivity of 43.0% and specificity of 97.8% in the total cohort. By application of these numbers to RIR, RIR by *Pasternak's cutoffs* ≤ 0.5 or ≥ 5.5 could predict unilateral PA with a sensitivity of 63.8% and a specificity of 95.2% (Table 3B). In the ROC curve for left lateralization, LIR by *ROC curve cutoffs*, the best cutoff value, which corresponded to Youden's index, was 3.1, while RIR by *ROC curve cutoffs* was 0.8. Likewise, *ROC curve cutoffs* to distinguish right lateralization were 3.9 for RIR and 0.8 for LIR (Figure 3).

We compared the diagnostic power of the *Scatterplot cutoffs*, *ROC curve cutoffs*, *Pasternak's cutoffs* (AV/IVC index ≥ 5.5 or ≤ 0.5), and *Funder's cutoffs* (AV/IVC index >2.5 or <1.0) for PA subtyping. Unilateral PA was divided into ipsilateral or contralateral disease to make the diagnosis in more detail. Figure 3 summarizes the sensitivity and specificity of subtyping with RIR and LIR derived from various criteria when

predicting ipsilateral or contralateral PA independently. In the order of *Funder's cutoffs*, *ROC curve cutoffs*, and *Pasternak's cutoffs*, the specificity increased regardless of LIR or RIR, or ipsilateral or contralateral disease prediction. Generally, the use of LIR and RIR for subtyping contralateral disease was superior in sensitivity to ipsilateral disease (Figure 3). The AUC of the ROC curves for ipsilateral and contralateral PA prediction of RIR were 0.892 and 0.986, respectively. Moreover, those for LIR were 0.860 and 0.985. The McNemar tests that compared ipsilateral and contralateral PA subtyping resulted in: $p=0.015$ for RIR; $p=0.008$ for LIR.

We also compared the diagnostic power of four cutoffs for unilateral disease regardless of contralateral or ipsilateral disease (Supplemental file 3). By McNemar test, the paired cutoffs were significantly different ($p<0.001$) except between the LIR by *Scatterplot cutoffs* and that by *Pasternak's cutoffs* ($p=0.500$).

Table 3. Evaluation of *Scatterplot cutoffs* and *Pasternak's cutoffs* (≤ 0.5 , ≥ 5.5) for the current study's cohort for prediction of unilateral (either ipsilateral or contralateral) aldosterone hypersecretion.A. *Scatterplot cutoffs.*

	LIR (<0.5, >5.4)			RIR (<0.5, >7.0)		
	Derivation cohort	Validation cohort	Total	Derivation cohort	Validation cohort	Total
<i>n</i>	218	34	252	228	44	272
Sensitivity	36.3	65.2	42.1	55.7	53.3	55.1
Specificity	100	81.8	98.6	100	85.7	98.6
PPV	100	88.2	96	100	88.9	97.2
NPV	68.6	52.9	67.3	75.3	46.2	71.5

B. *Pasternak's cutoffs.*

	LIR (≤ 0.5 , ≥ 5.5)			RIR (≤ 0.5 , ≥ 5.5)		
	Derivation cohort	Validation cohort	Total	Derivation cohort	Validation cohort	Total
Sens	37.4	65.2	43.0	66.0	56.7	63.8
Spec	99.2	81.8	97.8	96.9	78.6	95.2
PPV	97.1	88.2	94.2	94.1	85.0	92.0
NPV	68.9	52.9	67.5	79.4	45.8	75.0

Values are presented as %.

LIR is aldosterone/cortisol ratio (ACR) of left adrenal vein (LAV) to inferior vena cava (IVC) [ACR of LAV/ACR of IVC ratio] and RIR is ACR of right adrenal vein (RAV) to IVC [ACR of RAV/ACR of IVC ratio].

NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

There were 85 CT findings of unilateral PA. The number of patients having CT findings concordant with the AV/IVC index was 17, 12 with non-lateralizing CT, and 29 on the opposite side suggested by the *Scatterplot cutoffs*. The inappropriate adrenalectomy rate of CT imaging was 53.8% and decreased to 0% when the AV/IVC index [*Scatterplot cutoff* (RIR >7 or LIR >5.4) or *Pasternak's cutoff* (RIR ≥ 5.5 or LIR ≥ 5.5)] were combined. In addition, this combination of CT imaging and AV/IVC index cutoffs resulted in a decrease in failed lateralization rate from 17.6% to 8.1%.

Discussion

This study confirmed and modified values of the AVS parameter by Pasternak *et al.*¹¹ to subgroup PA in cases of incomplete AVS data due to unilateral cannulation failure. We have proposed the original cutoff values for our cohort, *Scatterplot*

cutoffs and *ROC curve cutoffs*, using LIR and RIR. Although the cutoff values were determined, the sensitivity and specificity were not high (Supplemental file 3). We also present LIR and RIR cutoffs derived from the ROC method for the ipsilateral and contralateral disease, and compare them with previous suggested diagnostic cutoff values, that is, *Pasternak's cutoffs* and *Funder's cutoffs*.^{11,14} The prediction of contralateral disease by RIR and LIR performed better in sensitivity and specificity to determine PA subtype compared with ipsilateral disease, as in a previous study.¹³

The success rate of AVS is usually dependent on the skill of the interventionist, vessel anatomy, respiration movement, and well-defined protocol.²¹ It is generally known that the success rate of RAV catheterization is lower than that of LAV due to anatomical variation, which was consistent with the current study. The generally accepted

	RIR		LIR				
	Sens	Spec	Sens	Spec			
Ipsilateral	7.0 ^a	26.4	99.5	33.8	100.0	5.5 ^{a, b}	
	5.5 ^b	45.3	97.7	73.5	81.5		
	3.9 ^c	75.5	90.9	80.9	63.6		3.1 ^c
	2.5 ^d	84.9	68.0	56.5	98.5		2.5 ^d
Contralateral	1.0 ^d	97.3	91.9	97.8	93.2	1.0 ^d	
	0.8 ^c	94.6	94.9	95.7	96.1		
	0.5 ^{a, b}	77.0	99.0	77.0	99.0		0.5 ^{a, b}
Cutoffs	RIR		LIR				
^a Scatterplot cutoffs	< 0.5 or > 7.0		< 0.5 or > 5.4				
^b Pasternak's cutoffs	≤ 0.5 or ≥ 5.5		≤ 0.5 or ≥ 5.5				
^c ROC curve cutoffs	≤ 0.8 or > 3.9		≤ 0.8 or > 3.1				
^d Funder's cutoffs	< 1.0 or > 2.5		< 1.0 or > 2.5				

Figure 3. Application of various cutoffs to the total study cohort. LIR is aldosterone/cortisol ratio (ACR) of left adrenal vein (LAV) to inferior vena cava (IVC) (ACR of LAV/ACR of IVC ratio) and RIR is ACR of right adrenal vein (RAV) to IVC (ACR of RAV/ACR of IVC ratio). ROC, receiver operating characteristic; Sens, sensitivity; Spec, specificity.

diagnostic criteria for subtyping PA, LI, which assumes the success of both AV catheterizations, cannot be used in the case of cannulation failure on one side. This results in the loss of a chance to manage PA properly and sometimes requires another AVS, an invasive procedure in which patients are exposed to an extra dose of radiation. Therefore, the clinical implication of the current study is that it can help to determine a management plan in PA patients with incomplete AVS data.

Lower potassium level, higher prevalence of hypokalemia, higher DDD, and a higher prevalence of unilateral lesions were observed in the validation cohort in the present study. Although the explanation for the differences between the derivation and validation cohorts remains unclear, the reasons for conducting the test for PA in each cohort might be responsible.

When analyzing SI and LI, abnormal excess cortisol levels can be problematic. Cases of simultaneous

PA and autonomous cortisol secretion have been reported recently.²² In addition, a retrospective report found a subclinical hypercortisolism prevalence of 21% in a series of 38 PA cases with unilateral aldosterone hypersecretion.²³ Elevated cortisol levels of the AV can complicate the exact calculation of ACR used to interpret AVS results. Some researchers have used absolute aldosterone values instead of ACR in the case of subclinical hypercortisolism or overt Cushing's syndrome.^{23,24} In this context, the current study has strength in the high accuracy of ACR by excluding patients with possible hypercortisolism. To exclude PA patients with cortisol co-secretion, we used the criteria for diagnosing subclinical hypercortisolism: cortisol level after 1 mg DST >5.0 µg/dL or >2.2 µg/dL along with one parameter among low levels of ACTH and DHEA-S, as described previously.¹⁷ These criteria were identified using the occurrence of immediate, postsurgical hypocortisolism indicating presurgical inappropriate cortisol elevation, one of the alternative gold standard criteria for the diagnosis of subclinical hypercortisolism. Furthermore, they also were associated with metabolic complications. Therefore, participants with cortisol after 1 mg DST between 1.8 µg/dL and 2.2 µg/dL, who were included in the present study, had a lower possibility of having subclinical hypercortisolism.

The upper RIR limit of the *Scatterplot cutoffs* was >7 while that of the LIR was >5.4. Meanwhile, the lower RIR and LIR cutoffs were the same (<0.5). When the values for RIR and LIR were aligned to set the *Scatterplot cutoffs* for the derivative cohort, there were no outliers in each item that could cause abnormally high cutoff values. The RIR distribution cluster in the bilateral PA was located at a higher level compared with the LIR. However, we are unaware of any studies that provide the reason for the difference in each side's upper limit. A possible assumption could be the difference in vascular anatomy and, accordingly, different catheter tip positions. Further carefully designed studies that take catheter tip position into account in both adrenal veins or the distribution of RIR and LIR in a different study population are necessary to demonstrate the reason for this difference.

The *Scatterplot cutoffs* for LIR <0.5 or >5.4 showed a relatively low specificity of 81.8% in the validation cohort, while that of the derivation

cohort was 100%. The 100% specificity for the *Scatterplot cutoffs* in the derivation cohort was inevitable due to the method used to obtain the cutoff values.¹¹ Since the derivation cohort's study population was about three times larger than the validation cohort, applying the reference values obtained from the derivation cohort to the validation cohort could have caused the gap in specificity between cohorts. Moreover, it may be necessary to re-evaluate these values in a new validation cohort with a similar number of patients as in the derivation cohort, so we will apply this in the next study to obtain more generalizability. We also propose that the BHA severity would have caused the low specificity in the validation cohort using LIR cutoff. In the case of severe BHA, LIR (and also RIR) can cause a false positive result on unilateral PA prediction. Side-to-side comparison of the ACR (lateralization index) is not high enough to discriminate laterality in such cases. Still, the ratio of each adrenal vein's ACR to that of IVC can be increased. The validation cohort had BHA patients with higher DDD and lower serum potassium level compared with the derivation cohort (data not shown), which infers the possibility of more severe BHA cases in the validation cohort and derives the results. Similarly, in the study of Strajina *et al.*,¹³ there were bilateral PA cases with AV/IVC index ≥ 5.5 , which had been proposed as the upper cutoff value to decide the ipsilateral disease by Pasternak *et al.*¹¹ These cases lowered specificity and caused 18% of unnecessary operations. Meanwhile, the cutoff value of ≤ 0.5 performed well in identifying contralateral cases.¹³ Therefore, the use of the AV/IVC index may be less useful in diagnosing ipsilateral PA.

There are mixed results regarding the relationship between contralateral suppression of aldosterone level and PA cure rate^{25–28} in unilateral PA cases. Despite some studies that do not emphasize the clinical implication of contralateral suppression,^{26,27} recent consensus statements suggest that it could help in PA subtyping, especially cases in the 'grey zone' by LI. We accepted the concept of contralateral suppression and analyzed cutoffs for predicting ipsilateral or contralateral disease. In this study, LIR ≤ 0.8 and RIR ≤ 0.8 by *ROC curve cutoffs* successfully identified patients with PA of the contralateral side with a sensitivity and specificity of around 95% (Figure 3).

To the best of our knowledge, this is the first study introducing different cutoff criteria for the right and left sides. We present separate cutoffs for LIR and RIR because cannulation failure can occur on the left side as well as the right side (Figure 3). In our analysis set, RAV and LAV failure occurred 23.2% and 8.0%, respectively. Clinicians can use LIR in the case of RAV cannulation failure, and vice versa. Using LIR and RIR for predicting contralateral disease showed higher sensitivity and specificity compared with ipsilateral disease prediction. Similar results were obtained from the study of Strajina *et al.*,¹³ as summarized above.

When comparing the cutoffs from previous studies with those of ours, *Funder's cutoffs* (>2.5 or <1) showed the highest sensitivity, which increases the possibility of detecting unilateral PA. Consequently, there would be a higher chance of curing PA by adrenalectomy. Still, the possibility of unnecessary surgery could happen, and it could be problematic in many ways, that is, ethical and socio-economic problems, and post-operative complications. On the contrary, since the ≥ 5 or ≤ 0.5 cutoffs had the highest specificity, the authors believe that the frequency of unnecessary surgery due to misinterpretation would be decreased. When comparing the four different criteria, the sensitivity was high in the order *Funder's cutoffs*, *ROC curve cutoffs*, *Pasternak's cutoffs*, and *Scatterplot cutoffs*. Therefore, clinicians may choose which criteria to adopt, and the decision-making process will require a thorough discussion with the patient considering the sensitivity and specificity of each criterion since the management plan can be different. Applying LIR or RIR is helpful in determining PA lateralization without repetitive AVS. We experienced several primary aldosteronism cases with unilateral catheterization failure but successfully subtyped PA using the LIRs in both ipsilateral and contralateral disease (Supplemental file 4).

Recently, Primary Aldosteronism Surgical Outcomes (PASO) investigators reported consensus criteria for adrenalectomy outcomes for unilateral PA.²⁹ Since the post-adrenalectomy outcomes can be another gold standard for unilateral PA, we selected biochemically cured patients in both institutions and found alternative cutoff values for unilateral disease using the scatterplot and ROC methods (Supplemental file 5).

There were 47 and 21 biochemically completely or partially cured patients in the derivation and validation cohorts, respectively. The range of *Scatterplot* and *ROC curve cutoffs* widened compared with the previous analysis. The sensitivity of RIR increased in all cutoffs but was not consistently changed in RIR and LIR specificity. Even with partially cured patients (complete + partial cure), these trends were similar. Further research studies with more patients and inclusion criteria from the PASO study will be needed to strengthen the evidence of the AV/IVC index utility.

There have been attempts to infer PA subtyping with image results only, such as CT or MRI. However, the sole use of CT for PA subtyping showed low accuracy in previous studies.^{3,4,30} When the CT images and cutoffs obtained from the AVS were used together to determine ipsilateral disease, the rates of “inappropriate adrenalectomy” and “failed lateralization” decreased in this study. A previous study showed a decrease in inappropriate adrenalectomy rate and an increase in failed lateralization in this particular setting.¹³ Different study populations, that is, those that excluded possible cortisol excess cases, might have caused this difference. Further detailed analyses on the combination of CT images and AVS data seem essential and helpful for improving the diagnosis rate of unilateral disease.

There are some limitations to the current study. First, it was a retrospective study based on medical records previously obtained from complete and successful AVS, which could cause selection bias. Second, the catheterization success rate was relatively low in both institutions, especially with a single attempt. Since contralateral aldosterone suppression is not found in 89–93% of PA in non-stimulated AVS studies,³¹ the cutoffs for contralateral disease in our study would not be applicable in such cases. Both institutions in this study used continuous intravenous ACTH infusion during AVS, so the cutoffs under non-ACTH infusion need to be studied.

In conclusion, when a single AV cannulation fails in AVS, we propose several cutoffs using the AV/IVC index, LIR or RIR, that could help clinicians to discriminate the PA lateralization. However, the AV/IVC index would be less helpful to subtype ipsilateral PA due to relatively low sensitivity and specificity compared with those

of contralateral PA. A future well-designed prospective study or meta-analysis will be needed to determine the diagnostic standards for PA subtype despite AV cannulation failure on one side.

Authors contribution

JHK and SHL conceived the idea for the manuscript and decided the overall theme and content. HSP, DH, SKC, SEK, JWK, and HKY collected the data. GK, JHY, and JA performed the analysis. SEL, SWP, and MSC wrote the first draft. JEJ, BJK, and JMK revised the manuscript. All authors critically reviewed and approved the final version.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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