Original Article

The diagnostic accuracy of adjusted unconventional indices for adrenal vein sampling in the diagnosis of primary aldosteronism subtypes

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Objective: Simple unconventional indices did not demonstrate a satisfactory accuracy for diagnosing unilateral primary aldosteronism when adrenal vein sampling is not bilaterally selective. This study aimed to evaluate the reliability of clinical/imaging-corrected unconventional indices for adrenal vein sampling in predicting unilateral primary aldosteronism.

Methods: Data of all consecutive patients with primary aldosteronism subtyped with adrenal vein sampling, referred to two Italian centers, were analyzed retrospectively. All patients with proved unilateral aldosterone hypersecretion underwent adrenalectomy.

Results: Unilateral disease was diagnosed in 58 cases (54.2%) and idiopathic hyperaldosteronism in 49 individuals (45.8%). The monoadrenal index (aldosterone-to-cortisol ratio in the adrenal vein) showed high accuracy in predicting ipsilateral disease and moderate accuracy in predicting contralateral aldosterone hypersecretion. The monolateral index (aldosterone-to-cortisol ratio in the adrenal vein vs. peripheral blood) revealed moderate accuracy in predicting ipsilateral disease and high accuracy in predicting contralateral aldosterone hypersecretion. Lesion side- and hypokalemia-corrected ROC curves for these unconventional indices revealed a significant improvement in the reliability of predicting ipsilateral/contralateral disease, reaching high accuracy in all models. For an immediate clinical application of our results, the adjusted cut-offs were calculated, according to the Youden's criterion and to a pre-established specificity of 95%, for all possible combinations of lesion side at imaging and presence/absence of hypokalemia.

Conclusion: This study demonstrated the high diagnostic accuracy of clinical-/imaging-corrected unconventional indices for adrenal vein sampling in the diagnosis of primary aldosteronism subtypes and suggests the use of these adjusted indices to select patients for adrenalectomy when adrenal vein sampling is not bilaterally selective.

Keywords: adrenal glands, adrenal tumor, adrenalectomy, aldosterone, aldosteronism, cortisol, diagnosis, endocrine hypertension, hypokalemia, secondary hypertension

Abbreviations: +LR, positive likelihood ratio; A/C, aldosterone/cortisol ratio; APA, aldosterone-producing adenoma; ARR, aldosterone-to-renin ratio; AUC, area under the curve; AVS, adrenal vein sampling; BP, blood pressure; CCT, captopril challenge test; CT, computed tomography; IHA, idiopathic hyperaldosteronism; IVC, inferior vena cava; −LR, negative likelihood ratio; MAI, monoadrenal index; MI, monolateral index; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ROC, receiver-operating characteristic; SIT, saline infusion test

INTRODUCTION

Primary aldosteronism is a heterogeneous group of disorders caused by an excessive aldosterone secretion that seems autonomous from renin [1–3] and is the most frequent form of secondary hypertension. Its prevalence increases with the severity of hypertension [4,5], reaching over 29% in individuals with resistant hypertension [6]. Diagnosing primary aldosteronism is important to give patients the opportunity of a specific surgical or medical treatment in order to reduce cardiovascular risk, development of organ damage and primary aldosteronism-associated mortality [7–9].

The last step of the diagnostic process is the subtype differentiation, which has a key role to distinguish between unilateral and bilateral primary aldosteronism. Adrenal vein sampling (AVS) is currently considered the gold standard for this aim but, because of the technical difficulties of its

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execution, it is characterized by low diffusion among centers worldwide, with a reported success rate ranging from 26 to 81% [10–12]. The reason mainly lies in the difficulty of cannulation of the right adrenal vein, which usually drains directly into the inferior vena cava (IVC) and is typically smaller and shorter than the left one. Many studies have demonstrated that an expert and dedicated radiologist is a key factor for significantly improving sampling success [10,13–15].

The major diagnostic indices for the assessment of lateralization of aldosterone hypersecretion are the lateralization index, defined as the dominant vs. nondominant adrenal vein aldosterone/cortisol ratio (A/C), and the contralateral index, defined as the nondominant adrenal vein vs. the inferior vena cava A/C [16]. These indices, however, have been validated and can be reliably interpreted only when AVS is bilaterally selective. Therefore, during last years, unconventional AVS indices have been proposed in order to determine the lateralization of aldosterone secretion even in the case of lack of selective cannulation of both adrenal veins.

In the present study, we evaluated the performance of two unconventional indices in predicting lateralized aldosterone hypersecretion: the monolateral index (MI), defined as A/C in the adrenal vein divided by A/C in IVC and the monoadrenal index (MAI), defined as A/C in the adrenal vein. In the literature, few studies have explored the performance of these indices, both in cosyntropin stimulated and in noncosyntropin stimulated conditions, reporting a moderate [17,18] and often not reproducible accuracy [19–21]. Moreover, the lack of accepted standards for the performance of selective AVS and the interpretation of its results contributes to the hesitancy towards the adoption of the unconventional indices in the case of nonconclusive AVS data. Therefore, many primary aldosteronism patients are denied curative surgery or undergo adrenalectomy without the evidence of lateralization, which may result in the removal of an adrenal gland in a patient with idiopathic hyperaldosteronism (IHA).

Therefore, this study aimed to investigate the reliability of these indices in predicting lateralization in unstimulated AVS procedures. The novelty of the present study was the attempt to integrate the information derived from these indices with that carried by other recognized predictors of unilateral hypersecretion, in order to create a unique clinical-/imaging-adjusted diagnostic score.

METHODS

Design and study population

Data of all patients with biochemical and subtype diagnosis of primary aldosteronism, referred between January 2009 and December 2019 to two tertiary referral centers in northern Italy (the Division of Endocrinology, Diabetes and Metabolism of the University of Turin and the Endocrinology Unit of the University of Padua), were collected from prospective registries and analyzed retrospectively. The study followed the Standards for Reporting Diagnostic accuracy studies (STARD) [22]. The protocol included patients who underwent successful AVS, defined as bilateral cortisol ratio between adrenal vs. peripheral vein greater than 2 (selectivity index), with at least 6–12 months of follow-up after eventual adrenalectomy. Exclusion criteria were: diagnosis of aldosterone- and cortisol-co-secreting adrenal tumors, nonselective (selectivity index <2) and cosyntropin-stimulated AVS.

Approvals from local ethics committees were obtained (no. 0029680) and patients provided their written informed consent in all centers (ClinicalTrials.gov no. NCT04378387).

Clinical and biochemical investigations

Clinical and biochemical evaluation at diagnosis were collected. Office BP values were measured according to guidelines [23]. BP control was defined as an average office BP less than 140/90 mmHg. Hypokalemia was defined as serum potassium levels less than 3.5 mmol/l. Plasma aldosterone concentration (PAC), plasma renin activity (PRA) and PAC after saline infusion test (SIT) were determined in all patients after the replacement of interfering drugs, according to ES guidelines [1]. Furthermore, before the hormonal testing, hypokalemia was corrected and patients were advised to maintain a normal sodium intake. Patients remained in the same therapy during the entire diagnostic workup (from first-line tests to AVS). Primary aldosteronism was diagnosed when the following criteria were met at the same time: aldosterone-to-renin ratio (ARR) greater than 300 (pg/ml)/(ng/ml/h) and plasma aldosterone concentration (PAC) after saline infusion test (SIT) greater than 100 pg/ml or ARR after captopril challenge test (CCT) greater than 300 (pg/ml)/(ng/ml per h) or PAC reduction after CCT less than 30% compared with the pretest value.

Differentiation of primary aldosteronism subtypes

In all patients with proven primary aldosteronism, computed tomography (CT) of the adrenal glands was performed to identify any adrenal lesions and to localize adrenal veins. Moreover, patients were eligible to AVS if they agreed to undergo unilateral adrenalectomy in case of demonstration of lateralized aldosterone hypersecretion. AVS was performed by two experienced radiologists between 0800 and 1100 h, using sequential cannulation and without cosyntropin stimulation. No more than 15 min elapsed between sampling of the left and right adrenal veins. AVS was performed via a percutaneous femoral vein approach and the adrenal veins were cannulated using a fluoroscopy guide.

A selectivity index greater than 2 was considered to be indicative of selective sampling. Intraprocedural cortisol measurement was routinely used in our centers to evaluate the correct placement of catheter. A lateralization index greater than 3 was considered to demonstrate lateralization of aldosterone production. When results of AVS were inconclusive, the repetition of AVS was offered to the patient.

All patients with lateralization of aldosterone secretion (lateralization index >3) underwent adrenalectomy; the diagnosis of unilateral primary aldosteronism was confirmed after surgery by histological examination, cure or significant amelioration of hypertension, normokalemia, normal ARR and low aldosterone levels, and/or the normal suppressibility of aldosterone. Outcomes of adrenalectomy were assessed according to the PASO criteria [24].

Unconventional indices

For each adrenal gland, we calculated the monolateral index (MI, A/C in the adrenal vein divided by A/C in IVC) and the monoadrenal index (MAI, A/C in the adrenal vein). The diagnostic accuracy of these unilateral indices in predicting the final diagnosis of unilateral primary aldosteronism was assessed classifying single adrenal glands into three secretive conditions: glands with ipsilateral hypersecretion, with contralateral hypersecretion or glands within a setting of bilateral hypersecretion.

Analytical methods

Serum aldosterone levels (pg/ml) were measured by RIA (ALDOCTK-2; Sorin Biomedica, Saluggia, Italy). The sensitivity of the assay was 10 pg/ml; the intra-assay and inter-assay coefficient of variation ranges from 1.7 to 5.3% and from 3.4 to 7%, respectively. PRA (ng/ml per h) was assessed by radioimmunoassay (RENCTK, Sorin Biomedica). The sensitivity of the assay was 0.20 ng/ml; the intra-assay and interassay coefficient of variation ranges from 5.4 to 9.9% and from 7.7 to 11.5%, respectively. Serum cortisol levels (μg/l) were determined by a competitive electrochemiluminescence immunoassay automated on Cobas e601 instrument (Roche Diagnostics GmbH, Germany). Analytical sensitivity was 0.018 μg/dl (0.500 nmol/l). Intra-assay and inter-assay precision for serum cortisol ranged from 3 to 5.7% and from 2.4 to 6.2%, respectively. All other biochemical variables were assayed in plasma or serum using standard methods.

Statistical analysis

Baseline characteristics of all patients are summarized using median and interquartile range (IQR) for continuous non-normally distributed variables (or mean and standard deviation for normally distributed ones). Categorical variables are summarized using percentage values. Shapiro–Wilk test was used to assess normality. Between-group differences in personal and clinical features were evaluated by the Student *t*-test or Mann–Whitney *U*-test for continuous variables and by the chi-square test or Fisher's exact test for categorical variables. Paired *t*-test or Wilcoxon signed-rank test were used for paired data comparison in patients before and after adrenalectomy. A P value less than 0.05 was considered statistically significant.

Receiver-operating characteristic (ROC) curves were computed to evaluate the performances of the unconventional indices (MI and MAI) for the reciprocal distinction between the three gland secretive conditions; more specifically, a pairwise classification analysis was performed in order to distinguish glands with ipsilateral disease from those with bilateral hypersecretion and glands with contralateral disease from those with bilateral hypersecretion.

After a logarithmic transformation, these indices were then included in multivariate logistic regression models, together with lesion side at imaging and the presence of hypokalemia, in order to improve their performance in the outcome prediction. The performances of the multivariate classifiers (the covariate-adjusted indices) obtained by the weighted combination of these predictors according to the regression coefficients of each model was again evaluated using ROC curves. In all the ROC curve analyses, the best cut-offs for the outcome prediction were identified according to Youden's index criterion, reporting the corresponding sensitivity, specificity, positive likelihood ratio (+LR) and negative likelihood ratio (−LR). The cut-offs corresponding to a specificity of 95% were reported, as they may represent the most useful ones for the purpose of a clinical decision-making process. Statistical analysis was performed using R 3.5.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2019).

RESULTS

One hundred and fifty-three AVSs were performed in our centers from January 2009 to December 2019. As shown in Fig. 1, 13 cosyntropin-stimulated, 32 nonbilaterally selective AVSs and 1 case with partial data were excluded from the study. Finally, 107 procedures met the inclusion criteria (68 male individuals, 63.5% and 49 female individuals, 36.5%). The subtype diagnosis of primary aldosteronism revealed 58 cases (54.2%) of lateralized aldosterone secretion (65.5% on the left and 34.5% on the right side) and 49 individuals (45.8%) with IHA.

No differences between unilateral primary aldosteronism and IHA groups were found in sex, center of diagnosis, age at diagnosis of hypertension and primary aldosteronism, duration of hypertension, weight, BMI, SBP, DBP, number of antihypertensive drugs, sodium, PRA, ARR, lesion size and bilateral selectivity indices (Table 1).

As expected, when compared with IHA patients, unilateral primary aldosteronism individuals had lower levels of potassium (2.9 ± 0.5 vs. 3.6 ± 0.5 mmol/l; $P < 0.001$), higher values of PAC (475, 306–726 vs. 355, 260–497 pg/ml; $P = 0.016$), PAC after SIT (225, 130–342 vs. 141, 111–202 pg/ml; $P = 0.002$), and PAC after CCT (436, 317–577 vs. 236, 147–262; $P < 0.001$). Unilateral primary aldosteronism group showed a lower rate of bilateral adrenal hyperplasia/normal adrenal glands at CT (7.4 vs. 49%; $P < 0.001$) and higher rate of left (55.5 vs. 26.5%; $P < 0.001$) and right adrenal nodules (24.1 vs. 16.3%; $P < 0.001$), compared with IHA patients (Table 1).

Postsurgery outcomes

Histological examination discovered 49 cases of APA, 6 adrenal hyperplasia and 2 micronodular hyperplasia. The re-evaluation at 6–12 months after adrenalectomy, according to PASO criteria [24], demonstrated the positive outcome of surgical treatment on BP, sodium, potassium, number of antihypertensive drugs, ARR, PAC and PAC after SIT, without significant effect on weight and BMI (Table S1, http://links.lww.com/HJH/B499). Complete biochemical success was achieved in 96.2% and partial in 3.8% of patients. Complete clinical success was reached in 41.5% and partial in 58.5% of patients. All patients that achieved complete success were amongst those who also achieved complete biochemical success (data not shown).

Diagnostic accuracy of unconventional indices

The diagnostic accuracy of MAI and MI was assessed to distinguish glands with ipsilateral disease from those with

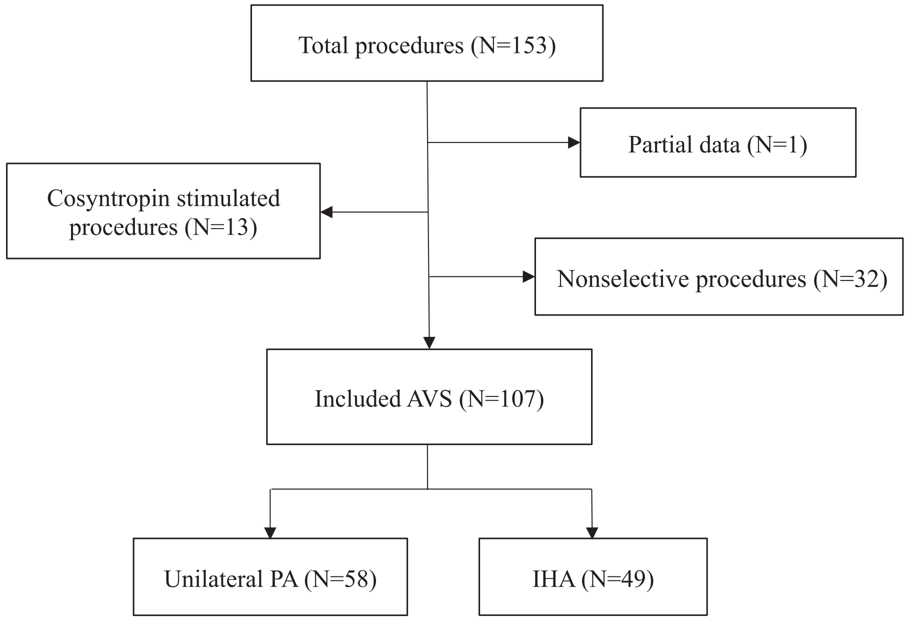

FIGURE 1 Study flow chart. AVS, adrenal vein sampling; IHA, idiopathic hyperaldosteronism; PA, primary aldosteronism.

bilateral hypersecretion and glands with contralateral disease from those with bilateral hypersecretion. MAI showed a high accuracy in predicting ipsilateral disease [AUC 0.90, 95% CI 0.83–0.95, cut-off >4.78 (pg/ml)/(μg/l), sensitivity 78%, specificity 90%, +LR 7.8, −LR 0.24] and a moderate accuracy in predicting contralateral aldosterone hypersecretion [AUC 0.79, 95% CI 0.71–0.86, cut-off <1.03 (pg/ml)/(μg/l), sensitivity 70%, specificity 78%, +LR 3.2, −LR 0.38].

The MI revealed a moderate accuracy in predicting ipsilateral disease (AUC 0.77, 95% CI 0.68–0.84, cut-off

TABLE 1. Clinical characteristics for all patients and differences between the idiopathic hyperaldosteronism and the unilateral primary aldosteronism groups

Variables/parameters	Overall data ($N = 107$)	Diagnosis: IHA ($N = 49$)	Diagnosis: Unilateral PA ($N = 58$)	P value
Center				
Turin	56.1%	65.3%	46.3%	0.074
Padua	43.9%	34.7%	53.7%	
Male sex	63.5%	69.4%	57.4%	0.227
Age at diagnosis of AH (years)	39 ± 11	40 ± 10	39 ± 12	0.888
Age at diagnosis of PA (years)	49 ± 11	49 ± 10	48 ± 12	0.636
Duration of hypertension (years)	6 (2–12)	9 (3–15)	5 (2–11)	0.346
Weight at diagnosis (kg)	79 ± 16	81 ± 17	78 ± 16	0.313
BMI (kg/m^2)	27.35 ± 4.26	27.85 ± 4.77	27.00 ± 3.95	0.355
SBP (mmHg)	160 (140–170)	160 (145–175)	157 (140–170)	0.366
DBP (mmHg)	100 (90–110)	100 (90–110)	100 (90–100)	0.160
No. of antihypertensive drugs	2 (1–3)	2 (1–3)	2 (1–3)	0.155
Sodium (mmol/l)	143 ± 2	143 ± 3	143 ± 2	0.800
Potassium (mmol/l)	3.2 ± 0.6	3.6 ± 0.5	2.9 ± 0.5	<0.001
PAC (pg/ml)	387 (285–598)	355 (260–497)	475 (306–726)	0.016
PRA (ng/ml/h)	0.20 (0.10–0.67)	0.20 (0.10–0.67)	0.21 (0.10–0.65)	0.841
ARR [(pg/ml)/(ng/ml per h)]	1553 (665–3075)	1249 (616–3020)	2209 (738–3322)	0.240
PAC after SIT (pg/ml)	176 (120–259)	141 (111–202)	225 (130–342)	0.002
PAC after CCT (pg/ml)	359 (229–482)	236 (147–262)	436 (317–577)	<0.001
Lesion size (mm)	13 (10–18)	15 (10–15)	13 (10–19)	0.907
Lesion side				
Absent/hyperplasia	27.1%	49.0%	7.4%	
Left	41.1%	26.5%	55.5%	<0.001
Right	21.5%	16.3%	24.1%	
Bilateral	10.3%	8.2%	13.0%	
Left SI	13.7 (5.8–22.3)	13.3 (5.7–22.9)	14.1 (6.0–21.1)	0.604
Right SI	19.7 (7.3–38.7)	22.0 (8.5–39.0)	17.1 (7.2–28.3)	0.244

AH, arterial hypertension; ARR, aldosterone-to-renin ratio; CCT, captopril challenge test; IHA, idiopathic hyperaldosteronism; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SI, selectivity index; SIT, saline infusion test.

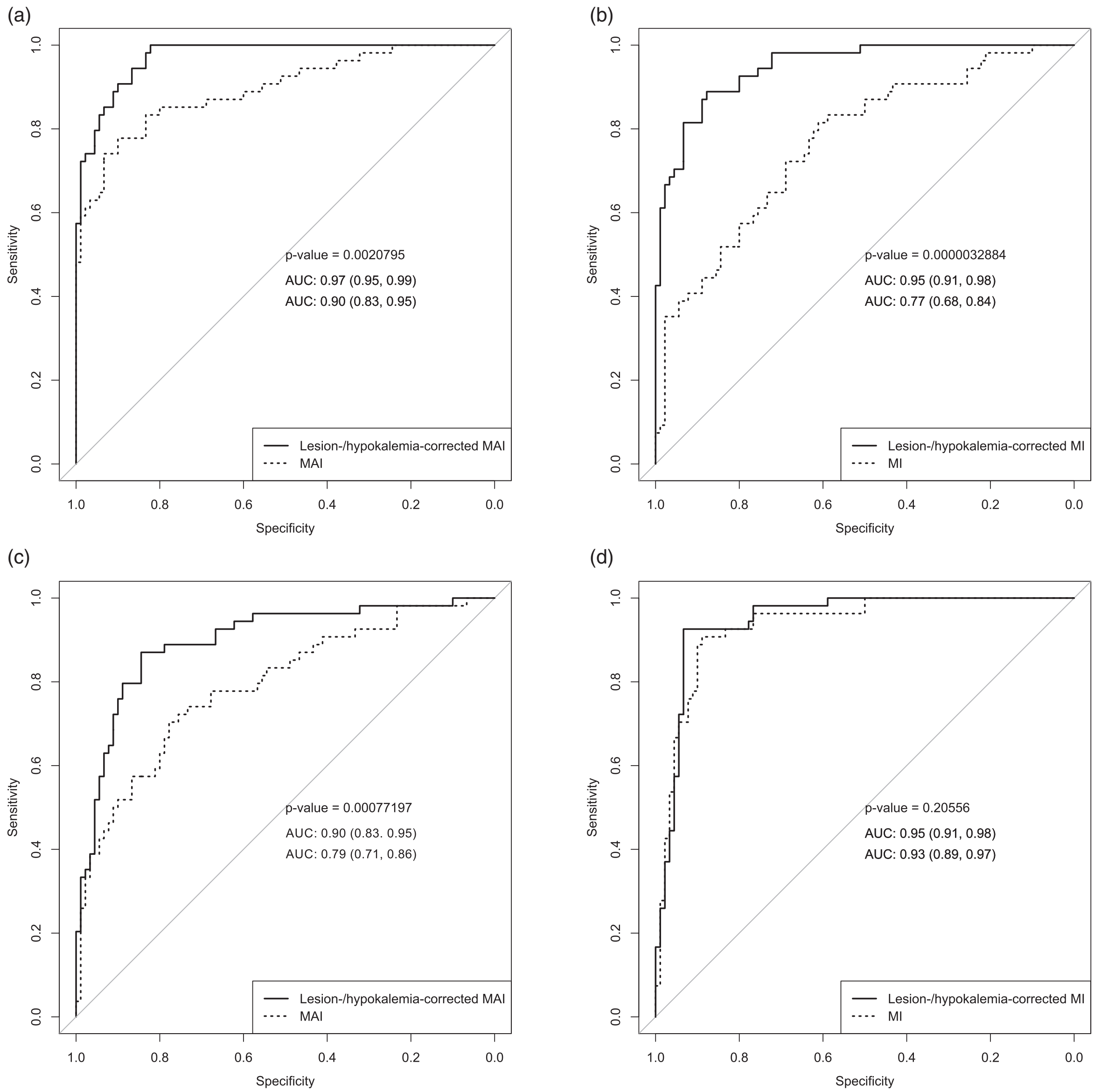

FIGURE 2 Comparison of receiver-operating characteristic curves of simple and corrected unconventional indices. Comparison of ROC curves of simple and lesion-/hypokalemia-corrected MAI (a and c) and MI (b and d) in the prediction of ipsilateral (a and b) and contralateral (c and d) aldosterone hypersecretion. AUC, area under the curve; MAI, monoadrenal index; MI, monolateral index; ROC, receiver-operating characteristic.

$>$1.76, sensitivity 81%, specificity 61%, +LR 2.1, −LR 0.3) and a high accuracy in predicting contralateral aldosterone hypersecretion (AUC 0.93, 95% CI 0.89–0.97, cut-off $<$0.51, sensitivity 91%, specificity 89%, +LR 8.3, −LR 0.1) (Fig. 2).

Diagnostic accuracy of corrected unconventional indices

Multivariate logistic regression models, considering as covariates lesion side at CT and hypokalemia, were used to create lesion- and hypokalemia-corrected MAI and MI.

Lesion side at imaging was initially considered as a three-level (ipsilateral lesion, contralateral lesion, bilateral/no lesions) unordered categorical variable; however, in all models predicting ipsilateral disease, no statistically significant differences were found between the 'contralateral lesion' and the 'bilateral/no lesions' categories; similarly in all models predicting contralateral disease, no statistically significant differences were found between the 'ipsilateral lesion' and the 'bilateral/no lesions' categories. Therefore, all logistic regression models were simplified by merging the lesion categories that did not significantly differed, thus reducing lesion side at imaging to a binary variable. Complete data about the final logistic regression models are available in the supplementary material (Tables S2–S5, http://links.lww.com/HJH/B499).

The ROC curves, evaluating the performances of the multivariate regression models, revealed a significant improvement in the accuracy of predicting ipsilateral and contralateral disease. In particular, for the prediction of ipsilateral aldosterone hypersecretion, both lesion-/hypokalemia-corrected MAI (AUC 0.97, 95% CI 0.95–0.99; Fig. 2a) and MI (AUC 0.95, 95% CI 0.91–0.98; Fig. 2b) achieved high accuracy. The same was also true for the diagnosis of contralateral disease, again with both lesion-/

TABLE 2. Cut-offs, sensitivity and specificity of the model equations of lesion- and hypokalemia-corrected unconventional indices, according to the Youden's criterion and by setting specificity at 95%

Index	Predicted side of hypersecretion	Model equation	Equation cut-offs (Youden's criterion)			Equation cut-offs (optimized specificity)		
			Cut-off	Se	Sp	Cut-off	Se	Sp
MI	Ipsilateral	$4.77 \cdot \log_{10}MI + 3.38 \cdot IL + 3.01 \cdot HK$	>5.26	89%	88%	>6.22	70%	95%
	Contralateral	$4.47 \cdot \log_{10}MI - 1.65 \cdot CL - 0.87 \cdot HK$	<−2.94	93%	93%	<−3.82	72%	95%
MAI	Ipsilateral	$6.03 \cdot \log_{10}MAI + 3.57 \cdot IL + 2.57 \cdot HK$	>6.26	100%	82%	>8.00	80%	95%
	Contralateral	$2.15 \cdot \log_{10}MAI - 2.03 \cdot CL - 1.77 \cdot HK$	<−2.07	87%	84%	<−3.76	52%	95%

In the model equations, IL and CL should be considered as binary variables equal to 1 if an ipsilateral/contralateral lesion is present at imaging and equal to 0 if not. The meaning of HK should be interpreted similarly. CL, contralateral lesion; HK, hypokalemia; IL, ipsilateral lesion; MAI, monoadrenal index; MI, monolateral index; Se, sensitivity; Sp, specificity.

hypokalemia-corrected MAI (AUC 0.90, 95% CI 0.83–0.95; Fig. 2c) and MI (AUC 0.95, 95% CI 0.91–0.98; Fig. 2d) achieving high accuracy. The improvement of covariate-adjusted unconventional indices was statistically significant for all the models (Fig. 2), with the exception of MI for contralateral disease prediction, in which the improvement was not significant as the predicting power of the uncorrected index was already strong. As already stated before, the cut-offs identified by Youden's criterion and those corresponding to a preestablished specificity of 95% were both taken into account (Table 2 summarizes the performances of these indices; Fig. 3 shows graphically the high accuracy achieved).

For an immediate clinical application of our results, we then calculated the thresholds of these covariate-adjusted unconventional indices in an explicit form, for all possible

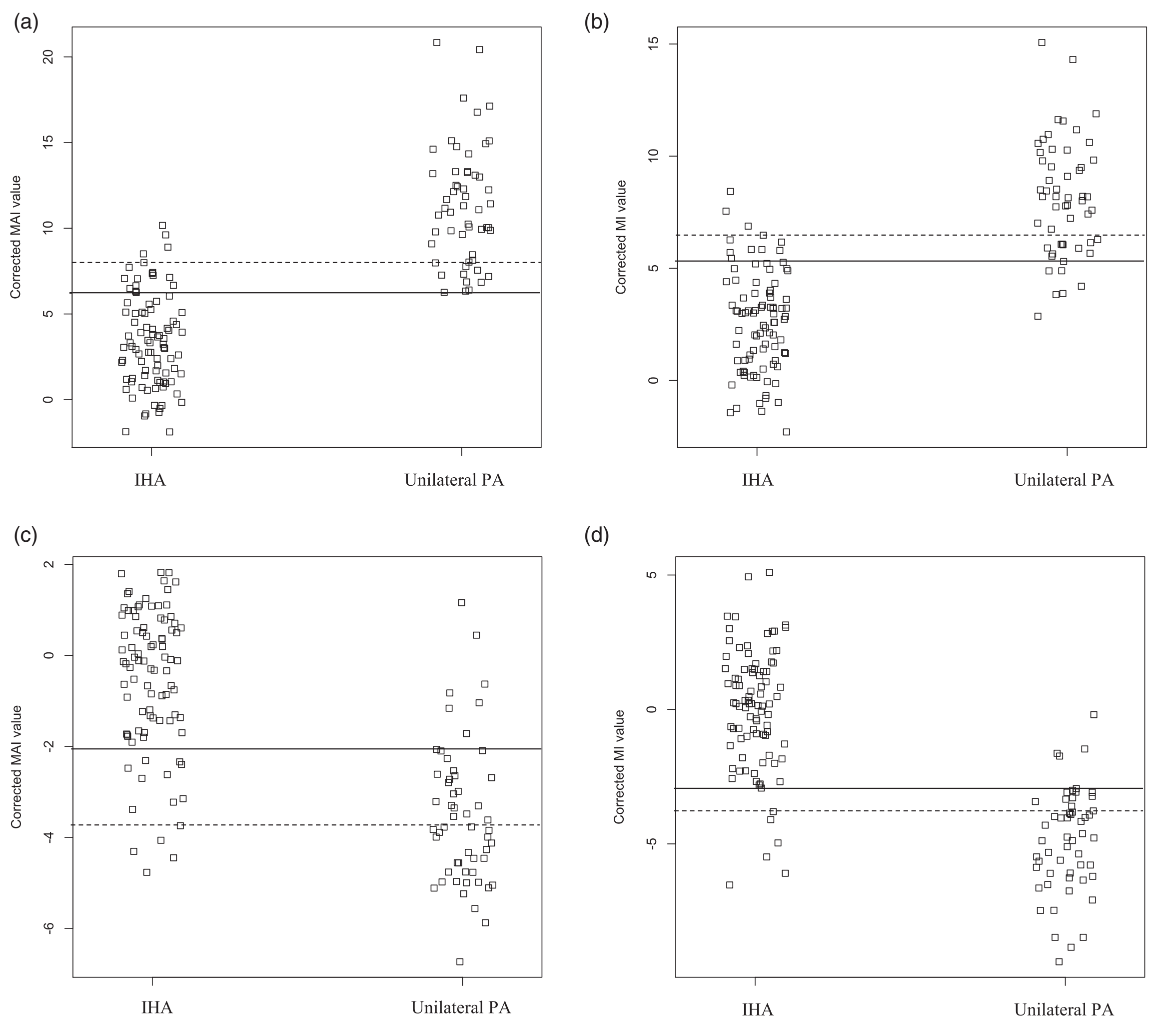

FIGURE 3 Strip charts of adjusted unconventional indices. The graphs show the high accuracy of the scores derived from logistic regression models, using MAI (a and c) and MI (b and d), adjusted for lesion side and presence of hypokalemia, in the prediction of ipsilateral (a and b) and contralateral (c and d) aldosterone hypersecretion. Values on the *y*-axes are those calculated according to the model equations reported in Table 2. Solid lines represent cut-offs according to Youden's criterion, whereas dotted lines thresholds with specificity of 95%. IHA, idiopathic hyperaldosteronism; MAI, monoadrenal index; MI, monolateral index; PA, primary aldosteronism.

TABLE 3. Thresholds of lesion- and potassium-corrected monolateral index and monoadrenal index for the diagnosis of ipsilateral/contralateral aldosterone hypersecretion, setting a specificity of 95%

		Normokalemia			Hypokalemia		
Index	Predicted side of hypersecretion	Ipsilateral lesion	Bilateral/no lesions	Contralateral lesion	Ipsilateral lesion	Bilateral/no lesions	Contralateral lesion
MI	Ipsilateral	>3.94	>20.14	>20.14	>0.92	>4.71	>4.71
	Contralateral	<0.14	<0.14	<0.33	<0.22	<0.22	<0.51
MAI	Ipsilateral	>5.43	>21.22	>21.22	>2.03	>7.95	>7.95
	Contralateral	<0.02	<0.02	<0.16	<0.12	<0.12	<1.04

MAI, monoadrenal index; MI, monolateral index.

combinations of the other covariates (i.e. lesion side at imaging and presence/absence of hypokalemia); these thresholds were computed both according to the Youden's criterion (Table S6, http://links.lww.com/HJH/B499) and after setting a preestablished specificity of 95% (Table 3).

DISCUSSION

The present study demonstrated the high diagnostic accuracy of corrected unconventional indices in the prediction of unilateral disease in a large series of patients with primary aldosteronism subtyped with AVS. International guidelines and expert consensus [1,2,25–27] recognize AVS as the gold standard for the diagnosis of primary aldosteronism subtypes, but even though it may appear as a straightforward diagnostic test, AVS is used only in few centers worldwide. This is not because of the potential associated complications, which have a low rate (0.6%) [10] and a positive outcome [28], but to technical difficulties in the interventional radiology approach. In fact, the catheterization of the right adrenal vein is difficult compared with the left because of the anatomical setting, the narrow diameter, the direct integration into the inferior vena cava (IVC) and the presence of variants in adrenal venous anatomy in 13% of cases [29]. Without a bilaterally selective procedure, the lateralization index, which is the most widely accepted index in the literature, is not applicable to guide the diagnosis of lateralization of aldosterone hypersecretion and the subsequent opportunity of surgical treatment. Therefore, the introduction of unconventional indices and statistical models [30] could help in determining the lateralization of aldosterone secretion in suboptimal AVS. In the literature, few studies tried to determine the diagnostic accuracy of unconventional indices in this setting, and even less in the case of noncosyntropin-stimulated procedures. Lin *et al.* [18] in a series of simultaneous unstimulated AVSs found a borderline moderate/high accuracy of MI in predicting ipsilateral or contralateral aldosterone hypersecretion, suggesting the use of thresholds with the highest specificity to avoid the possibility of removing a normal adrenal gland. Kline *et al.* [17] identified a cut-off with moderate accuracy for assessing contralateral aldosterone secretion during AVS under unstimulated condition, whereas in cosyntropin-stimulated AVS, the same authors identified a highly accurate threshold. The clinical relevance of contralateral suppression was reported by Wolley *et al.* [31] and Kline *et al.* [17], who demonstrated that unilateral primary aldosteronism with contralateral suppression had a better BP outcome after adrenalectomy. Also, Umakoshi *et al.* [32] reported higher rate of positive biochemical outcome and overall primary aldosteronism cure in primary aldosteronism patients with contralateral suppression, compared with individuals without it. On the contrary, Monticone *et al.* [33] and Tagawa *et al.* [34] did not find difference in BP levels in unilateral primary aldosteronism patients after adrenalectomy with and without evidence of contralateral suppression at the AVS.

In cosyntropin-stimulated AVS, Pasternak *et al.* [19] reported a left MI at least 5.5 for predicting ipsilateral aldosterone hypersecretion and a left MI 0.5 or less for the prediction of contralateral disease, using cut offs with 100% of specificity. Unfortunately, these thresholds did not prove to be applicable in noncosyntropin-stimulated AVS [21] and were not validated by subsequent studies [20,35].

In our knowledge, only Fujii *et al.* [36], in a large series of cosyntropin-stimulated AVS demonstrated a high accuracy of left MAI in predicting ipsilateral aldosterone hypersecretion, while a moderate accuracy of left MAI in the prediction of contralateral disease. Also, in the present study, the performance of uncorrected MAI was higher in the prediction of ipsilateral aldosterone hypersecretion, but the correction for lesion side and hypokalemia gave an important improvement to the diagnostic accuracy of this index for the prediction of all the outcomes. Moreover, in our study, we decided to use cut-offs with optimized specificity as we agree that it is crucial to avoid false-positive results that may lead to the surgical removal of an adrenal gland in the contest of IHA. It should be also considered that in the present study, the reliability of adjusted unconventional indices was derived only in comparison with IHA group, with a potential underestimation of the real accuracy of these indices. Despite this choice, we showed that the reached reliability is highly satisfactory. It has to be noted that our indices are not applicable in the case of AVS bilaterally not selective.

For all the models, we calculated the values of corrected indices in order to give an immediate clinical applicability to the study. Due to the absence of unit, simple and adjusted MI values are applicable in all centers, whereas for simple and corrected MAI cut-offs, a measurement conversion is needed in centers that adopt different units.

The reference standard of the present study was the assessment of lateralization, using lateralization index greater than 3, and the positive outcome of AVS-guided adrenalectomy that proved to be consistent with literature [24]. In fact, we showed complete clinical and biochemical success in the 41.5% of patients, with about the 58.5% of individuals showing marked improvement in BP control and complete biochemical cure in more than 95% of the cases.

The strengths of our study are the very low rate of false-positive diagnosis of primary aldosteronism, because of the diagnosis of florid cases of primary aldosteronism and to the diagnostic experience of our centers, which confers homogeneity to the studied population; the longstanding expertise in performing AVS of dedicated radiologists working in our centers; the presence of rigidly defined AVS criteria to assess lateralization and to guide the surgical indication; the presence of follow-up and the application of widely accepted criteria for the evaluation of outcomes in surgically treated patients.

The present study has some limitations. First of all, its retrospective design even if data were collected from prospective registries. Second, the potential for selection bias because of the tertiary nature of our centers. Third, our results apply only to AVS without cosyntropin stimulation, as aldosterone and cortisol levels after ACTH infusion are highly different from the unstimulated values.

Our study suggests the possibility of accurately determining lateralization of the aldosterone secretion even if AVS is not bilaterally selective or the performing radiologist has not a longstanding expertise to correctly cannulate the right adrenal vein. Primary aldosteronism is a frequent cause of organ damage among patients with arterial hypertension and aldosterone has a key role in the pathogenesis of cardiovascular disease. Considering the low probability of spontaneous remission of florid primary aldosteronism [37], the possibility to cure primary aldosteronism with adrenalectomy, the improvement of organ damage [38–40] and the reduced incidence of cardiometabolic complications with the resolution of hyperaldosteronism [41–43], we suggest the use of the proposed unconventional corrected indices to select patients for adrenalectomy when AVS is selective only on one side, particularly when the right adrenal vein cannulation is nonselective or impossible.

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Conflicts of interest

There are no conflicts of interest.

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