Endokrynologia Polska
DOI: 10.5603/EP.a2021.0030
Volume/Tom 72; Number/Numer 4/2021
ISSN 0423–104X, e-ISSN 2299–8306

Limited diagnostic utility of partially successful adrenal vein sampling for primary aldosteronism subtyping

Tomaž Kocjan[1, 2], *Gaj Vidmar*[2–4], *Rok Vrčkovnik*[1, 2], *Milenko Stanković*[2, 5]

[1]*Department of Endocrinology, Diabetes, and Metabolic Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia*
[2]*Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*
[3]*University Rehabilitation Institute, Ljubljana, Slovenia*
[4]*FAMNIT, University of Primorska, Koper, Slovenia*
[5]*Clinical Institute of Radiology, University Medical Centre Ljubljana, Ljubljana, Slovenia*

Abstract

Introduction: Failure of adrenal vein sampling (AVS) due to difficult cannulation of the right adrenal vein (AV) frequently precludes subtyping of patients with primary aldosteronism (PA) before adrenalectomy. According to a recent study, lateralized PA could be accurately predicted from partial AVS data based on the gradient of the aldosterone-to-cortisol ratios (ACR) between left AV and inferior vena cava (IVC) (LAV/IVC index). We aimed to validate the diagnostic utility of this index for PA subtyping in our cohort.

Material and methods: A retrospective cross-sectional study included all patients who underwent bilaterally successful AVS at our centre and were diagnosed with either bilateral PA according to AVS or with lateralized PA after successful adrenalectomy from November 2004 to the end of 2019. Final diagnoses were compared to originally suggested LAV/IVC index cut-offs of ≥ 5.5 for ipsilateral disease and of ≤ 0.5 for contralateral disease, respectively.

Results: The inclusion criteria were met in 168 patients: 46 women and 122 men, aged 54 years on average (range 32–72 years); 67 with lateralized and 101 with bilateral PA. LAV/IVC index using cut-offs of ≥ 5.5 or ≤ 0.5 anticipated ipsilateral (left lateralized) PA with a sensitivity of 32% and specificity of 97%, while a sensitivity of 47% and specificity of 95%, were found for contralateral (right lateralized) PA in our cohort. The overall inappropriate adrenalectomy rate was 29.7% ($p = 0.314$ for comparison between sides). When ascertaining ipsilateral disease (LAV/IVC index ≥ 5.5), 4 out of 16 patients (25%) would have been incorrectly sent to left adrenalectomy. Inappropriate right adrenalectomy would have occurred in 7 out of 21 patients (33.3%) when predicting contralateral disease (LAV/IVC index of ≤ 0.5). Thus, 11 patients with bilateral PA (6.5% of the entire cohort) would have been misclassified as lateralized PA and referred to surgery. Failed lateralization would have occurred in 61.2% of patients overall (53.3% for overlooked contralateral disease, 67.6% for missed ipsilateral disease; $p = 0.723$ for comparison between sides).

Conclusions: Based on our cohort, we conclude that application of the suggested LAV/IVC index cut-offs did not predict lateralized PA with the high accuracy previously reported. **(Endokrynol Pol 2021; 72 (4): 293–300)**

Key words: *adrenal venous sampling; endocrine disorders; primary aldosteronism; secondary hypertension*

Introduction

Primary aldosteronism (PA) is a major secondary cause of elevated blood pressure, with an recently estimated prevalence of 16–22% among the hypertensive population [1]. Importantly, it generates more detrimental cardiovascular, renal, and metabolic outcomes than equally severe essential hypertension [2–5]. Fortunately, targeted treatment is possible. If lateralized disease is reliably demonstrated, the therapeutic method of choice is unilateral laparoscopic adrenalectomy, which normalizes blood pressure in approximately 40% of patients and significantly alleviates hypertension in others, thereby reducing the risk of chronic complications [6, 7]. Other patients with PA are treated with mineralocorticoid receptor antagonists and dietary sodium restriction, which is a less favourable and more expensive option in the long run than surgery [4, 8, 9].

Currently, adrenal vein sampling (AVS) is the preferred method to select the right patients with PA for the operation, because the use of adrenal imaging alone can frequently lead to PA subtype misclassification and significantly lower cure rates [7, 10]. Unfortunately, AVS is not widely available, being an invasive, costly, and a technically difficult procedure with successful bilateral catheterization obtained in only about 75% of cases on average [11, 12]. The cannulation of the left adrenal vein (LAV) is often relatively uncomplicated; however, sampling from the small and short right adrenal vein (RAV), which drains straight into the inferior vena cava (IVC), is much more difficult and might be the main reason for a failed procedure [13–15]. Thus, in some patients, the investigation needs to be repeated,

Tomaž Kocjan, MD PhD, Department of Endocrinology, Diabetes, and Metabolic Diseases, University Medical Centre Ljubljana, Zaloska 7, SI-1525 Ljubljana, Slovenia, tel: +386 1 522 3114, fax: +386 1 522 2136; e-mail: tomaz.kocjan@kclj.si

which means additional costs and risks, or they are simply directed towards less optimal medical treatment [7]. Pasternak et al. have questioned this conventional approach by demonstrating that incomplete data from only left-sided AVS and IVC in the setting of failed cannulation of the RAV could correctly anticipate lateralization. In their surgical series of 62 patients with lateralized PA the LAV/IVC index calculated as the gradient of the cortisol-corrected aldosterone ratio (ACR) between LAV and IVC of ≥ 5.5 and ≤ 0.5 would forecast left- and right-sided disease, respectively, with a positive predictive value of 100% [16]. However, subsequent validations of the proposed model in other cohorts have recently disputed its original robust predictive utility because they yielded mixed and inconclusive results [17–19].

Primarily, we aimed to validate the diagnostic utility of the originally proposed LAV/IVC index [16] for PA subtyping in our sizeable cohort of surgical candidates who had successful AVS. Secondary objectives were to optimize the cut-offs of the same index for our institution and to test this clinical tool for the less likely scenario of LAV cannulation failure.

Material and methods

Study design

We conducted a retrospective cross-sectional study from November 2004 to the end of 2019 at the Slovenian national tertiary endocrine referral centre. All the data were extracted from the Slovenian AVS database. The data collection and its analysis were approved by the National Medical Ethics Committee (ID 0120-216/2020/3).

Patients

All patients with confirmed PA, who underwent AVS at our centre during the study period, were candidates for enrolment. PA was diagnosed according to the existing Endocrine Society guidelines [11, 20], as previously detailed elsewhere [21]. Further inclusion criteria were bilaterally successful AVS and definite diagnosis of either lateralized or bilateral PA. The AVS-based term "lateralized" was preferred over unilateral due to recent data, which suggests that most cases of presumably unilateral PA may actually display mild aldosterone excess from the contralateral gland [22].

Adrenal imaging and AVS

All patients with confirmed PA underwent a thin-slice computed tomography (CT) scan (Siemens, Erlangen, Germany). Any thickening of 5 mm or more was considered abnormal.

AVS preparation and technique have been reported previously [23]. In summary, AVS was performed in the morning between 8 and 9 a.m. by two interventional radiologists. Continuous ACTH stimulation (50 μg/h) was initiated 30 min before sampling and continued throughout the procedure. AVS was performed sequentially with the more challenging right adrenal vein always being cannulated and sampled first to keep the delay between the sides under 5 minutes in most of our AVS procedures [24]. When the selectivity index (SI), determined as the ratio of concentrations of cortisol from an adrenal vein and the infra-adrenal inferior vena cava (IVC), on both sides was at least 5, AVS was considered bilaterally successful. The lateralization index (LI) was calculated as the ratio of the higher over the lower cortisol-corrected aldosterone ratio [14, 15, 25]. Lateralized PA was diagnosed in patients who had successful AVS with an LI of more than 4 [25] and subsequent unilateral adrenalectomy with confirmed complete biochemical cure according to PASO criteria 6–12 months after the operation [6]. Bilateral PA was diagnosed in the context of bilaterally successful adrenal vein cannulation and LI below 3. Patients with equivocal LI values between 3 and 4 were excluded from the analysis [15, 25]. Figure 1 shows a flowchart of the patient selection for our study.

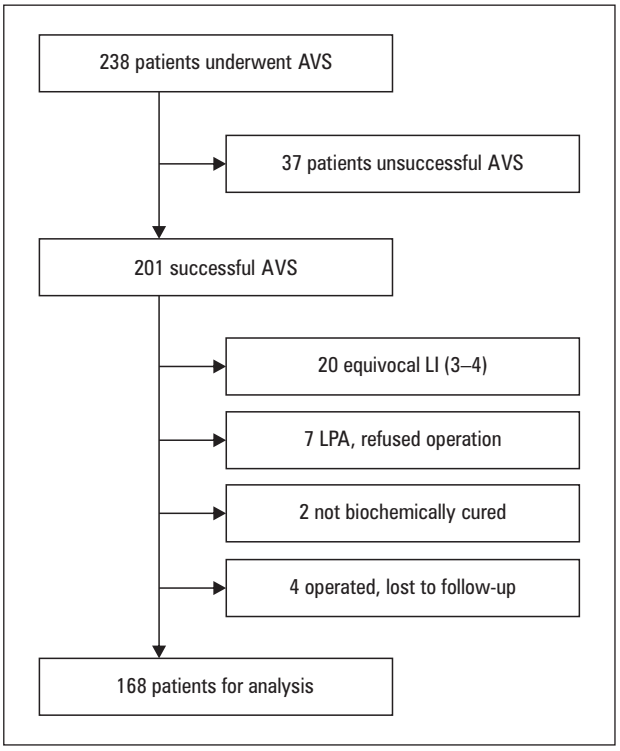

Figure 1. *Flowchart demonstrating the patient selection for our study population. AVS — adrenal vein sampling; LI — lateralization index; LPA — lateralized primary aldosteronism*

Supplementary AVS indices

As mentioned before, the AV/IVC index was calculated as the gradient of the ACR between AV and IVC to predict the laterality of PA. According to Pasternak, ipsilateral disease (lateralized aldosterone secretion from the ipsilateral side of the catheterized AV) was diagnosed if the LAV/IVC index was ≥ 5.5, and contralateral disease (lateralized aldosterone secretion from the contralateral side of the catheterized AV) if the LAV/IVC index was ≤ 0.5 [16]. We examined whether data from incomplete AVS with presumed right-sided failure could accurately predict lateralization in the same way as in the initial study. An inappropriate adrenalectomy rate, defined as removing the wrong adrenal in lateralized PA or any surgery in bilateral PA, and failed lateralization rate, defined as missed lateralized PA, were also calculated, as previously suggested [17]. The recently published cut-offs of ≥ 2.42 for diagnosing ipsilateral disease and of ≤ 0.08 for diagnosing contralateral disease, which demonstrated perfect specificity in a comparable single-centre report [18], were tested in our study cohort.

In addition, the optimization of AV/IVC index cut-offs was attempted for our institution, where we also examined the less common scenario with presumed AVS failure on the left side by applying the RAV/IVC index. The utilized AVS indices are summarized in Table 1.

Assays

Serum aldosterone was measured using an Active® Aldosterone RIA (Beckman Coulter, Immunotech, Czech Republic). Serum cortisol

Table 1. *Adrenal vein sampling indices, definition, clinical significance, and cut-offs in the present study. Adapted from [11, 15, 16]*

	Measurement	Clinical significance	Cut-off
Selectivity index (SI)	Cortisol $_{AV}$/cortisol $_{IVC}$	Adequacy of cannulation of the AV	> 5
Lateralization index (LI)	(Aldosterone/cortisol) $_{dominant\ AV}$ / /(aldosterone/cortisol $_{contralateral\ AV}$)	Differentiation between lateralized and bilateral PA	> 4: lateralized PA < 3: bilateral PA 3–4: equivocal result (the grey zone)
AV/IVC index	(Aldosterone/cortisol) $_{available\ AV}$ / /(aldosterone/cortisol) $_{IVC}$	Prediction of lateralization in the setting of unilateral AV cannulation failure	≥ 5.5: ipsilateral lateralized PA ≤ 0.5 contralateral lateralized PA

AV — adrenal vein; IVC — inferior vena cava; PA — primary aldosteronism

was measured with an automated chemiluminescent immunoassay (CLIA) on a Immulite® 2000 XPi (Siemens Healthcare, Gwynedd, United Kingdom). The respective within- and between-assay coefficients of variation were below 4.5% and 9.8% for aldosterone and below 6.8% and 9.4% for cortisol, respectively. Plasma renin activity (PRA) was measured using an Angiotensin I RIA KIT (Beckman Coulter, Immunotech, Czech Republic). The respective within- and between-assay coefficients of variation were below 11.3% and 20.9%, respectively.

Statistical analysis

Numerical variables were described as mean, SD, median, and range; categorical variables were presented as frequencies. The differences in the characteristics between patients with lateralized and bilateral PA were tested using the t-test and exact Mann-Whitney test for numerical variables, and Fisher's exact test for categorical variables. Receiver operating characteristic (ROC) curve analysis was used to determine the ability of a given marker to distinguish patients with lateralized from those with bilateral disease. The overall predictive value of a marker was assessed as the area under the ROC curve (AUC) with 95% confidence interval (CI). Optimal cut-off values were determined using either Youden's index or desired specificity, and sensitivity and specificity associated with each cut-off was reported. The statistical significance level was set at $p \leq 0.05$. Diagnostic accuracy was compared between LAV/IVC index-based and RAV/IVC index-based criteria using the exact McNemar test. Statistical analyses were conducted using IBM SPSS Statistics 25 (IBM Corp., Armonk, USA, 2017).

Results

Patient characteristics

A total of 238 patients underwent AVS during the study period (Fig. 1). The inclusion criteria were met in 168 patients, 46 women and 122 men, aged 54 years on average (range 32–72 years); 67 with lateralized (30 right; 37 left) and 101 with bilateral PA. Most of them had a unilateral adrenal nodule (56%; 21% right, 35% left) on CT scan, while bilateral adrenal abnormalities were present in 8% of the cases. The average tumour size was 16.4 ± 10.5 mm. Both adrenals were considered normal in 36% of cases. The main reason for work-up was hypertension with hypokalaemia (55%). Most of the remaining patients (39%) were referred due to resistant hypertension and some (6%) due to an adrenal incidentaloma. Additional clinical characteristics and laboratory parameters of the study group are presented by disease subtype in Table 2. As expected, lateralized patients had more severe PA with significantly lower potassium values, and higher aldosterone concentrations and aldosterone–renin ratios. There were no other meaningful differences in any other analysed clinical characteristics or laboratory parameters between the two groups.

AVS data

AVS results of the study group by final diagnosis are presented in Table 3. When compared to the bilateral group, the lateralized patients had higher aldosterone values in LAV and IVC, with a similar trend in RAV. Their LI values were also significantly higher, as anticipated. On the other hand, cortisol values in IVC were higher in bilateral patients.

The mean LAV/IVC index was 6.20 (median 4.32; range 1.68–39.71) for patients with left lateralized PA, 0.57 (0.51; 0.04–1.63) for patients with right lateralized PA, and 2.47 (2.22; 0.02–14.26) for the bilateral group. The mean RAV/IVC index was 9.02 (6.16; 1.14–72.70) for patients with right lateralized PA, 0.56 (0.40; 0.05–4.08) for patients with left lateralized PA, and 2.69 (2.31; 0.03–19.19) for the bilateral group. Figure 2 shows a logarithmic-scale dot-density plot of the LAV/IVC index categorized by final diagnosis, while the RAV/IVC index is represented likewise in Figure 3.

Prediction of lateralized disease

LAV/IVC index by Pasternak's cut-offs of ≥ 5.5 or ≤ 0.5 anticipated left lateralized PA with a sensitivity of 32% and specificity of 97%, while a sensitivity of 47% and specificity of 95% were found for right lateralized PA in our cohort. The recently introduced cut-offs of ≥ 2.42 or ≤ 0.08 by Suntornlohanakul performed even less optimally in our patients, both for ipsilateral and contralateral disease, so no further analysis was attempted (Tab. 4).

When using Pasternak's cut-offs, the overall inappropriate adrenalectomy rate in our cohort was 29.7% ($p = 0.314$ for comparison between sides). When as-

Table 2. *Clinical characteristics and laboratory parameters of the patients by final diagnosis*

Characteristic	Lateralized	Bilateral	p_t, $p_{M\text{-}W}$, or p_{FET}
Age [years]	52.9 (54.0) [34–70]	55.1 (55.0) [32–72]	0.105; 0.118
BMI [kg/m²]	30.0 (30.4) [18–45]	31.1 (30.3) [21–48]	0.173; 0.255
Potassium (lowest value)	3.3 (3.4) [2–4]	3.7 (3.7) [3–5]	< 0.001; 0.000
Creatinine [μmol/L]	78.1 (74.0) [33–165]	81.8 (78.0) [42–181]	0.305; 0.333
eGFR* [mL/min]	90.4 (90.0) [36–132]	86.4 (89.0) [34–122]	0.196; 0.160
DDD	4.9 (5.0) [0–10]	4.7 (4.0) [0–12]	0.620; 0.450
Systolic BP [mm Hg]	159 (155) [129–210]	157 (157) [100–213]	0.525; 0.722
Diastolic BP [mm Hg]	91 (90) [65–120]	88 (90) [61–132]	0.148; 0.142
Aldosterone [pmol/L]	1234 (981) [210–8760]	768 (702) [240–2010]	0.002; 0.001
Plasma Renin Activity (PRA)**	0.2 (0.2) [0.2–1.0]	0.2 (0.2) [0.2–0.9]	0.455; 0.128
Aldosterone-renin ratio (ARR)	8898 (5150) [1050–52000]	3565 (2900) [1200–18000]	< 0.001; 0.000
Tumour size [mm]	16.9 (16.0) [5–30]	15.9 (11.5) [5–43]	0.640; 0.077
Sex (female / male)	30%/70%	26%/74%	0.598
Reason for work-up***	64%/3%/33%	48%/8%/44%	0.110

BMI — body mass index; eGFR — estimated glomerular filtration rate; DDD — defined daily dose; BP — blood pressure. Descriptive statistics are reported as mean (median) [range] for numeric variables and number (percentage) for categorical variables; p_t — from independent-samples *t*-test for numeric variables; $p_{M\text{-}W}$ — from exact Mann-Whitney test for numeric variables; p_{FET} — from Fisher's exact test for categorical variables; *CKD EPI; **the lowest PRA value that was used for the statistical analysis was set at a minimum of 0.2 ng/mL/h, in order to avoid overinflating ARR [14]; *** hypokalaemia (and hypertension)/adrenal tumour/hypertension only; characteristics with p_t or $p_{M\text{-}W} < 0.05$ are shaded in grey

Table 3. *Adrenal vein sampling parameters of the patients by final diagnosis*

AVS parameter	Lateralized	Bilateral	p_t, $p_{M\text{-}W}$
Aldosterone in RAV [pmol/L]	190822 (36800) [116–2537000]	106186 (76550) [1640–385600]	0.070; 0.137
Cortisol in RAV [nmol/L]	21873 (19561) [566–78990]	23532 (22596) [5380–62767]	0.371; 0.267
Aldosterone in LAV [pmol/L]	181588 (71600) [34–1570000]	95171 (86700) [720–302000]	0.006; 0.637
Cortisol in LAV [nmol/L]	21405 (20003) [924–67347]	23541 (23148) [4828–64754]	0.197; 0.078
Aldosterone in IVC [pmol/L]	2587 (2310) [300–10680]	1930 (1730) [310–8980]	0.009; 0.005
Cortisol in IVC [nmol/L]	847 (877) [95–1255]	988 (927) [571–2607]	0.001; 0.009
Selectivity index — RAV	25.7 (23.6) [5–88]	24.5 (23.6) [6–53]	0.555; 0.945
Selectivity index — LAV	25.0 (22.9) [6–75]	24.5 (23.7) [5–51]	0.753; 0.968
Lateralization index	24.4 (11.1) [4–371]	1.7 (1.5) [1–3]	< 0.001; 0.000

RAV — right adrenal vein; LAV — left adrenal vein; IVC — inferior vena cava. Descriptive statistics are reported as mean (median) [range] for numeric variables; p_t — from independent-samples *t*-test; $p_{M\text{-}W}$ — from exact Mann-Whitney test; parameters with p_t or $p_{M\text{-}W} < 0.05$ are shaded in grey

certaining ipsilateral disease (LAV/IVC index ≥ 5.5), 4 out of 16 patients (25%) would have been incorrectly sent to left adrenalectomy. Inappropriate right adrenalectomy would have occurred in 7 out of 21 patients (33.3%) if a LAV/IVC index of ≤ 0.5 had been used to predict contralateral disease. Thus, 11 patients with bilateral PA (6.5% of the entire cohort) would have been misclassified as lateralized PA and referred to surgery. Failed lateralization would have occurred in 61.2% of patients overall; this rate was 53.3% for overlooked contralateral disease and 67.6% for missed ipsilateral disease (p = 0.723 for comparison between sides).

Ninety-three patients (55.3%) had a unilateral adrenal nodule on CT. If just the CT results had been considered, the inappropriate adrenalectomy rate would have been 46.2% overall. An adrenal gland on the wrong side would have been removed in one case, while all other patients were diagnosed with bilateral PA by AVS. On the other hand, according to CT, 19.4% of our patients would have failed to lateralize and would not have been offered the curative surgery.

The optimization of AV/IVC index cut-offs for our institution was done by ROC analysis. Both failed right and failed left adrenal vein cannulation were hypothesized. The AUCs were in the range 0.87–0.95, which indicates a good predictive ability. Optimal cut-offs according to the Youden index are shown in Table 5. Controlling specificity at 95%, the highest possible

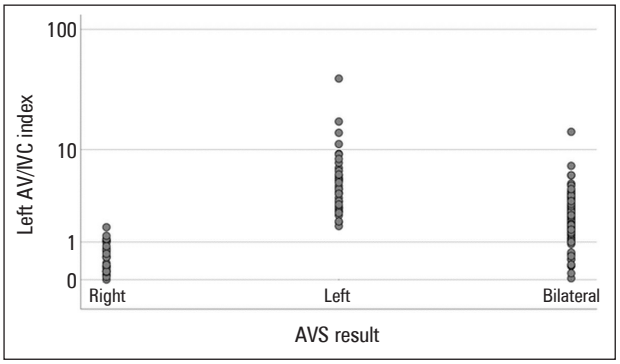

Figure 2. *Logarithmic-scale dot-density plot of the left adrenal vein and inferior vena cava (LAV/IVC) index, calculated as the gradient of the cortisol–corrected aldosterone ratio (ACR) between LAV and IVC, categorized by final diagnosis [right lateralized primary aldosteronism (PA), left lateralized PA, bilateral PA]; AVS — adrenal vein sampling*

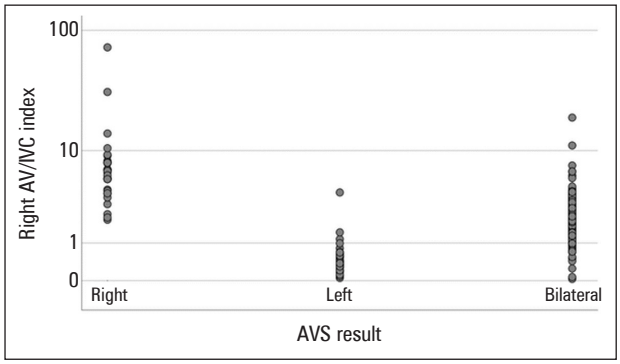

Figure 3. *Logarithmic-scale dot-density plot of the right adrenal vein and inferior vena cava (RAV/IVC) index, calculated as the gradient of the cortisol-corrected aldosterone ratio (ACR) between RAV and IVC, categorized by final diagnosis [right lateralized primary aldosteronism (PA), left lateralized PA, bilateral PA]; AVS — adrenal vein sampling*

Table 4. ***Measures of diagnostic validity of the Pasternak et al. [16] and Suntornlohanakul et al. [18] criteria for our sample utilizing LAV/IVC index to predict ipsilateral or contralateral disease without data from the right adrenal vein***

Authors	Disease	LAV/IVC index	Sensitivity (%)	Specificity (%)	PPV	NPV
Pasternak et al.	Ipsilateral	≥ 5.5	32	97	0.75	0.84
	Contralateral	≤ 0.5	47	95	0.67	0.89
Suntornlohanakul et al.	Ipsilateral	≥ 2.42	89	64	0.41	0.96
	Contralateral	≤ 0.08	10	99	0.75	0.84

LAV — left adrenal vein; IVC — inferior vena cava; PPV — positive predictive value; NPV — negative predictive value

Table 5. ***Summary of receiver operating characteristic (ROC) analyses of our data***

Prediction from	Prediction of	AUC (95% CI)*	Optimal cut-off	Sensitivity (%)**	Specificity (%)**
LAV/IVC index	Left unilateral disease	0.87 (0.81–0.93)	> 2.50	87	70
LAV/IVC index	Right unilateral disease	0.95 (0.91–0.98)	< 1.25	97	87
RAV/IVC index	Right unilateral disease	0.89 (0.81–0.97)	> 3.90	77	89
RAV/IVC index	Left unilateral disease	0.94 (0.89–0.98)	< 0.85	89	92

AUC — area under ROC-curve; CI — confidence interval; LAV — left adrenal vein; IVC — inferior vena cava; RAV — right adrenal vein; *all p-values for the null hypothesis that AUC = 0.5 were < 0.001; **sensitivity and specificity observed at optimal cut-off according to Youden index

sensitivity was 51%, with a LAV/IVC index of ≥ 4.3 to predict left lateralized PA. To attain a specificity of 99%, at a LAV/IVC index of ≥ 5.9, the sensitivity would decrease to 30%. On the other hand, a specificity of 95% would lead to a sensitivity of 57%, with a LAV/IVC index of ≤ 0.54 to predict right lateralized disease. Almost perfect specificity of 99%, at a LAV/IVC index of ≤ 0.28, would reduce the sensitivity to 40%.

Correspondingly, with a specificity of 95%, the highest attainable sensitivity was 67%, with a RAV/IVC index of ≥ 5.1 to predict right lateralized PA, while increasing specificity to 99% at a RAV/IVC index of ≥ 7.5 would decrease sensitivity to 33%. Controlling specificity at 95%, the highest possible sensitivity was 87%, with a RAV/IVC index of ≤ 0.69 to predict left lateralized disease. To achieve a specificity of 99%, at a RAV/IVC index of ≤ 0.06, the sensitivity would drop to 3%.

Diagnostic accuracy did not differ statistically significantly between LAV/IVC index-based (for which it was 82.7%) and RAV/IVC-index based prediction (for which it was 86.3%; p = 0.448).

Discussion

The present study does not support utilizing LAV/IVC index cut-offs of ≥ 5.5 and ≤ 0.5 in the setting of failed right AV cannulation during AVS to predict lateralized PA on either side, as originally suggested by Pasternak

et al. [16]. With that approach, the overall inappropriate adrenalectomy rate in our cohort would be 29.7%. Consequently, 11 of 168 patients (6.5%) would have been incorrectly sent to surgery. Wang et al. have recently reported likewise that 11% of their 222 patients would have had inappropriate adrenalectomy when selected for surgery by the same clinical tool [19]. Another validation study by Strajina et al. managed to prove the original positive predictive value of 100% for contralateral disease, but failed to show the same for ipsilateral disease, where the overall inappropriate adrenalectomy rate remained high at 18% [17]. Interestingly, we found no difference in predictive power for either side. Furthermore, no LAV/IVC index could correctly predict laterality in our cohort with a clinically acceptable level of sensitivity, which is in concordance with previously published data [19]. Contrary to the original study, we also tested the RAV/IVC index to predict lateralized disease in the less likely scenario of failed LAV cannulation and found similarly inadequate diagnostic performance. On the other hand, a small single-centre study by Suntornlohanakul et al. recently found the Pasternak's cut-offs as highly indicative for lateralized PA, both for ipsilateral and especially for contralateral disease [18]. However, as noted also by the authors themselves, their study cohort was rather unusual because it included predominantly female patients (77%) with biochemically severe PA and hypokalaemia in 90% of the cases. Unsurprisingly, 85% of this group had lateralized disease by AVS, which was comparable to Pasternak's original cohort with 73% of lateralized patients [16, 18]. In contrast, our group consisted of mostly male patients (72%) with less severe PA, less frequent hypokalaemia (55%), and predominantly bilateral disease (60%). Notably, patients with the above-mentioned clinical characteristics closely resemble the usual contemporary referrals for AVS, as shown by the recent international AVIS-2 study, which included 1625 patients with PA subtyped by AVS [26]. Similarly, both previously mentioned studies, which also failed to fully confirm the premise by Pasternak, included only about half of lateralized patients [17, 19]. Thus, the original cut-offs do not seem to be entirely relevant in settings where patients' characteristics or the disease-pattern differ from the original surgical cohort of patients with severe PA, who predominantly lateralized by AVS. Inferior performance of the optimized cut-offs for the Suntornlohanakul cohort [18], when tested to predict lateralization in our patients, further confirmed this assumption. Additionally, it is not possible to exclude the impact of different assay methods for aldosterone and cortisol on the diagnostic utility of the indices derived from partial AVS data. Ideally, referral centres should validate or appropriately adjust the published values to their local circumstances. Because there is no universal protocol for AVS, special care should be taken in centres that might use non-stimulated AVS. Indeed, it has been shown that the original cut-offs perform poorly and are not applicable to unstimulated AVS studies [27]. This finding may result from less frequent contralateral suppression, which was shown to be present in 62–76% of lateralized PA in non-stimulated AVS studies, and in 89–93% in stimulated ones [28].

If Pasternak's cut-offs were used for clinical decision making, all inappropriate adrenalectomies in our cohort would have occurred due to misclassification of patients with bilateral PA as lateralized PA. Although noncurative unilateral adrenalectomy should not be entirely dismissed as a treatment option for some patients with bilateral disease [7], optimal management of PA still critically depends on realizing whether the excess of aldosterone is secreted from one or both adrenal glands. This is essential not only to avoid inappropriate surgery, but also to enable many patients with lateralized disease to avoid lifelong medical treatment and considerably benefit from curative adrenalectomy [6, 11]. Importantly, by using Pasternak's criteria, failed lateralization would have occurred in 61.2% of our patients overall.

Adrenal CT scan is recommended as the first test in the subtype evaluation of PA by the guidelines [11]; however, according to a systematic review on 950 patients, it might have missed the type of PA in 37.8% of cases [29], which is similar to the present study. Consequently, AVS remains the only reliable method for subtype diagnosis, which is recommended before adrenal surgery in all patients with PA, apart from infrequent patients under 35 years of age with severe disease and unilateral abnormality on CT, who could probably proceed directly to surgery [30]. Therefore, every effort should be given to improve the AVS success rate. The procedure should follow a well-defined protocol, and it should be performed by a dedicated radiologist with higher workload [13, 23, 31]. Stimulated AVS maximizes the selectivity index, so it might be more suitable for less experienced and low-volume centres [15,31]. Difficulty of cannulating the RAV could be at least partially overcome by intra-procedural cone beam CT [23,32] and other technical developments, such as ultra-rapid on-site measurement of the cortisol level in adrenal veins [33].

Limitations of the present study include its retrospective design, which might have caused a patient selection bias. However, all important clinical and laboratory data were registered in our AVS database, almost without missing values. An additional potential source of error is the unknown autonomous cortisol co-secretion in some patients, because dexamethasone

suppression testing was initially not done routinely, but only in selected patients according to the guidelines [11]. Fortunately, this phenomenon seems to have only a limited impact on stimulated AVS parameters [34]. Broader applicability of the results is also questionable due to centre-specific laboratory assays and stimulated AVS protocol. Notably, selective cannulation of the LAV by a microcatheter instead of blood sampling from the common trunk of the inferior phrenic vein and the LAV was done in most of our cases [23], which might have influenced our AVS indices. Additionally, some of the patients who were diagnosed with bilateral disease might in fact have had lateralized disease, because there is no actual reference for the diagnosis of bilateral PA, which is an inherent problem in all similar studies.

On the other hand, our study relies on the PASO criteria for post-adrenalectomy biochemical cure as the gold standard for lateralized PA [6], which was not the case in all other similar reports [16–19]. Furthermore, our patients with ambiguous lateralization index between 3 and 4 were excluded from the analysis. Finally, our results are based on a considerable cohort of typical patients with PA [26], who were managed in a standardized way and according to the Endocrine Society clinical guidelines when achievable [11, 20].

Conclusions

Based on the present study, we conclude that the application of the suggested LAV/IVC index cut-offs did not predict lateralized PA with the high accuracy previously reported. Moreover, according to our analysis, no AV/IVC index was precise enough for reliable PA subtyping. Bilaterally successful AVS remains the gold standard for this purpose, so maximum effort should be employed to improve local performance of the method.

Acknowledgements
We appreciate the assistance of Vlasta Hocevar and Mateja Adamlje, RNs.

Funding
The authors received no specific funding for this work.

Conflict of interest
None declared.

References

1. Brown JM, Siddiqui M, Calhoun DA, et al. The Unrecognized Prevalence of Primary Aldosteronism: A Cross-sectional Study. Ann Intern Med. 2020; 173(1): 10–20, doi: 10.7326/M20-0065, indexed in Pubmed: 32449886.
2. Savard S, Amar L, Plouin PF, et al. Cardiovascular complications associated with primary aldosteronism: a controlled cross-sectional study. Hypertension. 2013; 62(2): 331–336, doi: 10.1161/HYPERTENSIONAHA.113.01060, indexed in Pubmed: 23753408.
3. Monticone S, Burrello J, Tizzani D, et al. Prevalence and Clinical Manifestations of Primary Aldosteronism Encountered in Primary Care Practice. J Am Coll Cardiol. 2017; 69(14): 1811–1820, doi: 10.1016/j.jacc.2017.01.052, indexed in Pubmed: 28385310.
4. Hundemer GL, Curhan GC, Yozamp N, et al. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study. Lancet Diabetes Endocrinol. 2018; 6(1): 51–59, doi: 10.1016/S2213-8587(17)30367-4, indexed in Pubmed: 29129576.
5. Monticone S, Sconfienza E, D'Ascenzo F, et al. Renal damage in primary aldosteronism: a systematic review and meta-analysis. J Hypertens. 2020; 38(1): 3–12, doi: 10.1097/HJH.0000000000002216, indexed in Pubmed: 31385870.
6. Williams T, Lenders J, Mulatero P, et al. Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort. Lancet Diabetes Endocrinol. 2017; 5(9): 689–699, doi: 10.1016/s2213-8587(17)30135-3, indexed in Pubmed: 28576687.
7. Hundemer GL, Vaidya A. Management of endocrine disease: The role of surgical adrenalectomy in primary aldosteronism. Eur J Endocrinol. 2020; 183(6): R185–R196, doi: 10.1530/EJE-20-0863, indexed in Pubmed: 33077688.
8. Hundemer GL, Curhan GC, Yozamp N, et al. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study. Lancet Diabetes Endocrinol. 2018; 6(1): 51–59, doi: 10.1016/S2213-8587(17)30367-4, indexed in Pubmed: 29129576.
9. Velema M, Dekkers T, Hermus Ad, et al. SPARTACUS investigators, SPARTACUS Investigators. Adrenal vein sampling versus CT scan to determine treatment in primary aldosteronism: an outcome-based randomised diagnostic trial. Lancet Diabetes Endocrinol. 2016; 4(9): 739–746, doi: 10.1016/S2213-8587(16)30100-0, indexed in Pubmed: 27325147.
10. Williams TA, Burrello J, Sechi LA, et al. Computed Tomography and Adrenal Venous Sampling in the Diagnosis of Unilateral Primary Aldosteronism. Hypertension. 2018; 72(3): 641–649, doi: 10.1161/HYPERTENSIONAHA.118.11382, indexed in Pubmed: 29987100.
11. Funder JW, Carey RM, Mantero F, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016; 101(5): 1889–1916, doi: 10.1210/jc.2015-4061, indexed in Pubmed: 26934393.
12. Wolley M, Thuzar M, Stowasser M. Controversies and advances in adrenal venous sampling in the diagnostic workup of primary aldosteronism. Best Pract Res Clin Endocrinol Metab. 2020; 34(3): 101400, doi: 10.1016/j.beem.2020.101400, indexed in Pubmed: 32115358.
13. Rossi GP, Barisa M, Allolio B, et al. The Adrenal Vein Sampling International Study (AVIS) for identifying the major subtypes of primary aldosteronism. J Clin Endocrinol Metab. 2012; 97(5): 1606–1614, doi: 10.1210/jc.2011-2830, indexed in Pubmed: 22399502.
14. Rossi GP, Auchus RJ, Brown M, et al. An expert consensus statement on use of adrenal vein sampling for the subtyping of primary aldosteronism. Hypertension. 2014; 63(1): 151–160, doi: 10.1161/HYPERTENSIONAHA.113.02097, indexed in Pubmed: 24218436.
15. Monticone S, Viola A, Rossato D, et al. Adrenal vein sampling in primary aldosteronism: towards a standardised protocol. Lancet Diabetes Endocrinol. 2015; 3(4): 296–303, doi: 10.1016/S2213-8587(14)70069-5, indexed in Pubmed: 24831990.
16. Pasternak JD, Epelboym I, Seiser N, et al. Diagnostic utility of data from adrenal venous sampling for primary aldosteronism despite failed cannulation of the right adrenal vein. Surgery. 2016; 159(1): 267–273, doi: 10.1016/j.surg.2015.06.048, indexed in Pubmed: 26435431.
17. Strajina V, Al-Hilli Z, Andrews JC, et al. Primary aldosteronism: making sense of partial data sets from failed adrenal venous sampling-suppression of adrenal aldosterone production can be used in clinical decision making. Surgery. 2018; 163(4): 801–806, doi: 10.1016/j.surg.2017.10.012, indexed in Pubmed: 29174432.
18. Suntornlohanakul O, Soonthornpun S, Srisintorn W, et al. Performance of the unilateral AV/IVC index in primary hyperaldosteronism subtype prediction: A validation study in a single tertiary centre. Clin Endocrinol (Oxf). 2020; 93(2): 111–118, doi: 10.1111/cen.14210, indexed in Pubmed: 32347973.
19. Wang TS, Kline G, Yen TW, et al. A Multi-institutional Comparison of Adrenal Venous Sampling in Patients with Primary Aldosteronism: Caution Advised if Successful Bilateral Adrenal Vein Sampling is Not Achieved. World J Surg. 2018; 42(2): 466–472, doi: 10.1007/s00268-017-4327-6, indexed in Pubmed: 29124355.
20. Funder JW, Carey RM, Fardella C, et al. Endocrine Society. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008; 93(9): 3266–3281, doi: 10.1210/jc.2008-0104, indexed in Pubmed: 18552288.
21. Kocjan T, Janez A, Stankovic M, et al. A new clinical prediction criterion accurately determines a subset of patients with bilateral primary aldosteronism before adrenal venous sampling. Endocr Pract. 2016; 22(5): 587–594, doi: 10.4158/EP15982.OR, indexed in Pubmed: 26789347.

22. Desrochers MJ, St-Jean M, El Ghorayeb N, et al. Basal contralateral aldosterone suppression is rare in lateralized primary aldosteronism. Eur J Endocrinol. 2020; 183(4): 399–409, doi: 10.1530/EJE-20-0254, indexed in Pubmed: 32698132.
23. Kocjan T, Jensterle M, Vidmar G, et al. Adrenal vein sampling for primary aldosteronism: a 15-year national referral center experience. Radiol Oncol. 2020; 54(4): 409–418, doi: 10.2478/raon-2020-0052, indexed in Pubmed: 32889797.
24. Almarzooqi MK, Chagnon M, Soulez G, et al. Adrenal vein sampling in primary aldosteronism: concordance of simultaneous vs sequential sampling. Eur J Endocrinol. 2017; 176(2): 159–167, doi: 10.1530/EJE-16-0701, indexed in Pubmed: 27836950.
25. Young WF, Stanson AW, Thompson GB, et al. Role for adrenal venous sampling in primary aldosteronism. Surgery. 2004; 136(6): 1227–1235, doi: 10.1016/j.surg.2004.06.051, indexed in Pubmed: 15657580.
26. Rossi GP, Rossitto G, Amar L, et al. Clinical Outcomes of 1625 Patients With Primary Aldosteronism Subtyped With Adrenal Vein Sampling. Hypertension. 2019; 74(4): 800–808, doi: 10.1161/HYPERTENSIONAHA.119.13463, indexed in Pubmed: 31476901.
27. Lee BC, Chang CC. TAIPAI Study Group. Regarding "Diagnostic utility of data from adrenal venous sampling for primary aldosteronism despite failed cannulation of the right adrenal vein". Surgery. 2016; 159(5): 1478–1479, doi: 10.1016/j.surg.2015.10.033, indexed in Pubmed: 26706611.
28. Monticone S, Satoh F, Giacchetti G, et al. Effect of adrenocorticotropic hormone stimulation during adrenal vein sampling in primary aldosteronism. Hypertension. 2012; 59(4): 840–846, doi: 10.1161/HYPERTENSIONAHA.111.189548, indexed in Pubmed: 22331382.
29. Kempers MJE, Lenders JWM, van Outheusden L, et al. Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. Ann Intern Med. 2009; 151(5): 329–337, doi: 10.7326/0003-4819-151-5-200909010-00007, indexed in Pubmed: 19721021.
30. Lim V, Guo Q, Grant CS, et al. Accuracy of adrenal imaging and adrenal venous sampling in predicting surgical cure of primary aldosteronism. J Clin Endocrinol Metab. 2014; 99(8): 2712–2719, doi: 10.1210/jc.2013-4146, indexed in Pubmed: 24796926.
31. Young WF, Stanson AW. What are the keys to successful adrenal venous sampling (AVS) in patients with primary aldosteronism? Clin Endocrinol (Oxf). 2009; 70(1): 14–17, doi: 10.1111/j.1365-2265.2008.03450.x, indexed in Pubmed: 19128364.
32. Maruyama K, Sofue K, Okada T, et al. Advantages of Intraprocedural Unenhanced CT During Adrenal Venous Sampling to Confirm Accurate Catheterization of the Right Adrenal Vein. Cardiovasc Intervent Radiol. 2019; 42(4): 542–551, doi: 10.1007/s00270-018-2135-5, indexed in Pubmed: 30519725.
33. Yoneda T, Karashima S, Kometani M, et al. Impact of New Quick Gold Nanoparticle-Based Cortisol Assay During Adrenal Vein Sampling for Primary Aldosteronism. J Clin Endocrinol Metab. 2016; 101(6): 2554–2561, doi: 10.1210/jc.2016-1011, indexed in Pubmed: 27011114.
34. O'Toole SM, Sze WCC, Chung TT, et al. Low-grade Cortisol Cosecretion Has Limited Impact on ACTH-stimulated AVS Parameters in Primary Aldosteronism. J Clin Endocrinol Metab. 2020; 105(10), doi: 10.1210/clinem/dgaa519, indexed in Pubmed: 32785656.