



# Primary Aldosteronism: Does Underlying Pathology Impact Clinical Presentation and Outcomes Following Unilateral Adrenalectomy?

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## Abstract

**Introduction** Patients undergoing unilateral adrenalectomy for primary aldosteronism (PA) may have a solitary adenoma, unilateral hyperplasia, or multiple adenomas on final pathology. This study investigated whether the underlying pathological diagnosis was associated with differences in clinical presentation and postoperative outcomes.

**Methods** A retrospective cohort study of patients undergoing unilateral adrenalectomy for PA from 2004 to 2015 at our institution was performed. Baseline clinical and laboratory parameters, as well as postoperative biochemical and hypertension cure rates, were compared across the three aforementioned pathological groups.

**Results** Of 206 patients who met criteria for inclusion, 152 (73.8%) had a single adenoma, 33 (16%) had unilateral hyperplasia, and 21 (10.2%) had multiple unilateral adenomas. Patients with unilateral hyperplasia were more likely to be male (81.2% vs 57.9%,  $P = .03$ ), undergo left-sided adrenalectomy (78.8% vs 47.4%,  $P < .01$ ), and had a lower median adrenal venous sampling lateralization index (9.8 vs 19.8,  $P = .04$ ) compared to those with solitary, but not multiple unilateral adenomas. No differences were seen in age, duration of hypertension, preoperative plasma aldosterone levels, plasma renin activities, 24-h urinary aldosterone excretion, serum potassium concentrations, and the number of preoperative antihypertensive medications across all three pathological groups. All patients achieved biochemical cure following adrenalectomy, and no significant differences in the rates of hypertension cure or improvement were observed in comparisons across pathological subtype.

**Conclusions** Clinical presentation and postoperative outcomes are similar regardless of underlying pathology in patients with PA. Because one in four patients may harbor unilateral hyperplasia or multiple adenomas, total unilateral adrenalectomy should be performed as the operation of choice over adrenal-sparing approaches.

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## Introduction

Primary aldosteronism (PA) is the most common cause of secondary hypertension and has a prevalence of 5–20% in the hypertensive population [1, 2]. It is a syndrome characterized by excess aldosterone production and renin suppression, resulting in hypertension and potentially hypokalemia. Patients with PA are at increased risk of cardiovascular and renal sequelae when compared with age-, sex-, and blood pressure (BP)-matched patients with

essential hypertension, thus highlighting the importance of early diagnosis and appropriate therapy [3–5].

Once a diagnosis of PA has been established, making the distinction between unilateral and bilateral disease is essential, as the former can be cured by surgical removal of the affected adrenal gland. Conversely, patients with bilateral disease are treated medically with mineralocorticoid receptor (MR) antagonists because neither the aldosterone hypersecretion nor the hypertension is alleviated by unilateral adrenalectomy in this scenario. Traditionally, unilateral disease has been synonymous with an aldosterone-producing adenoma, while bilateral disease is most commonly associated with idiopathic adrenal hyperplasia. However, in recent years, other forms of unilateral PA have been described, including unilateral adrenal hyperplasia [6–10] and multiple unilateral adrenal adenomas [11–13]. While unilateral hyperplasia was previously believed to be a very rare subtype of PA [9], recent data suggest that this entity is more common than previously thought, with an incidence of around 10–36% in various series [6, 7, 10, 14–16]. On the other hand, studies describing multiple unilateral adenomas in patients with PA are mostly limited to case reports or small institutional series [11, 12, 17, 18].

Few studies have explored whether differences in histopathological diagnosis have an impact on clinical presentation, biochemical evaluation, and postoperative outcomes following unilateral adrenalectomy for PA [6, 7, 10, 16, 19]. However, these studies involved comparisons between patients with single adenomas and unilateral hyperplasia only, or analyzed unilateral hyperplasia and multiple adenomas together in one group, despite the two being recognized as distinct pathological entities [20, 21]. Therefore, we sought to investigate whether clinical presentation and postoperative outcomes in patients with PA differ according to the presence of a solitary adenoma, unilateral hyperplasia, or multiple unilateral adenomas on final pathology.

## Methods

We performed a retrospective review of all adult patients undergoing unilateral adrenalectomy for PA at Mayo Clinic, Rochester, MN, between January 2004 and December 2015. Data were collected on patient demographics, clinical presentation, biochemical values, and postoperative follow-up. All preoperative laboratory variables and BP readings were obtained from the most recent outpatient clinic visit prior to adrenalectomy. We excluded patients with concomitant glucocorticoid secretion, those who underwent partial adrenalectomy, those with adrenal venous sampling (AVS) results demonstrating non-lateralization of aldosterone hypersecretion (i.e., a lateralization

index [LI] of  $<3$ ), and those without postoperative biochemical evaluation of aldosterone levels.

The aldosterone-to-renin ratio (ARR) was used as a case detection test for PA in hypertensive patients in the setting of spontaneous hypokalemia (potassium  $<3.6$  mEq/L), with a plasma aldosterone concentration of  $\geq 10$  ng/dL and a suppressed plasma renin activity of  $<1$  ng/mL/h. In those patients who did not have spontaneous hypokalemia, PA was confirmed by an inability to suppress aldosterone excretion with an oral sodium loading test. If plasma renin activity was not suppressed, spironolactone and eplerenone were discontinued at least 4 weeks before evaluation. Patients on preoperative potassium supplements or a MR antagonist with a documented serum potassium of  $<3.6$  mmol/L before initiating this medication were also defined as having preoperative hypokalemia. The nadir potassium was defined as the lowest serum potassium concentration recorded during a patient's diagnostic workup.

Once a diagnosis of PA was confirmed, all patients underwent adrenal-directed abdominal imaging with computed tomography (CT) or magnetic resonance imaging (MRI). In patients younger than 35 years, if imaging demonstrated a definitive unilateral adenoma with normal contralateral adrenal morphology, unilateral adrenalectomy was performed. In patients older than 35 years, or in those with bilateral abnormalities or normal-appearing adrenals on imaging, AVS was performed, as previously described [22], during continuous cosyntropin infusion (50  $\mu$ g/h started 30 min before sequential sampling of the adrenal veins and continued throughout the procedure). Selective catheterization of the adrenal veins was confirmed based on an adrenal vein to inferior vena cava (IVC) cortisol gradient of  $>5:1$ . We calculated the LI by dividing the adrenal vein aldosterone-to-cortisol (A/C) ratio on the dominant side by the A/C ratio on the nondominant side. A LI of  $\geq 3$  indicated unilateral aldosterone excess and was used as a potential indication for adrenalectomy. We also calculated the contralateral suppression index (CSI) by dividing the adrenal vein A/C ratio of the nondominant side by the IVC A/C ratio.

Surgical pathology slides were independently reviewed by two pathologists in order to categorize patients into one of three histopathological diagnosis groups: Single adenoma was defined as a solitary, well-circumscribed, encapsulated adrenocortical clear-cell adenoma compressing the non-neoplastic uninvolved adrenal gland; multiple unilateral adenomas were defined as the presence of two or more adenomas within the same adrenal gland; and unilateral adrenal hyperplasia was defined as the presence of diffuse hyperplasia of cells, resembling those of normal zona glomerulosa, with or without macro-micronodules composed of nests of clear cells.

Biochemical cure (complete biochemical success) in this study was defined as correction of hypokalemia (if present pre-surgery) and a postoperative aldosterone level of  $<5$  ng/dL, typically checked the day after adrenalectomy. Hypertension cure (complete clinical success) was defined as a BP of  $<140/90$  mm Hg without the need for any antihypertensive medications. Hypertension improvement (partial clinical success) was defined as similar BP on fewer antihypertensive medications or a reduction in BP with either the same amount or less antihypertensive medications. Absent clinical success was defined as unchanged or increased BP levels with either the same amount or an increase in antihypertensive medication. Postoperative BP measurements were obtained from the latest outpatient follow-up appointment.

All values are reported as mean  $\pm$  standard deviation (SD) or median (interquartile range, IQR) when appropriate for continuous data and percentages for categorical data. To evaluate for differences in outcomes between the three histopathological groups, we used Fisher's exact test or Pearson's  $\chi^2$  test for discrete data and the analysis of variance or Kruskal–Wallis tests for continuous data. Individual subgroup comparisons were performed, using Tukey or Steel–Dwass post hoc tests, if the overall  $P$  value for the comparison across the three groups was  $<0.05$ . Due to the exploratory nature of this study, statistical adjustment for multiple outcome comparisons was not carried out. All statistical analyses were performed using JMP software (version 11.0; SAS Institute, Inc, Cary, NC). The study protocol was reviewed and approved by the Institutional Review Board of the Mayo Foundation.

## Results

During the study period, 252 patients underwent unilateral adrenalectomy for PA. Twenty-two patients were excluded because there was no information on postoperative biochemical evaluation of potassium or aldosterone levels, and 15 patients were excluded due to non-lateralization at AVS. Seven patients were excluded as they underwent partial adrenalectomy, and two patients were excluded due to cortisol co-secretion. Therefore, 206 patients met our criteria for inclusion in the final analysis (Fig. 1). There were 131 men and 75 women with an overall mean age of  $51.8 \pm 10.7$  years at the time of surgery. Thirteen patients (6.3%) were  $<35$  years old at the time of surgery, with evidence of a unilateral adenoma on preoperative CT, and therefore did not undergo AVS. The median duration of preoperative hypertension was 10 years (IQR, 5–17 years). Hypokalemia was present in 188 patients (91.3%) prior to surgery. Preoperative patient characteristics are summarized in Table 1.

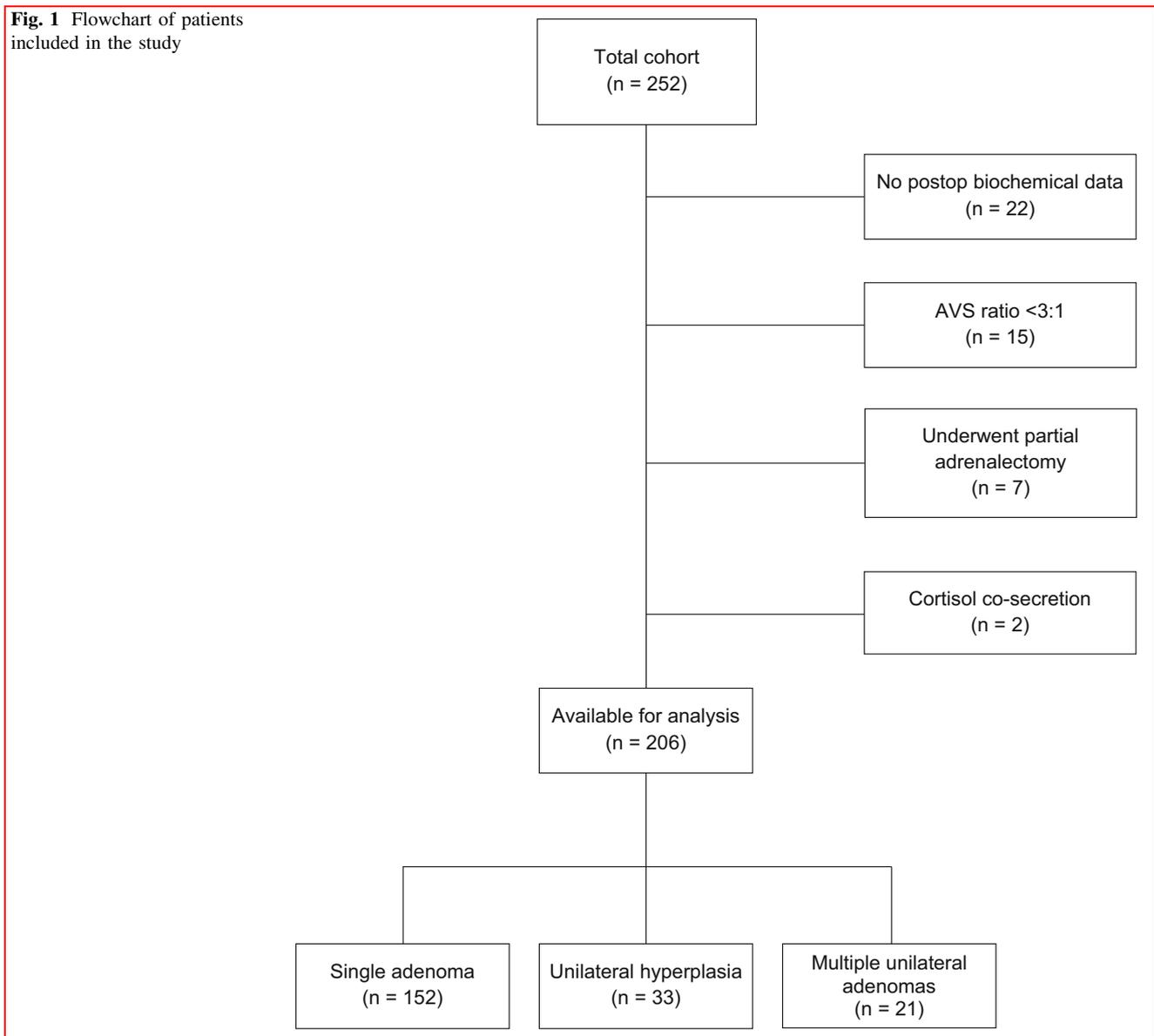
Histopathological examination revealed a single adenoma in 152 patients (73.8%), unilateral adrenal hyperplasia in 33 patients (16%), and multiple unilateral adenomas in 21 patients (10.2%; Table 2). Patients with unilateral hyperplasia were significantly more likely to be male (81.2% vs 57.9%,  $P = .03$ ) and were more likely to undergo left-sided adrenalectomy (78.8% vs 47.4%,  $P < .01$ ), compared to those with a solitary adenoma. In the 193 cases (93.7%) in which AVS was successfully performed, patients with unilateral hyperplasia had a lower median LI (9.8 vs 19.8,  $P = .03$ ) compared to those with a single adenoma. These differences were not significant when subgroup comparisons were made with the unilateral multiple adenomas group. Furthermore, there were no significant differences in age, body mass index, preoperative BP, duration of hypertension, preoperative plasma aldosterone levels, renin activities, ARR, 24-h urinary aldosterone excretion, serum potassium concentrations, the number of preoperative antihypertensive medications, and the percentage of patients who were hypokalemic or on potassium supplementation before surgery, across all three groups. However, patients with multiple adenomas were more likely to be treated with a MR antagonist preoperatively compared to those with a single adenoma (47.6% vs 21%,  $P = .03$ ) and unilateral hyperplasia (47.6% vs 9.1%,  $P < .01$ ).

Median duration of BP follow-up in patients with BP data available was 18 months (IQR, 1.2–52.8 months). At the time of last follow-up, biochemical cure was seen in all patients (Table 3). Hypertension cure was achieved in 29 patients (24%), with hypertension improvement seen in a further 84 patients (69.4%). Eight patients (6.6%) had either the same or worsened BP with the same or more antihypertensive medications (i.e. absent clinical success). Notably, BP follow-up data were missing for 85 patients (41.3%), who were followed up outside of our institution, leaving 121 patients (58.7%) with data that could be used to calculate clinical cure rates. With this in mind, no statistically significant differences were found across the three pathological subtypes with respect to postoperative clinical and biochemical outcome measures, including the number of postoperative antihypertensive medications, serum potassium and creatinine levels, and duration of BP follow-up.

## Discussion

Unilateral PA was traditionally believed to be a disease caused almost exclusively by an aldosterone-producing adenoma. However, it is now recognized that patients with surgically treated disease also demonstrate varying patterns of hyperplasia or multiple adenomas on final pathology.

**Fig. 1** Flowchart of patients included in the study



Our findings suggest that, compared to solitary adenomas, unilateral hyperplasia is more common in males, has a predilection for the left adrenal gland, and is associated with a lower mean LI at AVS. Furthermore, multiple unilateral adenomas were found to be more common than previously reported. Regardless, postoperative outcomes were similar across all groups, irrespective of underlying pathology.

Several studies have compared clinical characteristics and cure rates between PA patients with unilateral hyperplasia and solitary adenomas [6, 10, 14, 16, 19]. Weisbrod and colleagues [16] reported a 16% incidence of unilateral hyperplasia in their series of 95 patients, which is identical to the rate reported in our study. However, in contradistinction to our findings, no differences were seen in factors

such as sex, laterality of disease, or AVS ratios, when compared to patients with solitary adenomas. Nonetheless, in concordance with our study, postoperative outcomes were similar across both histopathological groups. Iacobone et al. [10] also found no difference in postoperative biochemical and clinical cure rates in patients with single adenomas compared to those with unilateral hyperplasia. In contrast, Trésallet and co-workers [7] observed that the presence of an aldosterone-producing adenoma (as opposed to unilateral hyperplasia) on final pathology was the only independent predictor of hypertension cure. Interestingly, they reported a higher incidence of unilateral hyperplasia in males, which we also observed in our cohort. This lack of concordance in the literature may, in part, be explained by heterogeneity in the criteria used to classify postoperative

**Table 1** Baseline demographics and clinical characteristics

Variable	Entire cohort ( <i>n</i> = 206)
Sex, male ( <i>n</i> , %)	131 (63.6)
Age at operation, years	51.8 ± 10.7
BMI, kg/m <sup>2</sup>	31 ± 5.4
Duration of hypertension, years (median, IQR)	10 (5, 17)
BP systolic	142 ± 19.3
BP diastolic	84.5 ± 12.4
No. of preoperative BP medications (median, IQR)	3 (2, 4)
Preoperative creatinine, mg/dL	1.0 ± 0.3
Hypokalemic preoperatively, yes ( <i>n</i> , %)	188 (91.3)
Nadir preoperative potassium, mmol/L	3.5 ± 0.6
No. of patients on potassium supplements ( <i>n</i> , %)	162 (78.6)
Daily potassium dosage, mEq	60.6 ± 83.1
Preoperative MR antagonist, yes ( <i>n</i> , %)	45 (21.8)
Preoperative plasma aldosterone, ng/dL	36.1 ± 42.2
Preoperative plasma renin activity, ng/mL/h	0.7 ± 0.7
Preoperative ARR	61.5 ± 68.8
Preoperative 24-h urinary aldosterone	47.7 ± 52.4
AVS performed, yes ( <i>n</i> , %)	193 (93.6)
LI (median, IQR)	17.3 (8, 33.8)
CSI (median, IQR)	0.3 (0.1, 0.5)
Side of adrenalectomy, left ( <i>n</i> , %)	110 (53.4)

Values are expressed as mean ± standard deviation, unless otherwise specified

*BMI* body mass index, *BP* blood pressure, *mEq* milliequivalents, *MR* mineralocorticoid receptor, *ARR* aldosterone-to-renin ratio, *AVS* adrenal venous sampling, *LI* lateralization index, *CSI* contralateral suppression index, *IQR* interquartile range

outcomes, and difficulties in making a clear-cut distinction between adenoma and hyperplasia on routine histopathology [20].

Our finding that unilateral hyperplasia was more prevalent on the left, compared to the right side (78.8% vs 21.2%), is an interesting observation that has also been reported by others [8, 14]. In a prospective series that included 56 patients with unilateral nodular hyperplasia, Walz and colleagues [14] reported an incidence of left-sided hyperplasia in 78.5% of their cohort, which is almost identical to our study. Similarly, Novitsky et al. [8] noted an incidence of 73% in their smaller series of 15 patients. Although these findings point toward a potential lateralizing asymmetry, there is limited evidence to support a fundamental predisposition for the development of left-sided adrenal hyperplasia. Morphometric studies of fetal adrenal development have demonstrated greater thickness, volume, and surface area of the left adrenal gland during

gestation [23]. Furthermore, in an autopsy study of over 300 patients, Lam et al. [24] found a significantly greater size and mean weight of the left adrenal compared with the right. Although speculative, it is possible that increased tissue mass in the left adrenal may predispose to greater opportunities for hyperplastic transformation.

The presence of multiple unilateral adenomas in PA has been described as a rare entity in the literature, although the frequency is seldom cited outside of case reports [11, 12, 18, 25]. In a previous study from our institution, Quillo et al. [6] found that in 167 patients, 6.5% had multiple adenomas on final pathology. Although baseline characteristics, clinical outcomes, and biochemical cure rates were no different when compared to patients with single adenomas, multiple adenomas were analyzed together with unilateral hyperplasia as a collective “nonsingle adenoma” group. Proye and colleagues [26] also studied 100 patients with PA, 5% of whom had multiple adenomas. In agreement with our findings, no differences in the rates of biochemical cure and hypertension improvement were found, when comparisons were made with patients who had solitary adenomas, hyperplasia, or an adenoma arising on a background of hyperplasia. Conversely, Obara et al. [17] concluded that the presence of multiple adenomas, or an adenoma associated with macronodules, portended an eightfold increased risk of postoperative persistent hypertension compared to that of a single adenoma. These incongruent findings may also be explained by the aforementioned differences in outcome measures, discrepancies in how histopathological distinctions were made between the various PA subtypes, and small subgroup sizes. For example, although we observed that patients with multiple unilateral adenomas were more likely to be treated with a MR antagonist preoperatively, this is likely to be coincidental in a small sample, rather than a true association.

Over a quarter of the patients in our cohort who underwent successful adrenalectomy were found to have unilateral hyperplasia or multiple adenomas (i.e. nonsingle adenoma pathology). This is a pertinent finding in relation to the debate on partial adrenalectomy, which some have proposed as a strategy to reduce the risk of adrenal insufficiency, particularly in small peripherally located adenomas [27]. Others have cautioned against the possibility of incomplete removal of abnormal adrenal tissue and have highlighted the occurrence of persistent postoperative aldosterone elevation, even in patients who underwent enucleation of what was believed to be a solitary adenoma on preoperative imaging [28, 29]. The relatively high prevalence of nonsingle adenoma pathology in our series, and the similarities in clinical and biochemical presentation when compared with single adenomas, lends credence to the argument for total unilateral adrenalectomy in all cases of lateralized PA, regardless of preoperative findings.

**Table 2** Baseline demographics and clinical characteristics according to pathology

Variable	APA ( <i>n</i> = 152)	UAH ( <i>n</i> = 33)	UMA ( <i>n</i> = 21)	<i>P</i> values			
				Overall	APA versus UAH	APA versus UMA	UAH versus UMA
Age at operation, years	51.6 ± 10.8	52.9 ± 10	52 ± 12	.83			
Sex, male ( <i>n</i> , %)	88 (57.9)	27 (81.2)	16 (76.2)	.02	.03	.15	.73
BMI, kg/m <sup>2</sup>	31.2 ± 5.8	30.8 ± 3.1	29.7 ± 5.3	.67			
Duration of hypertension, years (median, IQR)	10 (4.5, 16)	11 (4.5, 20)	14 (6.5, 25)	.13			
BP systolic	143.4 ± 18.7	137.5 ± 20	139.2 ± 22.3	.23			
BP diastolic	85.4 ± 12.2	82.2 ± 13.6	81.3 ± 11.6	.19			
No. of preop BP meds (median, IQR)	3 (2, 4)	3 (3, 4)	4 (3, 5)	.06			
Preoperative creatinine, mg/dL	1.0 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	.05			
Hypokalemic preoperatively, yes ( <i>n</i> , %)	138 (90.8)	30 (90.9)	20 (95.2)	.79			
Nadir preop potassium, mmol/L	3.5 ± 0.7	3.4 ± 0.6	3.5 ± 0.6	.94			
No. of patients on potassium supplements ( <i>n</i> , %)	120 (79)	26 (78.8)	16 (76.2)	.96			
Daily potassium dosage, mEq	62.7 ± 89.5	51.1 ± 58	60.7 ± 69.8	.80			
Preoperative MR antagonist, yes ( <i>n</i> , %)	32 (21)	3 (9.1)	10 (47.6)	< .01	.43	.04	< .01
Preoperative plasma aldosterone, ng/ dL	36.7 ± 47.5	34.4 ± 17.1	34.9 ± 28.4	.72			
Preoperative plasma renin activity, ng/mL/h	0.7 ± 0.8	0.6 ± 0.1	0.7 ± 0.5	.60			
Preoperative ARR	61.8 ± 74.8	62.2 ± 48.7	58.1 ± 48.5	.69			
Preoperative 24-h urinary aldosterone	47.6 ± 56.4	46.5 ± 33.5	50.9 ± 51.9	.64			
AVS performed, yes ( <i>n</i> , %)	139 (91.5)	33 (100)	21 (100)	0.1			
LI (median, IQR)	19.8 (9.2, 36.8)	9.8 (6.3, 22.9)	20.7 (7.9, 39.2)	.04	.03	1.00	.28
CSI (median, IQR)	0.2 (0.1, 0.5)	0.3 (0.2, 0.6)	0.2 (0.1, 0.5)	.15			
Side of adrenalectomy, left ( <i>n</i> , %)	72 (47.4)	26 (78.8)	12 (57.1)	< .01	< .01	1.00	.36

Values are expressed as mean ± standard deviation, unless otherwise specified

APA aldosterone-producing adenoma, UAH unilateral adrenal hyperplasia, UMA unilateral multiple adenomas, BMI body mass index, BP blood pressure, mEq milliequivalents, MR mineralocorticoid receptor, ARR aldosterone-to-renin ratio, AVS adrenal venous sampling, LI lateralization index, CSI contralateral suppression index, IQR interquartile range

A significant limitation of our study is that we were unable to perform staining for aldosterone synthase (CYP11B2) using in situ hybridization or immunohistochemistry. This would have allowed us to confirm the specific area of the adrenal gland responsible for aldosterone hypersecretion, particularly in patients thought to have multifocal disease. Without this, some specimens believed to contain multiple adenomas may in fact have had only one functional lesion, or may have been inaccurately classified as macronodular hyperplasia, due to difficulties in distinguishing these entities on routine histopathology alone. Indeed, in a study of 120 patients by Volpe et al., [30] the final pathological diagnosis was changed in 7% of cases following immunohistochemical

analysis, as aldosterone synthase expression was observed in the adjacent cortex rather than the adenoma initially thought to be responsible for aldosterone hypersecretion. Typical practice at our institution is not to check aldosterone levels beyond postoperative day 1 or 2 if there is evidence of suppression (i.e., our definition of biochemical cure). Although this approach has been utilized by others [31], it has been shown that aldosterone levels in the immediate perioperative period may be transiently suppressed, even in patients with persistent disease [32]. Therefore, patients in our study may have been misclassified as biochemically cured based on a single serum aldosterone level, and measurement of the ARR 6–12 months after surgery would have allowed cure to be

**Table 3** Postoperative outcomes according to pathology in patients undergoing unilateral adrenalectomy for primary aldosteronism

Variable	Entire cohort (n = 206)	APA (n = 152)	UAH (n = 33)	UMA (n = 21)	Total no. of pts with data available	P value
Biochemical cure (n, %)	206 (100) (n = 206)	152 (100) (n = 152)	33 (100) (n = 33)	21 (100) (n = 21)	206 (100)	1.00
Hypertension cure (n, %)	29 (24) (n = 121)	23 (25.8) (n = 89)	3 (15.8) (n = 19)	3 (23.1) (n = 13)	121 (58.7)	0.67
Hypertension improvement (n, %)	84 (69.4) (n = 121)	59 (66.3) (n = 89)	15 (79) (n = 19)	10 (76.9) (n = 13)	121 (58.7)	0.93
Absent clinical success (n, %)	8 (6.6) (n = 121)	7 (7.9) (n = 89)	1 (5.3) (n = 19)	0 (0) (n = 13)	121 (58.7)	0.54
BP systolic	126 ± 11.9 (n = 121)	125.4 ± 11 (n = 89)	128.3 ± 14.4 (n = 19)	126.5 ± 14 (n = 13)	121 (58.7)	0.63
BP diastolic	79 ± 10.3 (n = 121)	78.6 ± 9.8 (n = 89)	80.1 ± 12.4 (n = 19)	79.5 ± 10.3 (n = 13)	121 (58.7)	0.85
No. of postoperative BP medications (median, range)	1 (0, 5) (n = 124)	1 (0, 5) (n = 92)	2 (0, 5) (n = 19)	1 (0, 4) (n = 13)	124 (60.2)	0.66
Postoperative creatinine, mg/dL	1.0 ± 0.4 (n = 198)	1.0 ± 0.4 (n = 146)	1.1 ± 0.3 (n = 32)	1.0 ± 0.2 (n = 20)	198 (96.1)	0.06
Postoperative potassium, mmol/L	4.5 ± 0.4 (n = 133)	4.5 ± 0.4 (n = 98)	4.5 ± 0.5 (n = 22)	4.5 ± 0.3 (n = 13)	133 (64.6)	0.99
Duration of follow-up, months, in pts with BP data available (median, IQR)	18.0 (1.2, 52.8)	16.8 (1.2, 46.8)	32.4 (7.2, 90)	6.5 (2.4, 34.8)	121 (58.7)	0.16

Values are expressed as mean ± standard deviation, unless otherwise specified

APA aldosterone-producing adenoma, UAH unilateral adrenal hyperplasia, UMA unilateral multiple adenomas, BP blood pressure, IQR interquartile range

determined with greater certainty. Another significant limitation of our study is the lack of BP follow-up data for >40% of patients. This may be explained by the nature of our practice as a quaternary referral center, which meant that many patients received follow-up with their local primary care providers or endocrinologists. This may have led to attrition bias, and therefore, our findings regarding BP outcomes should be interpreted with caution. Although the overall size of the cohort was large in comparison with other studies in the literature, the relatively small sample sizes of the individual pathological subtypes may have limited the statistical power of the study to detect a difference in outcomes between the groups. Nonetheless, the strengths of our study include the fact that AVS was successfully performed in the majority of patients and that biochemical outcomes were consistently assessed in every patient.

## Conclusions

Unilateral adrenal hyperplasia and multiple adenomas share similar clinical and biochemical characteristics to single adenomas in PA, although unilateral hyperplasia may have a male preponderance, and a tendency to occur in

the left adrenal gland. Nonetheless, postoperative outcomes are similar regardless of underlying pathology, so preoperative distinction between these subtypes is not essential. Because one in four patients may harbor unilateral hyperplasia or multiple adenomas, we recommend total unilateral adrenalectomy over adrenal-sparing approaches.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Young WF (2007) Primary aldosteronism: renaissance of a syndrome. *Clin Endocrinol (Oxf)* 66(5):607–618
2. Funder JW, Carey RM, Mantero F et al (2016) The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 101(5):1889–1916
3. Milliez P, Girerd X, Plouin PF et al (2005) Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* 45(8):1243–1248
4. Rossi GP, Bernini G, Desideri G et al (2006) Renal damage in primary aldosteronism: results of the PAPY study. *Hypertension* 48(2):232–238

5. Rossi GP, Sechi LA, Giacchetti G et al (2008) Primary aldosteronism: cardiovascular, renal and metabolic implications. *Trends Endocrinol Metab* 19(3):88–90
6. Quillo AR, Grant CS, Thompson GB et al (2011) Primary aldosteronism: results of adrenalectomy for nonsingle adenoma. *J Am Coll Surg* 213(1):106–112
7. Trésallet C, Salepçioğlu H, Godiris-Petit G et al (2010) Clinical outcome after laparoscopic adrenalectomy for primary hyperaldosteronism: the role of pathology. *Surgery* 148(1):129–134
8. Novitsky YW, Kercher KW, Rosen MJ et al (2005) Clinical outcomes of laparoscopic adrenalectomy for lateralizing nodular hyperplasia. *Surgery* 138(6):1009–1017
9. Morioka M, Kobayashi T, Sone A et al (2008) Primary aldosteronism due to unilateral adrenal hyperplasia. Report of two cases and review of the literature. *Endocr J* 47(4):443–449
10. Iacobone M, Citton M, Viel G et al (2012) Unilateral adrenal hyperplasia: a novel cause of surgically correctable primary hyperaldosteronism. *Surgery* 152(6):1248–1255
11. Leung A, Sasano H, Nishikwa T et al (2013) Multiple unilateral adrenal adenomas in a patient with primary hyperaldosteronism. *Endocr Pract* 14(1):76–79
12. Hashimoto N, Kawamura Y, Nakamura T et al (2011) A case of primary aldosteronism caused by multiple adrenocortical macronodules. *Intern Med* 50(6):585–590
13. Stowasser M, Gordon RD (2013) The renaissance of primary aldosteronism: What has it taught us? *Hear Lung Circ* 22(6):412–420
14. Walz MK, Gwosdz R, Levin SL et al (2008) Retroperitoneoscopic adrenalectomy in Conn's syndrome caused by adrenal adenomas or nodular hyperplasia. *World J Surg* 32(5):847–853. <https://doi.org/10.1007/s00268-008-9513-0>
15. Sigurjonsdottir HA, Gronowitz M, Andersson O et al (2012) Unilateral adrenal hyperplasia is a usual cause of primary hyperaldosteronism. Results from a Swedish screening study. *BMC Endocr Disord* 12:17
16. Weisbrod AB, Webb RC, Mathur A et al (2013) Adrenal histologic findings show no difference in clinical presentation and outcome in primary hyperaldosteronism. *Ann Surg Oncol* 20(3):753–758
17. Obara T, Ito Y, Okamoto T et al (1992) Risk factors associated with postoperative persistent hypertension in patients with primary aldosteronism. *Surgery* 112(6):987–993
18. Ito Y, Fujimoto Y, Obara T, Kodama T (1990) Clinical significance of associated nodular lesions of the adrenal in patients with aldosteronoma. *World J Surg* 14(3):330–334. <https://doi.org/10.1007/BF01658518>
19. Hennings J, Andreasson S, Botling J et al (2010) Long-term effects of surgical correction of adrenal hyperplasia and adenoma causing primary aldosteronism. *Langenbeck's Arch Surg* 395(2):133–137
20. Gioco F, Seccia TM, Gomez-Sanchez EP et al (2015) Adrenal histopathology in primary aldosteronism: Is it time for a change? *Hypertension* 66(4):724–730
21. Mete O, Duan K (2018) The many faces of primary aldosteronism and cushing syndrome: a reflection of adrenocortical tumor heterogeneity. *Front Med* 5:54
22. Young WF, Stanson AW (2009) What are the keys to successful adrenal venous sampling (AVS) in patients with primary aldosteronism? *Clin Endocrinol (Oxf)* 70(1):14–17
23. Zhang Z, Meng H, Hou Z et al (2013) Fetal adrenal gland in the second half of gestation: morphometrical assessment with 3.0T post-mortem MRI. *PLoS ONE* 8(10):e75511
24. Lam KY, Chan ACL, Lo CY (2001) Morphological analysis of adrenal glands: a prospective analysis. *Endocr Pathol* 12(1):33–38
25. Katayama Y, Takata N, Tamura T et al (2005) A case of primary aldosteronism due to unilateral adrenal hyperplasia. *Hypertens Res* 28(4):379–384
26. Proye CAG, Mulliez EAR, Carnaille BML et al (1998) Essential hypertension: first reason for persistent hypertension after unilateral adrenalectomy for primary aldosteronism? *Surgery* 124(6):1128–1133
27. Walz MK, Peitgen K, Saller B et al (1998) Subtotal adrenalectomy by the posterior retroperitoneoscopic approach. *World J Surg* 22(6):621–627. <https://doi.org/10.1007/s002689900444>
28. Ishidoya S, Ito A, Sakai K et al (2005) Laparoscopic partial versus total adrenalectomy for aldosterone producing adenoma. *J Urol* 174(1):40–43
29. Nanba AT, Nanba K, Byrd JB et al (2017) Discordance between imaging and immunohistochemistry in unilateral primary aldosteronism. *Clin Endocrinol (Oxf)* 87(6):665–672
30. Volpe C, Hamberger B, Höög A et al (2015) Primary aldosteronism: functional histopathology and long-term follow-up after unilateral adrenalectomy. *Clin Endocrinol (Oxf)* 82(5):639–647
31. Swearingen AJ, Kahramangil B, Monteiro R et al (2018) Analysis of postoperative biochemical values and clinical outcomes after adrenalectomy for primary aldosteronism. *Surgery* 163(4):807–810
32. Kline GA, Darras P, Leung AA et al (2018) Surprisingly low aldosterone levels in peripheral veins following intravenous sedation during adrenal vein sampling. *J Hypertens* 37(3):596–602

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