Hypertension outcomes of adrenalectomy for unilateral primary aldosteronism

Igor Hartmann1 · Frantisek Hruska1 · Jan Vaclavik2,3 · Eva Kocianova4 · Zdenek Frysak5 · Marika Nesvadbova1 · Zbynek Tudos6 · Filip Ctvrtlik6 · Klara Benesova7

Received: 21 July 2021 / Accepted: 19 January 2022 / Published online: 11 February 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract
Purpose To evaluate laboratory and clinical results after unilateral adrenalectomy in patients with primary aldosteronism (PHA).
Methods A cross-sectional analysis was performed using data from patients who underwent transperitoneal laparoscopic adrenalectomy for PHA, between January 2008 and December 2019. Surgical indications were based on adrenal venous sampling without ACTH stimulation. Analyses included patient demographics; preoperative clinical, pharmacological, laboratory, and radiological data; and postoperative results assessed after a median of 4 months. Antihypertensive drug use was quantified by estimating the daily defined dose (DDD) of antihypertensive medication, thus enabling standardized comparison of dosage between the drug classes. Statistical assessments included univariable and multivariable logistic regression analysis.
Results This study enrolled 87 patients. The patients were taking 5.4 DDD of antihypertensive medication before surgery, and 3.0 DDD after surgery. Complete biochemical success of surgery was reached by 67 patients (77%), 19 patients (22%) had partial biochemical success. Complete clinical success with normalization of blood pressure and withdrawal of all antihypertensive drugs was achieved in 19 patients (22%). 57 patients (65%) exhibited a reduction of DDD after surgery and/or improvement of blood pressure—partial clinical success. Thus, in 76 (87%) of all enrolled patients, surgery had an overall positive effect on hypertension control. Multivariable logistic regression showed that complete clinical success was independently associated with female gender and baseline sum of antihypertensive drugs DDD < 4.
Conclusion A majority of patients undergoing unilateral adrenalectomy for PHA achieved markedly improved hypertension control, despite almost halving their antihypertensive medication. Almost a quarter of patients were cured and able to cease using all antihypertensive drugs.

Keywords Primary aldosteronism · Secondary hypertension · Daily defined dose · Antihypertensive drug treatment · Unilateral adrenalectomy

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s12020-022-02988-y.

1 Department of Urology, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic
2 Department of Internal Medicine and Cardiology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic
3 Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic
4 Department of Internal Medicine I—Cardiology, University Hospital and Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic
5 Department of Internal Medicine III, University Hospital and Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic
6 Department of Radiology, University Hospital and Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic
7 Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic
**Introduction**

Primary hyperaldosteronism (PHA) is a disease caused by aldosterone (ALD) hypersecretion from the adrenal cortex, and is among the most common causes of secondary hypertension. Between 5 and 10% of patients with arterial hypertension exhibit PHA and in primary clinical care, PHA is found in up to 4.3% of hypertensive patients. Moreover, the PHA prevalence is as high as 13% in patients with severe hypertension, 17–29% in those with resistant hypertension, and 34% in patients with obstructive sleep apnea [1–4]. PHA is associated with increased risks of cardiovascular, cerebrovascular, and renal morbidities [5, 6]. In ~95% of cases, PHA is caused by an aldosterone-producing adenoma (APA) (i.e., Conn’s syndrome), unilateral or bilateral adrenal hyperplasia, or idiopathic hyperaldosteronism (IAH). Other rarer related conditions include familial hyperaldosteronism types I and II (2%) and an aldosterone-producing carcinoma (1–2%) [7].

The clinical picture of PHA tends to be non-specific. Some symptoms may result from hypokalaemia, including fatigue, muscle weakness, constipation, paraesthesia, and arrhythmias. However, recent reports suggest that low serum potassium is a less frequent finding compared to past reports. The majority of patients with PHA suffer from moderate to severe arterial hypertension, and are often resistant to antihypertensive treatment. Patients with PHA also suffer from cardiovascular events more frequently than other patients with hypertension [8].

Successful PHA treatment requires identification of the sources of ALD overproduction. Unilateral overproduction of ALD is an indication that adrenalectomy should be considered. When successful, such treatment reduces the ALD hyperproduction, with a corresponding positive effect on hypertension, which can potentially result in the complete correction and normalization of hypokalemia [9]. On the other hand, patients presenting with IAH are treated with mineralocorticoid receptor antagonists since, in such cases, unilateral adrenalectomy does not result in improvement of clinical symptoms and bilateral adrenalectomy causes addisonism [2].

Initial efforts to identify the source of ALD overproduction may include imaging methods, such as CT and MRI, however, these methods do not produce the most reliable results. Adenomas may evade detection because they are so small that they are below the resolution threshold. Moreover, adenomas can coexist with hyperplasia, and macronodular hyperplasia can mimic an adenoma. Another frequent finding is the presence of a hormonally inactive incidentaloma [10]. Adrenal venous sampling (AVS) is the best method for distinguishing unilateral and bilateral hypersecretion of ALD [11–13].

In the present study, we aimed to evaluate the clinical and laboratory effects of adrenalectomy as a treatment for PHA. An additional goal was to identify parameters that predict the beneficial effects of surgery for hypertension treatment.

**Materials and methods**

We performed a cross-sectional analysis of data from patients who had undergone adrenalectomy for PHA at the Department of Urology at the University Hospital in Olomouc, between January 2008 and December 2019. All patients were referred for surgery based on endocrinological, radiological, and surgical examinations. The patients received postoperative follow-up at an institutional internal medicine, cardiology or endocrinology clinic. For this study, we analyzed the records of these patients. Written informed consent was obtained from the patients, and complete follow-up records were required for each patient’s enrolment into the study.

**Clinical and laboratory examinations**

We initially identified patients with arterial hypertension who had not responded well to pharmacotherapy and who also had confirmed ALD overproduction. According to current international guidelines, hypertension was defined as systolic blood pressure (BP) >140 mmHg and/or diastolic BP >90 mmHg [14, 15]. (Note for U.S. readers: since 2017, arterial hypertension is defined in the U.S. as systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg). In each case, both plasma renin activity (PRA) and serum ALD were analyzed to determine the aldosterone-renin ratio (ARR). The normal ranges are 10–172 pg/mL for ALD, and 0.5–1.9 ng/mL/h for PRA and <30 for ARR. An ARR of >30 indicated possible hyperaldosteronism. According to the guidelines, screening laboratory tests were performed with concomitant antihypertensive therapy (including with interfering antihypertensive drugs, but after minimum 4 weeks withdrawal of potassium-sparing or potassium-wasting diuretics) [14, 15].

To confirm autonomous ALD overproduction, we consequently performed a test in which 2000 mL of saline was infused over a 4 h period after discontinuation of interfering medications in all patients who were able to tolerate such discontinuation (patients only took calcium channel blockers and alpha adrenoceptor blockers for 14 days prior testing). Failure of suppression of ALD after saline infusion <68 pg/mL was regarded as confirmatory for PHA.

To quantify the number of antihypertensive drugs, we estimated the daily defined dose (DDD) of antihypertensive medications, thus enabling standardized comparison of dosages between the drug classes [16]. The DDD is the maintenance average dose of a certain medication [17]. For instance, hydrochlorothiazide has a DDD of 25 mg, i.e., if a
hypertensive drugs preoperatively and postoperatively. To assess the effect of surgery in each patient we calculated the “Total DDD” as a sum of DDDs of all used anti-hypertensive drugs preoperatively and postoperatively.

Radiological examination

All patients underwent radiological examination using computed tomography (CT) or magnetic resonance imaging (MRI). Regardless of radiological findings, all patients with PHA also underwent AVS without ACTH stimulation. The criteria for successful catheterization included the identification of a higher concentration of cortisol in the adrenal vein compared to in the peripheral vein. Based on sufficiently selective sampling at our center, we determined that the cortisol concentration in the adrenal vein compared to the peripheral vein should exhibit a ratio of greater than 2:1. Our criteria for successful lateralization were based on current valid recommendations [14].

Aldosterone (ALD) hypersecretion without ACTH stimulation was regarded as unilateral if the ALD/cortisol ratio on one side was over four times greater than the other side, i.e., the lateral ALD/cortisol ratio was over 4:1. A lateral ALD/cortisol ratio of below 3:1 was considered to indicate bilateral ALD hypersecretion. When the ratio was between 3:1 and 4:1, correct interpretation of the results required consideration of the clinical status and imaging findings, or a potential repetition of the test. In patients with a ratio of under 3:1 and a simultaneous finding of an adenoma with a diameter of >3 cm, surgical intervention was indicated because of the possible malignancy of this tumor.

Surgical examination

Based on the results of endocrinological and radiological examinations, indications for unilateral adrenalectomy were established. Then the patients were evaluated by a urologist, to determine their operability. The surgeon also reviewed any previous abdominal surgeries, and the patient’s general condition and BMI, before recommending appropriate surgery. The preferred surgery was a laparoscopic trans-peritoneal adrenalectomy. Compared to open adrenalectomy, laparoscopic adrenalectomy is associated with shorter hospital stays and potentially fewer complications [2]. Retroperitoneal adrenalectomy was not considered as a primary approach, as this is not a preferred method within our department.

Postoperative follow-up

After surgery, patients underwent both clinical and laboratory examinations at the internal medicine, cardiology or endocrinology departments to evaluate their overall health status, BP, potassium levels, PRA, ALD, and ARR. These evaluations were performed with concomitant use of interfering medication, unless the drugs were discontinued due to cure or improvement of hypertension.

The clinical and biochemical success were evaluated according to the Primary Aldosteronism Surgery Outcome (PASO study) international consensus [18] as following:

1. Complete clinical success - Normal BP (office systolic BP <140 mmHg and diastolic BP <90 mmHg) without the aid of antihypertensive medication.
2. Partial clinical success - the same BP as before surgery with less antihypertensive medication (decreased Total DDD) or a reduction in BP with either the same amount or less antihypertensive medication.
3. Absent clinical success - unchanged or increased BP with either the same amount or an increase in antihypertensive medication.
4. Complete biochemical success - correction of hypokalaemia (if present pre-surgery) and normalization of the ALD-to-renin ratio.
5. Partial biochemical success - correction of hypokalaemia (if present pre-surgery) and a raised ALD-to-renin ratio with ≥50% decrease in baseline plasma ALD concentration.
6. Absent biochemical success - Persistent hypokalaemia (if present pre-surgery) or persistent raised ALD-to-renin ratio.

Statistical analysis

Analyses were performed using standard descriptive statistical methods. Continuous data were described as mean with standard deviation or median with 5–95 percentile range for continuous data, and categorical data as absolute and relative frequencies. Preoperative and postoperative characteristics of patients were compared using a paired Wilcoxon test. To assess possible differences between groups of patients according to their outcome, we used the Mann–Whitney U test for continuous variables, and Fisher’s exact test for categorical variables. To evaluate the predictive power of patient characteristics in terms of the endpoint, we performed univariable and multivariable logistic regression, and the results are presented as odds ratio (OR), 95% confidence interval (CI), and statistical significance. A backward stepwise algorithm was used to select the optimal model, and the area under the ROC curve (AUC) was computed to evaluate the model’s overall predictive power. Analyses were performed using SPSS V.25.0.0.1., and the level of statistical significance was set at \( \alpha = 0.05 \).
Between January 2008 and December 2019, 87 patients with unilateral hyperaldosteronism underwent transperitoneal laparoscopic adrenalectomy. Table 1 presents the characteristics of these treated patients. The mean age of patients was 57 years and the majority were men (60.9%). Most patients presented clinically with resistant arterial hypertension, therefore their mean of face BP was 163/95 mmHg despite using a mean of 5.4 Total DDD of antihypertensive drugs.

All patients were treated laparoscopically, and no serious adverse events were observed. The clinical and laboratory outcomes of the surgeries were assessed after a median of 4 months (range, 1–82 months). Postoperatively, the of face BP decreased significantly by mean 32/14–131/81 mmHg (P < 0.001). The Total DDD of used antihypertensive drugs decreased by 2.4 to a mean of 3.0 (P < 0.001). Table 2 presents the effects of surgery on selected clinical and laboratory parameters. Table 3 shows the changes of antihypertensive medication after surgery.

Mean ALD-to-renin ratio decreased postoperatively from 562 to 36. In 67 patients (77%), the ALD-to-renin ratio was normalized after surgery, and these patients were regarded as “complete biochemical success”. 19 patients (22%) had “partial biochemical success”, and 1 patient (1%) had absent biochemical success. (Please see Fig. 1).

**Table 1 Patients’ characteristics (N = 87)**

| Preoperative data | n (% of N) or mean ± SD, median (5–95th percentile) |
|-------------------|-----------------------------------------------------|
| **Gender**        |                                                    |
| Male              | 53 (60.9%)                                          |
| Female            | 34 (39.1%)                                          |
| **Age, years**    |                                                    |
| <50               | 23 (26.4%)                                          |
| 50–59             | 27 (31.0%)                                          |
| ≥60               | 37 (42.5%)                                          |
| **BMI, kg/m²**    | 30.1 ± 5.0, 29.8 (22.2–39.5)                        |
| **Coronary artery disease** |                        |
| Yes               | 8 (9.2%)                                            |
| No                | 79 (90.8%)                                          |
| **Diabetes mellitus** |                                                |
| Yes               | 24 (27.6%)                                          |
| No                | 63 (72.4%)                                          |
| **Duration of hypertension, months** | 110 ± 83, 76 (22–240) |
| **Duration of hypertension, years** | 32 (36.8%), 29 (33.3%), 26 (29.9%) |
| **Systolic blood pressure, mmHg** | 163 ± 27, 160 (130–220) |
| **Diastolic blood pressure, mmHg** | 95 ± 19, 95 (65–130) |
| **Antihypertensive therapy, Total DDD** | 5.4 ± 2.6, 5.6 (2.0–10.4) |

**Table 1 (continued)**

| Operative data | n (% of N) or mean ± SD, median (5–95th percentile) |
|----------------|-----------------------------------------------------|
| **Histology**  |                                                    |
| Adenoma        | 40 (46.0%)                                          |
| Hyperplasia    | 47 (54.0%)                                          |
| **Post-operative data** |                                                |
| Time post-surgery, months | 14 ± 25, 4 (1–82) |
| Systolic blood pressure, mmHg | 131 ± 17, 129 (105–160) |
| Diastolic blood pressure, mmHg | 81 ± 11, 80 (65–100) |
| **Antihypertensive therapy, DDD** | 3.0 ± 2.5, 3.0 (0.0–7.3) |

**Table 2**

| Serum aldosterone, pg/mL | 724 ± 1195, 287 (175–2,052) |
| Plasma renin, pg/mL      | 0.23 ± 0.34, 0.10 (0.05–0.64) |
| Aldosterone-to-renin ratio | 562 ± 773, 311 (37–2000) |
| Serum potassium level, mmol/L | 3.24 ± 0.47, 3.20 (2.60–4.02) |
| Plasma sodium, mmol/L    | 141.4 ± 2.9, 141 (136–146) |
| Creatinine clearance, mL/s | 1.30 ± 0.23, 1.39 (0.85–1.50) |
| **Sampling ratio**       | 7.4 ± 6.0, 5.0 (2.6–19.0) |
| **Adrenalectomy side**   |                                                    |
| Left                     | 46 (52.9%)                                          |
| Right                    | 41 (47.1%)                                          |
| **Imaging findings on surgery side** |                                                |
| No findings              | 22 (25.3%)                                          |
| Adenoma                  | 57 (65.5%)                                          |
| Hyperplasia              | 8 (9.2%)                                           |
| **Imaging findings on opposite side** |                                                |
| No findings              | 69 (79.3%)                                          |
| Adenoma                  | 12 (13.8%)                                          |
| Hyperplasia              | 6 (6.9%)                                           |

**Results**

Between January 2008 and December 2019, 87 patients with unilateral hyperaldosteronism underwent transperitoneal laparoscopic adrenalectomy. Table 1 presents the characteristics of these treated patients. The mean age of patients was 57 years and the majority were men (60.9%). Most patients presented clinically with resistant arterial hypertension, therefore their mean office BP was 163/95 mmHg despite using a mean of 5.4 Total DDD of antihypertensive drugs.

All patients were treated laparoscopically, and no serious adverse events were observed. The clinical and laboratory outcomes of the surgeries were assessed after a median of 4 months (range, 1–82 months). Postoperatively, the office BP decreased significantly by mean 32/14–131/81 mmHg (P < 0.001). The Total DDD of used antihypertensive drugs decreased by 2.4 to a mean of 3.0 (P < 0.001). Table 2 presents the effects of surgery on selected clinical and laboratory parameters. Table 3 shows the changes of anti-hypertensive medication after surgery.

Mean ALD-to-renin ratio decreased postoperatively from 562 to 36. In 67 patients (77%), the ALD-to-renin ratio was normalized after surgery, and these patients were regarded as “complete biochemical success”. 19 patients (22%) had “partial biochemical success”, and 1 patient (1%) had absent biochemical success. (Please see Fig. 1).
19 patients (22%) did not require any antihypertensive drugs and had normalized BP after surgery and were regarded as “complete clinical success.” The majority, 57 patients (65%) had exhibited a reduction of DDD after surgery and/or improvement of BP—“partial clinical success.” Clinical success of surgery was absent in 11 patients (13%) (Fig. 1). Thus, in 76 (87%) of all enrolled patients, surgery had an overall positive effect on hypertension control.

Table 4 shows the univariable analysis of predictors of the “complete clinical success” of the treatment. The statistically significant predictors of clinical success were female gender and less intensive preoperative antihypertensive treatment (lower preoperative Total DDD).

We did not find any statistically significant preoperative predictor of the “complete biochemical success”, as shown in Table S1 (online supplementary).

Multivariable logistic regression analysis revealed that “complete clinical success” with the clinical cure of hypertension was independently associated with female gender and Total DDD < 4 (Table 5).

22 (25.3%) patients had no imaging findings on surgery side, but following histology found hyperplasia in 19 (86.4%) and adenoma in 3 (13.6%) of these patients. Patients with no imaging findings on the operated adrenal gland were more likely to be men a needed higher number of antihypertensive drugs both preoperatively and postoperatively, as shown in Table S2 (online supplementary). The rates of clinical and laboratory success of surgery did not differ significantly between patients with and without abnormal imaging findings on surgery side (Table S2), although, numerically, the complete clinical success was less common in patients with no abnormal imaging findings on surgery side (4.5 vs. 24.6%).

**Discussion**

One of the most important clinical outcomes in treatment of hyperaldosteronism is to control hypertension that is frequently severe and associated with end-organ damage. In the present study of patients who underwent adrenalectomy...
for hyperaldosteronism caused by unilateral hypersecretion of ALD, we found that the main clinical outcome was better control of hypertension. Nevertheless, not all patients were able to discontinue their use of all antihypertensive medication after surgery. Uncured hypertension (partial or absent clinical success) likely resulted from coexisting irreversible vascular changes that were induced by hypertension itself and/or by direct long-standing exposure to ALD [19, 20].

In our cohort, 87% of surgically treated patients achieved hypertension control, as indicated by an overall reduction of DDD or BP. Only 22% of patients achieved clinical cure (complete clinical success; Total DDD of 0). Other published studies have described hypertension cure rates ranging between 15.3 and 55%, as defined by a BP of <140/90 mmHg without the use of antihypertensive drugs [21–24]. Within our cohort, 65% of patients exhibited partial

---

**Table 4** Univariable analysis of predictors associated with “complete clinical success” of treatment

| Predictor                        | Complete clinical success (n = 19) | Partial or none clinical success (n = 68) | P     |
|----------------------------------|-----------------------------------|------------------------------------------|-------|
| Gender                           | Male                              | 6 (31.6%)                                | 47 (69.1%) | 0.007 |
|                                  | Female                            | 13 (68.4%)                               | 21 (30.9%)  | 0.089 |
| Age, years                       |                                   | 52 ± 12                                  | 58 ± 9      | 0.261 |
| <50                              |                                   | 7 (36.8%)                                | 16 (23.5%)  | 0.192 |
| 50–59                            |                                   | 7 (36.8%)                                | 20 (29.4%)  | 0.253 |
| ≥60                              |                                   | 5 (26.3%)                                | 32 (47.1%)  | 0.253 |
| BMI, kg/m²                       |                                   | 28.2 ± 5.1                               | 30.6 ± 4.8   | 0.077 |
| Coronary artery disease          | Yes                               | 0 (0.0%)                                 | 8 (11.8%)    | 0.892 |
|                                  | No                                | 19 (100.0%)                              | 60 (88.2%)   | 0.192 |
| Diabetes mellitus                | Yes                               | 3 (15.8%)                                | 21 (30.9%)   | 0.253 |
|                                  | No                                | 16 (84.2%)                               | 47 (69.1%)   | 0.253 |
| Duration of hypertension, months |                                   | 63 (9; 300)                              | 80 (24; 240) | 0.297 |
| Duration of hypertension, years  | <5                                | 9 (47.4%)                                | 23 (33.8%)   | 0.521 |
|                                  | 5–9                               | 6 (31.6%)                                | 23 (33.8%)   | 0.521 |
|                                  | ≥10                               | 4 (21.1%)                                | 22 (32.4%)   | 0.521 |
| Systolic blood pressure, mmHg    |                                   | 155 ± 22                                 | 165 ± 28     | 0.188 |
| Diastolic blood pressure, mmHg   |                                   | 94 ± 28                                  | 96 ± 16      | 0.406 |
| Antihypertensive therapy, Total DDD |                           | 3.8 ± 2.3                               | 5.8 ± 2.5    | 0.001 |
| Serum aldosterone, pg/mL         |                                   | 325 (173; 8338)                          | 278 (178; 2000) | 0.789 |
| Plasma renin, pg/mL              | 0.11 (0.05; 2.65)                 | 0.10 (0.05; 0.64)                        | 0.615 |
| Aldosterone-to-renin ratio       | 296 (37; 2551)                    | 313 (32; 2000)                           | 0.655 |
| Serum potassium level, mmol/L     |                                   | 3.29 ± 0.50                              | 3.22 ± 0.47  | 0.578 |
| Plasma sodium, mmol/L            |                                   | 140.6 ± 3.1                              | 141.7 ± 2.8  | 0.137 |
| Creatinine clearance, mL/s       | 1.40 (0.94; 1.70)                 | 1.38 (0.82; 1.50)                        | 0.921 |
| Sampling ratio                   | 5.1 (2.5; 16.2)                   | 4.8 (2.6; 19.4)                          | 0.426 |
| Adrenalectomy side               | Left                              | 11 (57.9%)                               | 35 (51.5%)   | 0.796 |
|                                  | Right                             | 8 (42.1%)                                | 33 (48.5%)   | 0.796 |
| Imaging finding on surgery side  | No findings                       | 1 (5.3%)                                 | 21 (30.9%)   | 0.052 |
|                                  | Adenoma                           | 16 (84.2%)                               | 41 (60.3%)   | 0.521 |
|                                  | Hyperplasia                       | 2 (10.5%)                                | 6 (8.8%)     | 0.521 |

Bold values identify statistical significance p < 0.05
Categorical variables are described using absolute and relative frequencies, quantitative normally distributed variables are presented as mean ± SD, and quantitative non-normally distributed variables are presented as median (5–95th percentile)
P values were calculated using Fisher’s exact test or the Mann–Whitney U test. Total DDD = sum of daily defined doses of used antihypertensive drugs

---

**Table 4** (continued)

| Predictor                        | Complete clinical success (n = 19) | Partial or none clinical success (n = 68) | P     |
|----------------------------------|-----------------------------------|------------------------------------------|-------|
| Imaging finding on opposite side | No findings                       | 15 (78.9%)                               | 54 (79.4%)  | 0.892 |
|                                  | Adenoma                           | 3 (15.8%)                                | 9 (13.2%)   | 0.301 |
|                                  | Hyperplasia                       | 1 (5.3%)                                 | 5 (7.4%)    | 0.301 |
| Histology                        | Adenoma                           | 11 (57.9%)                               | 29 (42.6%)  | 0.301 |
|                                  | Hyperplasia                       | 8 (42.1%)                                | 39 (57.4%)  | 0.301 |

Bold values identify statistical significance p < 0.05
Categorical variables are described using absolute and relative frequencies, quantitative normally distributed variables are presented as mean ± SD, and quantitative non-normally distributed variables are presented as median (5–95th percentile)
P values were calculated using Fisher’s exact test or the Mann–Whitney U test. Total DDD = sum of daily defined doses of used antihypertensive drugs

---

**Table 5** Multivariable logistic regression model using a backward stepwise algorithm for selection of independent predictors of successful clinical cure of primary hyperaldosteronism

| Predictor                        | OR (95% CI) | P     |
|----------------------------------|-------------|-------|
| Gender                           | Male        | Reference category |
|                                  | Female      | 3.71 (1.16; 11.87) | 0.027 |
| Antihypertensive therapy         | Total DDD ≥ 4 | Reference category |
|                                  | Total DDD < 4 | 5.30 (1.68; 16.67) | 0.004 |

Bold values identify statistical significance p < 0.05
AUC (95% CI): 0.777 (0.653–0.901); P < 0.001; sensitivity, 63.2%; specificity, 79.4%. Total DDD = sum of daily defined doses of used antihypertensive drugs

---

for hyperaldosteronism caused by unilateral hypersecretion of ALD, we found that the main clinical outcome was better control of hypertension. Nevertheless, not all patients were able to discontinue their use of all antihypertensive medication after surgery. Uncured hypertension (partial or absent clinical success) likely resulted from coexisting irreversible vascular changes that were induced by hypertension itself and/or by direct long-standing exposure to ALD [19, 20].

In our cohort, 87% of surgically treated patients achieved hypertension control, as indicated by an overall reduction of DDD or BP. Only 22% of patients achieved clinical cure (complete clinical success; Total DDD of 0). Other published studies have described hypertension cure rates ranging between 15.3 and 55%, as defined by a BP of <140/90 mmHg without the use of antihypertensive drugs [21–24]. Within our cohort, 65% of patients exhibited partial
clinical success, with improved BP control and reduction of DDD. Previous studies have shown that this important group includes an average of 47% of patients (range, 35–66%) [18].

The number of antihypertensive drug classes themselves does not accurately reflect the total consumption of antihypertensive drugs used to control BP. Thus, the defined daily dose (DDD) has been adopted to enable analysis of the consumption of many prescribed, in the present study, antihypertensive drugs [16]. Use of the DDD allows clinicians to better counsel patients with primary aldosteronism (PHA) regarding the predicted postoperative change in antihypertensive drug consumption. Our present investigation is one of only a few studies to adopt the DDD concept [25]. Antihypertensive therapy defined by the Total DDD was reduced from 5.4 before to 3.0 after surgery, i.e., our cohort showed a mean postoperative decrease of 2.4 DDD.

Previous studies have reported the following independent factors affecting the persistence of hypertension after adrenalectomy: male sex, advanced age, increased BMI, hypertension duration of >6 years, preoperative use of ≥3 types of antihypertensive drugs, and adrenal gland size [26–32]. Zarnegar et al. proposed a scoring system to predict the benefits of adrenalectomy for patients, which combines four independent factors: the number of antihypertensive medications used, BMI, hypertension duration, and female gender [33].

In our study, hypertension reversal (complete clinical success) was independently associated with only with female gender and use of less powerful antihypertensive treatment (Total DDD < 4). Notably, hypertension resolution or improvement was the most important clinical outcome of the surgery. Contrary, partial or complete biochemical success was achieved in 99% of the participating patients.

In cases of hyperaldosteronism, adrenalectomy should only be indicated in cases with clearly demonstrated unilateral ALD hypersecretion. If the preoperative algorithm for localization of hypersecretion exclusively relies on imaging methods, it is likely that up to 25% of patients will not be correctly identified. Our present data confirmed these findings, showing that 25.3% of our patients undergoing adrenalectomy had AVS-confirmed unilateral ALD secretion but had normal findings according to adrenal imaging [11]. AVS is the only method that can conclusively distinguish unilateral from bilateral ALD hypersecretion. Therefore, AVS is commonly considered a necessary prerequisite for adrenalectomy in all patients with PHA, regardless of the apparent findings on CT or MRI scans [12, 14].

The importance of AVS appears to be particularly significant in elderly patients, who also show a greater incidence of non-functional adenomas. In addition, young patients (age <35 years), and cases of unilateral adrenal lesions with radiological features consistent with cortical adenoma seen on a CT scan, may not require AVS before proceeding to unilateral adrenalectomy [14].

Notably, if both adrenal veins are not successfully catheterized, it may be necessary to repeat AVS, treat a patient medically, or consider surgery based on the findings of alternative diagnostic tests [2]. For 17 patients in the present study, we had to repeat AVS to obtain conclusive results.

Microscopic differentiation between an adenoma and adrenal hyperplasia may prove to be rather challenging. In cases of nodular hyperplasia, more nodules may be found, and the adrenal cortex surrounding these nodules will appear hyperplastic. In contrast, the histology of adenomas usually presents with extranodular atrophy [34, 35]. In our study, histological examinations were performed by several different histopathologists, therefore, it was practically impossible to clearly distinguish between the various forms of hyperplasia. Cortical adenoma can occur simultaneously with adrenal hyperplasia, but it has generally been reported that adrenal adenoma is the most common cause of unilateral ALD hypersecretion. However, a greater proportion of adrenal hyperplasia has been reported among patients with unilateral hypersecretion accurately diagnosed based on AVS [36]. In the present study, clinical outcomes were identical between patients with histological evidence of hyperplasia vs. patients with evidence of an adenoma. This fact is consistent with studies that have reported unilateral adrenal hyperplasia to be far more frequent than previously thought [37–42].

A limitation of our present study is the small number of included patients, since the studied condition is rather rare. Another possible limitation is that, before the publication of the PASO consensus [18], the first postoperative outpatient visit was performed earlier than currently recommended 6–12 months after surgery, to enable us further reduce antihypertensive medication, if required. However, subsequent clinical visits in these patients confirmed persistent clinical and biochemical effects of the surgery.

A strength of our study is the use of the DDD concept to enable analysis of the usage of combinations of multiple drugs.

Conclusions

Here we report outcomes of patients who underwent adrenalectomy for unilateral hyperaldosteronism indicated based on AVS. This study is one of only few investigations to adopt the DDD concept. Among surgically treated patients, 83% exhibited improved hypertension control, as shown by an overall reduction of DDD, while 24% achieved clinical cure (DDD of 0).
Data availability

Yes.

Funding The study was supported by the Ministry of Health of the Czech Republic, grant no. 17-31847A.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. A. Hannemann, H. Wallaschofski, Prevalence of primary aldosteronism in patient’s cohorts and in population-based studies – a review of the current literature. Horm. Metab. Res. 44, 157–162 (2012)
2. J.W. Funder, R.M. Carey, F. Mantero et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: An endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 101, 1889–1916 (2016)
3. J.M. Brown, M. Siddiqui, D.A. Cahloun et al. The unrecognized prevalence of primary aldosteronism: a cross-sectional study. Ann. Intern. Med. 173(1), 10–20 (2020)
4. M. Parasiliti-Capriamo, C. Lopez, N. Prencipe et al. Prevalence of primary aldosteronism and association with cardiovascular complications in patients with resistant and refractory hypertension. J. Hypertens. 38(9), 1841–8 (2020)
5. J.M. Brown, M. Siddiqui, D.A. Cahloun et al. The unrecognized prevalence of primary aldosteronism: a cross-sectional study. Ann. Intern. Med. 173(1), 10–20 (2020)
6. Z.W. Chen, C.S. Hung, V.C. Wu et al. Primary aldosteronism and cerebrovascular diseases. Endocrinol. Metab. 3, 429–34 (2018)
7. B.K. Goh, Y.A. Tan, K.T. Chang et al. Primary hyperaldosteronism secondary to unilateral adrenal hyperplasia: an unusual cause of surgically correctable hypertension. A review of 30 cases. World J. Surg. 31(1), 72–9 (2007)
8. P. Milliez, X. Gireud, P.F. Ploun et al. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J. Am. Coll. Cardiol. 45, 1243–48 (2005)
9. F. Lumachi, M. Ermani, S.M. Basso et al. Long-term results of adrenalectomy in patients with aldosterone-producing adenomas: a multivariate analysis of factors affecting unresolved hypertension and review of the literature. Am. Surg. 71(10), 864–9 (2005)
10. M. Omura, H. Sasano, J. Saito et al. Clinical characteristics of aldosterone-producing microadenoma, macroadenoma, and idiopathic hyperaldosteronism in 93 patients with primary aldosteronism. Hypertens. Res. 29(11), 883–9 (2006)
11. A. Toniato, P. Bernante, G.P. Rossi et al. The role of adrenal venous sampling in the surgical management of primary aldosteronism. World J. Surg. 30, 624–627 (2006)
12. T. Nishikawa, M. Omura, F. Satoh et al. Guidelines for the diagnosis and treatment of primary aldosteronism. Task Force Committee on Primary Aldosteronism, The Japan Endocrine Society. Endocr. J. 58(9), 711–721 (2011)
13. W.F. Young, A.W. Stanson, G.B. Thompson et al. Role for adrenal venous sampling in primary aldosteronism. Surgery 136, 1227–1235 (2004)
14. B. Williams, G. Mancia, W. Spiering et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J. Hypertens. 36(10), 1953–2041 (2018)
15. T. Unger, C. Borghi, F. Charchar et al. 2020 International Society of Hypertension global hypertension practice guidelines. J. Hypertens. 38(6), 982–1004 (2020)
16. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2013. Oslo (2012).
17. R. Modolo, A.P. de Faria, A.M. Ritter et al. Defined daily dose (DDD) and its potential use in clinical trials of resistant hypertension. Int. J. Cardiol. 202, 515–6 (2016)
18. T.A. Williams, J.W.M. Lenders, P. Mulatero et al. Primary Aldosteronism Surgery Outcome (PASO) investigators. 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. 5(9), 689–699 (2017)
19. Y. Zhou, M. Zhang, S. Ke et al. Hypertension outcomes of adrenalectomy in patients with primary aldosteronism: a systematic review and meta-analysis. BMC Endocr. Disord. 17(1), 61 (2017)
20. S. Monticone, F. D’Ascenzo, C. Moretti et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 6(1), 41–50 (2018)
21. H. Wachtel, I. Cerullo, E.K. Bartlett et al. Long-term blood pressure control in patients undergoing adrenalectomy for primary hyperaldosteronism. Surgery 156(6), 1394–1403 (2014)
22. L. Pasquier, M. Kirouani, F. Fanget et al. Assessment of the Aldosteronoma resolution score as a predictive resolution score of hypertension after adrenalectomy for aldosteronoma in French patients. Langenbecks Arch. Surg. 402(2), 309–314 (2017)
23. P.J. Worth, N.R. Kunio, I. Siegfried et al. Characteristics predicting clinical improvement and cure following laparoscopic adrenalectomy for primary aldosteronism in a large cohort. Am. J. Surg. 210(4), 702–709 (2015)
24. X. Zhang, Z. Zhu, T. Xu et al. Factors affecting complete hypertension cure after adrenalectomy for aldosterone-producing adenoma: outcomes in a large series. Urol. Int. 90(4), 430–434 (2013)
25. T. Usumi, K. Kawamura, T. Imamoto et al. Assessment of postoperative changes in antihypertensive drug consumption in patients with primary aldosteronism using the defined daily dose. Asian J. Surg. 37(4), 190–4 (2014)
26. C.Y. Lo, P.C. Tam, A.W. Kung et al. Primary aldosteronism. Results of surgical treatment. Ann. Surg. 224, 125–130 (1996)
27. L.M. Brun, J.F. Moley, G.M. Doherty et al. Outcomes analysis in patients undergoing laparoscopic adrenalectomy for hormonally active adrenal tumors. Surgery 130, 629–634 (2001)
28. P. Meria, B.F. Kempf, J.F. Hermieu et al. Laparoscopic management of primary hyperaldosteronism: clinical experience with 212 cases. J. Urol. 169(1), 32–5 (2003)
29. T.C. Pang, C. Bambach, J.C. Monaghan et al. Outcomes of laparoscopic adrenalectomy for hyperaldosteronism. ANZ J. Surg. 77, 768–773 (2007)
30. B.K. Goh, Y.H. Tan, S.K. Yip, P.H. Eng et al. Outcome of patients undergoing laparoscopic adrenalectomy for primary hyperaldosteronism. JSLS 8, 320–325 (2004)
31. M. Murashima, S.O. Terrotota, D.L. Fraker et al. Adrenal venous sampling for primary aldosteronism and clinical outcomes after unilateral adrenalectomy: a single-center experience. J. Clin. Hypertens. 11, 316–323 (2009)
32. N. Sukor, R.D. Gordon, Y.K. Ku et al. Role of unilateral adrenalectomy in bilateral primary aldosteronism: a 22-year single
center experience. J. Clin. Endocrinol. Metab. 94, 2437–2445 (2009)
33. R. Zarnegar, W.F. Young Jr, J. Lee et al. The aldosteronoma resolution score: predicting complete resolution of hypertension after adrenalectomy for aldosteronoma. Ann. Surg. 247(3), 511–8 (2008)
34. R.V. Lloyd, B.R. Douglas, W.F. Young Jr. Endocrine diseases: Atlas of nontumor pathology. First series, Facicle 1. (AFIP, Washington DC), 2002) 218
35. J. Rosai. Lesions of the adrenal cortex. ed. by Rosai J, Rosai and Ackerman’s surgical pathology, 9th ed Mosby, 1119 (2004)
36. A.R. Quillo, C.S. Grant, G.B. Thompson et al. Primary aldosteronism: results of adrenalectomy for nonsingle adenoma. J. Am. Coll. Surg. 213(1), 106–113 (2011)
37. Y.W. Novitsky, K.W. Kercher, M.J. Rosen et al. Clinical outcomes of laparoscopic adrenalectomy for lateralizing nodular hyperplasia. Surgery 138(6), 1009–16 (2005)
38. J. Hennings, S. Andreasson, J. Botling et al. Long-term effects of surgical correction of adrenal hyperplasia and adenoma causing primary aldosteronism. Langenbecks Arch. Surg. 395(2), 133–7 (2010)
39. M.K. Walz, R. Gwosdz, S.L. Levin et al. Retroperitoneoscopic adrenalectomy in Conn’s syndrome caused by adrenal adenomas or nodular hyperplasia. World J. Surg. 32(5), 847–53 (2008)
40. C. Trésallet, H. Salepcioglu, G. Godiris-Petit et al. Clinical outcome after laparoscopic adrenalectomy for primary hyperaldosteronism: the role of pathology. Surgery 148(1), 129–34 (2010)
41. M. Iacobone, M. Citton, G. Viel et al. Unilateral adrenal hyperplasia: a novel cause of surgically correctable primary hyperaldosteronism. Surgery 152(6), 1248–55 (2012)
42. A.B. Weisbrod, R.C. Webb, A. Mathur et al. Adrenal histologic findings show no difference in clinical presentation and outcome in primary hyperaldosteronism. Ann. Surg. Oncol. 20(3), 753–8 (2013)