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Renal Function Evolution and Hypoaldosteronism Risk After Unilateral Adrenalectomy for Primary Aldosteronism

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ABSTRACT

Few studies demonstrated a percentage decrease in the estimated glomerular filtration rate (eGFR) at a single time and the rate of hypoaldosteronism after adrenalectomy for primary aldosteronism (PA). Our aim was to investigate the evolution of renal function and the hypoaldosteronism risk after adrenalectomy for PA. Aldosterone, renin, eGFR, and electrolyte levels were determined before and at 1 week, 1, 3 and 6 months after unilateral adrenalectomy in 94 PA patients (40 men and 54 women). The main outcome was the postoperative eGFR decline using analysis of covariance with the preoperative eGFR as a covariate. eGFR decreased during first postoperative week compared to 3 months before surgery. During the first 6 months, eGFR remained stable at similar levels to the first week after surgery. Age ($p = 0.001$), aldosterone levels ($p = 0.021$) and eGFR 3 months before surgery ($p < 0.0001$) had a significant correlation with eGFR during first postoperative week. High aldosterone levels at diagnosis were correlated with decline in renal function in the univariate model ($p = 0.033$). In the multivariate analysis, aldosterone levels at diagnosis had a tendency to be an independent predictor of renal function after surgery ($p = 0.059$). Postoperative biochemical hypoaldosteronism was diagnosed in 48 % of the cases after adrenalectomy, but prolonged hyperkalemia occurred in only 4 cases (4.5 %). Our findings showed a decrease of eGFR after unilateral adrenalectomy for PA. Additionally, aldosterone levels at diagnosis correlated with postoperative renal function. Postoperative biochemical hypoaldosteronism occurred in almost half of the patients, but prolonged hyperkalemia with fludrocortisone replacement was less frequent.

Introduction

Hypertension affects between 10 and 40 % of the general population and is a leading risk factor for cardiovascular death [1]. Primary aldosteronism (PA) is the most common cause of endocrine hypertension [2–4]. The prevalence of PA ranges from 10 % to 25 % in the hypertensive population [5]. Unilateral PA accounts for approximately 40 % of the cases and is preferentially treated with unilateral adrenalectomy [2]. Although almost all PA patients improve blood pressure control after surgery, complete clinical success after biochemical cure has been reported only in about 50 % (ranging from 35 to 80 %) of patients with unilateral PA after adrenalectomy [2, 6–8].

It has been well established that aldosterone excess is associated with an increased risk of cardiovascular and cerebrovascular complications in patients with PA [9, 10]. Aldosterone and salt induce renal inflammation and fibrosis in hypertensive rats through production of reactive oxygen species and activation of mitogen-activated protein kinase [11]. PA patients showed more renal impairment and a high prevalence of proteinuria when compared to hypertensive matched individuals [12, 13]. Moreover, high aldosterone levels in PA patients can promote glomerular hyperfiltration and, consequently, false elevation of the estimated glomerular filtration rate (eGFR) before PA treatment [13]. In agreement with this hypothesis, few studies reported a decrease in renal function following unilateral adrenalectomy [14–16]. Pre-operative aldosterone levels, age and potassium levels were predictors of eGFR decline after unilateral adrenalectomy. High systolic preoperative blood pressure was associated with eGFR decline after 12 months of unilateral adrenalectomy in a single study [14]. Moreover, Kobayashi et al. [17] demonstrated that a greater acute fall in eGFR was associated with a smaller long-term decline in renal function after mineralocorticoid treatment in PA patients, but this association was not observed in PA patients after adrenalectomy.

Besides the kidney function, the rate and effect of postoperative hypoaldosteronism after adrenalectomy for unilateral PA were evaluated only by a few studies [18–20]. The presentation of postoperative hypoaldosteronism might be transient hyperkalemia and very low/undetectable aldosterone levels or persistent hyperkalemia associated or not with hypotension. Recently, Wada et al. [21] demonstrated that prolonged hypoaldosteronism is likely to develop in patients with aldosteronoma after adrenalectomy who are older and have impaired renal function. Fludrocortisone replacement is the proposed treatment for persistent hyperkalemia, hyponatremia and/or hypotension until the transient hypoaldosteronism has been resolved [19, 20].

The aim of our study was to investigate the evolution of kidney function at different time points after unilateral adrenalectomy in unilateral PA and to determine predictive factors for the eGFR decline. In addition, we evaluated the incidence and effect of biochemical and clinical hypoaldosteronism after surgery.

Patients and Methods

We performed a retrospective cohort study to evaluate PA patients with unilateral disease submitted to unilateral adrenalectomy between 2010 and 2022 in a quaternary academic center. We have included all consecutive patients with PA that underwent unilateral adrenalectomy. The study was approved by the Ethics Committees of the Hospital das Clínicas, University of São Paulo Medical School. This is an observational study and complied with the STROBE guidelines.

Clinical, biochemical and imaging data were collected from patient records. Serum aldosterone, plasma direct renin concentration (DRC), eGFR, and electrolytes as sodium and potassium levels were determined at the diagnosis, preoperative period, and 1 week, 1, 3 and 6 months after laparoscopic unilateral adrenalectomy. The eGFR was calculated based on the following formula: eGFR (ml/min/1.73 m^2) = 186 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ (× 0.742, if female) [22].

The primary endpoint was the evaluation of renal function during follow-up (pre- and post-adrenalectomy) and the factors associated with a decline in postoperative eGFR. We have excluded 3 cases that did not have renal function at the first week after adrenalectomy. The secondary endpoint was the incidence of postoperative biochemical hypoaldosteronism (aldosterone during first week after surgery ≤ 4 ng/dl and suppressed renin) and its effect on renal function and electrolytes. During the first week post-surgery, nonsteroidal anti-inflammatory drugs are not used for pain relief after laparoscopic adrenalectomy due to the risk of worsening renal function. In our protocol, the patients received dipyrone and opioids (usually tramadol or codeine) for pain relief.

The algorithm for PA investigation followed the 2016 Endocrine Society Guideline for PA management [2]. In our Institution, a positive screening for PA, defined as an aldosterone/DRC ratio > 2 ng/dl/μIU/ml (or 55.5 pmol/l/μIU/ml) with concomitant aldosterone levels > 10 ng/dl (or 277 pmol/l), has a true positive rate of 95 % for PA diagnosis [23].

Confirmatory test was not performed in PA patients with spontaneous hypokalemia, suppressed renin levels plus plasma aldosterone concentration > 20 ng/dl (554 pmol/l). All other patients performed at least one confirmatory test. We have employed the following confirmatory tests: 1) Saline infusion test (infusion of 2 liter of 0.9 % saline over 4 h): aldosterone > 10 ng/dl (277 pmol/l) at 4 hours confirmed PA; 2) Captopril challenge test (oral intake of 50 mg captopril after 1 h in seated position): absence of aldosterone suppression > 30 % confirmed PA; 3) Furosemide upright test (intravenous injection of 40 mg furosemide in upright position maintained for 2 h): plasma renin activity < 2 ng/ml/h (DRC <10 μIU/ml) confirmed PA [24].

Sequential adrenal venous sampling (AVS) was performed under cosyntropin continuous infusion by an experienced interventional radiologist. Successful catheterization was defined by a selectivity index ≥ 5. Unilateral disease was defined by a lateralization index ≥ 4. Bilateral PA was defined by bilateral aldosterone excess in AVS [25]. Unilateral disease was determined by biochemical PA cure after unilateral adrenalectomy. Undetermined lateralization included patients that did not undergo AVS and/or did not present biochemical PA cure after unilateral adrenalectomy [26].

Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes (ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts). Patients with blood pressure at goal while taking four or more antihypertensive medications are considered to have controlled resistant hypertension [27, 28].

Clinical and biochemical success after adrenalectomy for unilateral disease was evaluated according to the Primary Aldosteronism Surgical Outcome (PASO) criteria [29]. Biochemical cure was defined as correction of hypokalemia and normalization of the aldosterone-to-renin ratio after 6 months of surgery. In patients with a raised aldosterone-to-renin ratio post-surgery, aldosterone secretion should be suppressed in a confirmatory test. Complete clinical success was defined as a blood pressure < 140 × 90 mmHg without anti-hypertensive drugs after 6 months of follow-up. The cut-off of blood pressure ≥ 140 × 90 mmHg was used to define stage 1 hypertension in both European and Brazilian guidelines for the management of arterial hypertension [27, 28].

Aldosterone and DRC were measured using an automated chemiluminescence-based assay (LIAISON kit, DiaSorin, Salugia, Italy) in all patients. Aldosterone concentration was measured in serum and DRC in plasma with ethylenediaminetetraacetic acid. Functional sensitivity (lowest concentration at which the analyte can be reliably detected) was 3 ng/dl (83 pmol/l) for aldosterone and 4 µIU/ml for DRC. DRC normal range in seated position varies from 4.6 to 46 µU/ml. Aldosterone normal range in seated position varies from 2.5 to 39.2 ng/dl (69 to 1.087 pmol/l). The inter-assay coefficient of variation for the aldosterone assay ranged from 12 % at lower concentrations to 6 % at higher concentrations. The inter-assay coefficient of variation for the renin assay was 5.5 %. The intra-assay coefficient of variation was up to 5.3 % for aldosterone and up to 11.7 % for DRC.

Statistical analysis

Descriptive statistics were presented as absolute and relative frequencies for qualitative variables, and as means with standard deviations or medians with interquartile ranges for quantitative variables. The correlation between eGFR at 1 week post-surgery and age, aldosterone, and renin concentration was estimated using Pearson's correlation coefficient. The comparison of the mean eGFR at 1 week post-surgery among different qualitative and quantitative variables, including sex, aldosterone levels at diagnosis, hypertension severity, PA cure after adrenalectomy, hypokalemia, number of anti-hypertensive drugs, and renin, was performed using the t-test, assuming the normality assumption was satisfied. The normality assumption was assessed using the Shapiro–Francia test.

The main analysis involved fitting univariable and multivariable linear regression models considering eGFR at 1 week post-surgery as outcome adjusted by eGFR 3 months before surgery and the following covariates: sex, age, aldosterone at diagnosis, renin, hypertension severity, PA cure after adrenalectomy, and the number of anti-hypertensive drugs. The variable eGFR 3 months before surgery was used as an adjustable covariable, model known as the ANCOVA test [30]. Multiple imputation analyses were performed as described by Van Buuren [31]. For the linear regression model, missing data were imputed with 20 replicates using MICE (Multiple Imputation with Chained Equations) with predictive mean matching.

All hypotheses were two-sided, and statistical significance was considered if the p-value was less than 0.05. The statistical analyses were conducted using the R statistical software R (R Core Team, v4.1.2).

Results

A total of 94 patients with PA who underwent unilateral adrenalectomy were included (▶ **Table 1**). Forty patients (42.5 %) were men and 54 (57.5 %) were women, with a mean age of diagnosis of 48 years (± 11.8). Women were younger than men at the diagnosis of PA (45 ± 11.52 vs. 52.2 ± 11.12; p = 0.03). At diagnosis, the mean aldosterone and renin levels were 29.35 ng/dl [interquartile range (IQR) 23.13; 44.53] and 4.0 µIU/ml (IQR 4.00; 4:00), respectively. Hypokalemia at diagnosis was evidenced in 79 out of 94 (84 %) of the patients. Biochemical cure of PA after unilateral adrenalectomy was achieved in 84 out of 94 cases (89.36 %). AVS was performed more often in men than in women (67.5 % vs. 48.15 %; p = 0.034), but PA cure and complete clinical success were not different among the sexes (▶ **Table 1**).

▶ **Table 1** Demographic and clinical characteristics of the patients submitted to unilateral adrenalectomy for primary aldosteronism.

Variable	Total (n = 94)	Male (n = 40)	Female (n = 54)	p-Value*
Age (years) (mean ± SD)	48.06 ± 11.84	52.20 ± 11.12	45.00 ± 11.52	0.003#
Resistant hypertension n (%)	79 (84.04)	33 (82.50)	46 (85.19)	0.780
Hypokalemia n (%)	79 (84.04)	33 (82.50)	46 (85.19)	0.780
≥ 3 Antihypertensive drugs n (%)	75 (79.79)	32 (80.00)	43 (79.63)	0.999
Renin at diagnosis (µUI/ml) (median: IQR)	4.00 (4.00; 4.00)	4.00 (4.00; 4.00)	4.00 (4.00; 4.00)	0.158
Aldosterone at diagnosis (ng/dl) (median: IQR)	29.35 (23.13; 44.53)	27.35 (22.10; 42.10)	29.80 (23.33; 45.32)	0.513
Aldosterone-to-renin ratio (median: IQR)	7.34 (5.18; 10.67)	6.62 (5.04; 10.19)	7.45 (5.80; 11.33)	0.426
Adrenal venous sampling n (%)	53 (56.38)	27 (67.50)	26 (48.15)	0.034
PA cure after unilateral adrenalectomy n (%)	84 (89.36)	38 (95.00)	46 (85.119)	0.132
Complete clinical success n (%)	37 (39.36)	13 (32.50)	24 (44.44)	0.285

SD denotes standard deviation. IQR: Interquartile range. *Fisher exact test; #T-test, U Mann–Whitney test.

▶ **Table 2** Renal function and biochemical evolution before unilateral adrenalectomy and at 1 week, 1, 3 and 6 months after surgery.

	3 Months before surgery	First week after surgery	1 Month after surgery	3 Months after surgery	6 Months after surgery
Creatinine (mg/dl)	1.15 ± 0.05	1.37 ± 0.068	1.36 ± 0.094	1.32 ± 0.087	1.26 ± 0.081
eGFR (ml/min/1.73 m^2)	53.6 ± 1.71	46.4 ± 1.79	46.1 ± 2.66	47.1 ± 2.52	48.2 ± 2.49
Aldosterone (ng/dl)	47.6 ± 4.03	8.04 ± 0.95	7.83 ± 1.19	9.85 ± 2.04	12.9 ± 4.11
Renin (μUI/ml)	25.1 ± 7.07	9.05 ± 2.14	23 ± 6.67	18.1 ± 3.66	24.4 ± 5.72

Mean ± standard error. eGFR: Estimated glomerular filtration rate.

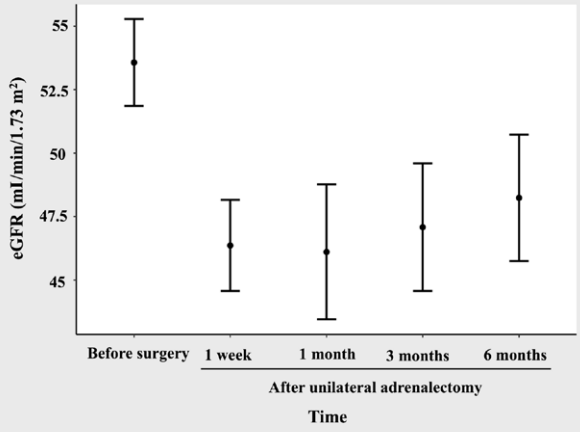
All patients were under spironolactone treatment 3 months before surgery. In our cohort, 37 patients (40 %) had normal blood pressure without any anti-hypertensive treatment (complete clinical success) after adrenalectomy. Fifty-seven patients (60 %) had an improvement in blood pressure control with less anti-hypertensive drugs. During the first month after surgery, these 57 patients were treated with amlodipine (5–10 mg/day) and/or hydralazine (50 mg bid or tid), because these two medications do not interfere in renal function. Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors were not used during the first month because of the risk of worsening hyperkalemia and inducing hypoaldosteronism.

During follow-up, the eGFR reduced in the first postoperative week compared to 3 months before surgery (▶ **Table 2**). During the first 6 months after adrenalectomy, eGFR remained stable at similar levels to the first week after surgery (▶ **Fig. 1**). Age (r = –0.33, p = 0.001), aldosterone levels 3 months before surgery (r = –0.26, p = 0.021) and eGFR 3 months before surgery (r = 0.75, p < 0.001) had a significant correlation with eGFR during first postoperative week (▶ **Fig. 2**). Renal function during the first week post-surgery did not correlate with preoperative renin levels.

Following adrenalectomy, renin levels decreased at the first week of surgery compared to preoperative renin levels, which were within the normal range under spironolactone treatment (▶ **Table 2**). Renin levels increased significantly after 3 months of adrenalectomy when compared to immediate postoperative levels. Aldosterone concentration decreased significantly during the first week of surgery and remained at lower limits of the normal range during the 6 months after surgery.

Next, we performed univariate and multivariate linear regression analysis to search for predictors of eGFR decrease after 1 week of surgery (▶ **Table 3**). Sex, age, renin level, hypokalemia, biochemical cure of PA after surgery and the number of antihypertensives were not predictors of eGFR during the first week post-surgery. High aldosterone levels at diagnosis were statistically correlated with a decline in renal function in the univariate model (p = 0.022). In the multivariate analysis, aldosterone levels at diagnosis had a tendency to be an independent predictor of renal function after surgery (p = 0.059).

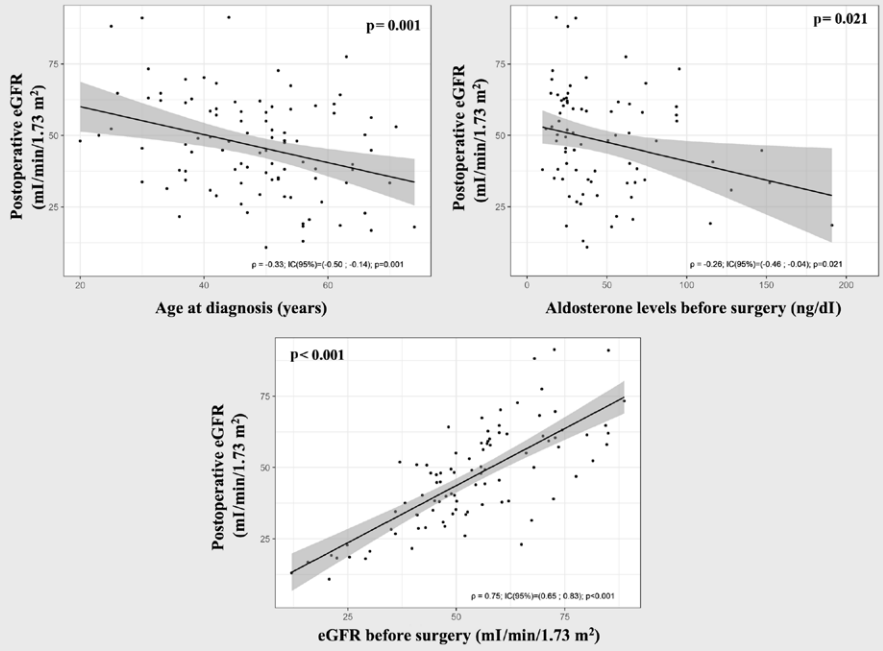
Postoperative biochemical hypoaldosteronism (aldosterone ≤ 4 ng/dl and suppressed renin) was diagnosed in 48 % of the cases during the first week after adrenalectomy (▶ **Table 4**). Sodium and potassium levels were not different between patients with or without hypoaldosteronism. Age at diagnosis and renin levels before surgery did not correlate with postoperative hypoaldosteronism. Interestingly, the patients with hypoaldosteronism had lower levels of aldosterone at diagnosis (31.5 ± 21.1 ng/dl vs. 50.4 ± 44.4 ng/dl, respectively; p = 0.008) and higher eGFR after 1 week of adrenalectomy (54 ± 15 ng/dl vs. 40 ± 17.5 ml/min/1.73 m^2, respectively; p < 0.001). Mild transient hyperkalemia (5.0–5.5 mEq/l) was evidenced in 10 patients (11.2 %) during the first week after adrenalectomy. Four out of 89 PA patients (4.5 %), older than 60 years and with resistant hypertension, presented biochemical hypoaldosteronism associated with persistent hyperkalemia and hypotension. These four cases were treated with fludrocortisone replacement therapy (0.1 mg) for a period varying from 6 months to 2 years.



▶ **Fig. 1** Estimated glomerular filtration rate (eGFR) before unilateral adrenalectomy and at 1 week, 1, 3 and 6 months after surgery.

Discussion

In this study, we evaluated the evolution of renal function and the hypoaldosteronism risk after unilateral adrenalectomy for PA. Few reports [14–16] previously evaluated renal function at single time point (at 1 month, 6 months or 12 months) after adrenalectomy for unilateral PA, but our study investigated the evolution of renal



▶ **Fig. 2** Correlations between age (r = –0.352, p = 0.001), aldosterone levels 3 months before surgery (r = –0.281, p = 0.015) and eGFR 3 months before surgery (r = 0.750, p < 0.0001) with eGFR during first postoperative week. eGFR: Estimated glomerular filtration rate.

▶ **Table 3** Linear regression for risk factors associated with first week postoperative estimated glomerular filtration rate (eGFR).

Variable		Univariable model				Multivariable model			
		Estimate	SE	Statistic	p	Estimate	SE	Statistic	p
Sex	Male	REF				REF			
	Female	–1.189	2.474	–0.480	0.632	–0.145	2.660	–0.054	0.957
Age	1-unit	0.047	0.118	0.400	0.690	0.016	0.125	0.129	0.898
Aldosterone at diagnosis (ng/dl)	1-unit	–0.076	0.035	–2.168	**0.033**	–0.070	0.037	–1.913	0.059
Aldosterone 3 months before surgery (ng/dl)	1-unit	–0.042	0.036	–1.163	0.249				
Renin at diagnosis (µUI/ml)	1-unit	–0.298	2.005	–0.149	0.882				
Renin 3 months before surgery (µUI/ml)	1-unit	0.010	0.020	0.521	0.604				
Resistant hypertension	Yes	REF				REF			
	No	4.737	3.268	1.450	0.151	3.445	3.344	1.030	0.306
Hypokalemia	Yes	REF							
	No	4.737	3.268	1.450	0.151				
PA cure after surgery	Yes	REF				REF			
	No	–1.929	4.294	–0.449	0.654	–3.363	4.438	–0.758	0.451
Number of antihypertensives	< 3	REF							
	≥ 3	2.548	3.157	0.807	0.422				

Missing data were imputed with 20 replicates using Multiple Imputation with Chained Equations (MICE) with predictive mean matching was performed.
SE: Standard error. REF: Reference category.

▶ **Table 4** Comparison of renal function and electrolytes in patients with and without postoperative biochemical hypoaldosteronism.

	Total (n = 89)	Aldosterone after 1 week of surgery		P*
		≤ 4 (n = 43)	≥ 5 (n = 46)	
Renin before adrenalectomy (μUI/ml)				
Mean ± SD	26 ± 66.26	21 ± 49.32	30 ± 78.34	0.629
Median (IQR)	4.0 (4, 11)	4 (4, 11)	4 (4, 10)	
Range	4.0, 433	4.0, 275	4.0, 433	
eGFR after 1 week of adrenalectomy (ml/min/1.73 m²)				< 0.001
Mean	46 ± 17.7	54 ± 14.95	40 ± 17.52	
Median (IQR)	47 (33.7, 59)	53 (42.45, 62)	37 (27.1, 48)	
Range	10.8, 91	18.2, 91	10.8, 91	
Sodium after 1 week of adrenalectomy (mEq/l)				0.519
Mean	141 ± 3.19	141 ± 3.69	141 ± 2.68	
Median (IQR)	141 (139, 142)	140 (139, 142)	142 (139, 142)	
Range	133, 160	136, 160	133, 145	
Potassium after 1 week of adrenalectomy (mEq/l)				0.216
Mean ± SD	4 ± 0.55	4 ± 0.55	4 ± 0.56	
Median (IQR)	4 (3.9, 5)	4 (3.75, 5)	4 (4, 5)	
Range	2.6, 6	3.5, 6	2.6, 6	

eGFR: Estimated glomerular filtration rate. IQR: Interquartile range. *Wilcoxon rank sum test.

function and risk of hypoaldosteronism during the first 6 months after adrenalectomy at consecutive time points (1 week, 1 month, 3 months and 6 months) after surgery.

The eGFR had a reduction during the first postoperative week compared to eGFR 3 months before surgery. High systolic preoperative blood pressure was associated with eGFR decline after 12 months of unilateral adrenalectomy in a single study [14]. In our study, aldosterone levels at diagnosis correlated with postoperative renal function at the first week after adrenalectomy. Indeed, preoperative aldosterone levels, age and potassium levels were previously defined as predictors of eGFR decline after unilateral adrenalectomy [15, 16].

Recently, Mermejo et al. [32] showed that postoperative suppressed renin levels became detectable between fifteen and thirty days after unilateral adrenalectomy in 13 patients with unilateral PA. Evaluating a large cohort of 94 PA patients, we demonstrated that renin levels increased during the first month of adrenalectomy, but renin concentrations became higher when compared to immediate postoperative levels only after 3 months of adrenalectomy. Similar to renin levels, aldosterone concentration decreased significantly during the first week of surgery, but remained at lower limits at the normal range during the 6 postoperative months.

Prolonged hypoaldosteronism accompanied by hyperkalemia was observed in 5–7 % of PA patients in two previous studies [19, 20]. Although the frequency of prolonged hyperkalemia was low, transient hyperkalemia occurred in 11–13 % of the cases [19, 20]. Older age (≥ 53 years), longer duration of hypertension (> 10 years), and impaired preoperative renal function (eGFR < 58.2 ml/min) were associated with prolonged postoperative hyperkalemia, and mineralocorticoid receptor antagonist use did not prevent postoperative hyperkalemia [20]. Similar to these previous findings, we demonstrated a rate of transient and prolonged hyperkalemia of 11.2 % and 4.5 % in PA patients after adrenalectomy, respectively. In our cohort, all cases with prolonged hyperkalemia and hypoaldosteronism were older than 60 years old and had a past history of resistant hypertension longer than 10 years. Interestingly, preoperative renin levels were not different between patients with and without postoperative hypoaldosteronism.

All previous studies evaluated the percentage decrease of eGFR after surgical treatment as the main outcome [14–16]. However, it should be emphasized that the use of percentage change from baseline as an outcome is a statistically inefficient method [30]. The analysis of covariance (ANCOVA) with baseline score as a covariate has the highest statistical power. Therefore, one strength of this study included the ANCOVA analysis of the postoperative eGFR using the preoperative eGFR as a covariate instead of using percentage change as the main outcome. Another strong point was the large number of PA patients. One limitation of our study is the

retrospective design. However, the database was established by collecting information on consecutive patients with PA who underwent unilateral adrenalectomy.

In conclusion, our findings demonstrated a decrease in renal function after unilateral adrenalectomy for PA using analysis of covariance instead of percentage eGFR decrease. Additionally, aldosterone levels at diagnosis correlated with postoperative renal function at the first week after adrenalectomy. Although biochemical hypoaldosteronism and transient hyperkalemia were frequent, clinical hypoaldosteronism occurred in 5 % of our cohort. Therefore, this evidence supports the clinical relevance of a close monitoring of renal function after adrenalectomy for unilateral PA to improve patient outcome and avoid complications related to renal insufficiency, hyperkalemia and/or hypoaldosteronism.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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