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Is acute kidney injury after laparoscopic adrenalectomy related to the progression of chronic kidney disease in patients with primary aldosteronism?

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Purpose: This study was conducted to investigate the predictors of kidney outcome after laparoscopic adrenalectomy in patients with primary aldosteronism (PA).

Materials and Methods: We retrospectively reviewed the medical records of 74 patients who underwent unilateral adrenalectomy for the treatment of PA from January 2011 to December 2019. Patient characteristics and serial data on postoperative changes in kidney function were analyzed and compared between the two groups according to the presence of acute kidney injury (AKI). Postoperative AKI was defined as a decline in the estimated glomerular filtration rate (eGFR) of >50% or an increase in the serum creatinine level of ≥0.3 mg/dL at 1 week after surgery compared with perioperative levels. Chronic kidney disease (CKD) was defined as an eGFR < 60 mL/min/1.73 m^2 present for 3 months.

Results: Nineteen patients (25.7%) had postoperative AKI. Patients who experienced postoperative AKI had higher aldosterone-to-renin ratios, higher rates of dyslipidemia, and more left ventricular hypertrophy than did patients without postoperative AKI (p=0.015, 0.036, and 0.033, respectively). Twenty-eight patients (37.8%) had CKD at 6 months after surgery, including 15 patients who had newly progressed to CKD postoperatively. In the multivariate regression analysis of patients without preoperative CKD, the only independent predictor of the progression to CKD was preoperative albuminuria (p=0.007).

Conclusions: In this study, one-quarter of the patients had postoperative AKI after unilateral adrenalectomy for the treatment of PA. However, postoperative AKI was not directly correlated with CKD progression. Preoperative albuminuria was an independent predictor of the progression of CKD.

Keywords: Acute kidney injury; Adrenalectomy; Chronic kidney disease; Hyperaldosteronism; Treatment outcome

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INTRODUCTION

Primary aldosteronism (PA), a common form of secondary hypertension, is caused by autonomous aldosterone production with suppressed plasma renin activity and is characterized by uncontrolled high blood pressure (BP) and hypokalemia [1,2]. The reported prevalence of PA among hypertensive patients has increased up to 10% because of improvements in clinicians' understanding of this condition caused by excessive aldosterone secretion, as well as the introduction of the aldosterone-renin ratio as a screening test marker, which has led to an increase in the rate of detection [3,4]. PA was previously considered a benign disease with relatively few complications; however, recent studies have revealed cardiovascular and kidney complications caused by long-term exposure to high aldosterone levels [5-8]. The increased risk for cardiovascular events, including stroke, coronary artery disease, atrial fibrillation, and heart failure, was demonstrated in patients with PA in a reported meta-analysis [9]. Relatively less clinical evidence on kidney complications in patients with PA has been reported; however, recent studies have begun to focus on kidney damage in PA [10]. Glomerular hyperfiltration is one of the pathways to preventing progressive kidney damage in various kidney injuries, along with aldosterone-induced sequential glomerular hyperfiltration [11]. However, glomerular hyperfiltration is decreased after treatment of PA, as shown by the rapid postoperative decline of the estimated glomerular filtration rate (eGFR) [12,13].

This study investigated postoperative clinical outcomes, including kidney function, in patients with PA, and examined the association between eGFR decrease and long-term kidney outcomes.

MATERIALS AND METHODS

1. Study population

We retrospectively reviewed the medical records of patients who underwent unilateral adrenalectomy for PA at Chonnam National University Hwasun Hospital (Hwasun, Korea) between January 2011 and December 2019. Adult patients (≥18 years old) followed up for more than 6 months postoperatively were included in this study. We excluded patients with insufficient data, known end-stage kidney disease, and cancer. A total of 74 patients were included in the final analysis. This study was conducted in accordance with the Declaration of Helsinki and was reviewed by the Institutional Review Board of the Chonnam National University Hwasun Hospital (approval number: CNUHH-2019-200).

The diagnosis of PA was based on the guidelines of The Endocrine Society and the Japanese Society of Hypertension [2,14]. Patients with elevated aldosterone-to-renin ratios (ARRs) of >200 pg/mL/(ng/mL·h) were diagnosed with PA by at least one confirmatory test, including the saline load test or captopril challenge test. Antihypertensive medications were replaced with α-blockers or calcium channel blockers before diagnostic tests. For lateralization of unilateral adrenal adenomas, computed tomography or magnetic resonance imaging and sequential adrenal venous sampling were performed. Baseline clinical data including age, sex, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of hypertension, number of diseases, and the presence of left ventricular hypertrophy (LVH) were collected and analyzed. Hypertension was defined as SBP ≥140 mmHg, or DBP ≥90 mmHg, or an initiated administration of antihypertensive medication. Resistant hypertension was defined as remaining high BP above goal despite the use of three or more antihypertensive agents of different classes. LVH was defined as an increment of the left ventricular (LV) mass derived from two-dimensional echocardiography-based LV measurements. As per the American Society of Echocardiography, an estimated LV mass of >102 g/m^2 for male and >88 g/m^2 for female was used for diagnosing LVH [8,9]. Antihypertensive medication use was expressed in terms of the defined daily dose (DDD), and the average daily maintenance doses were calculated. The World Health Organization Anatomical Therapeutic Chemical/DDD Index 2017 (https://www.whocc.no/atc_ddd_index/) was used to calculate the DDD. Hypokalemia was defined by a serum potassium level of <3.5 mEq/L. Symptoms of PA included muscle cramps, weakness, fatigue, and excessive thirst, which were generally related to hypokalemia.

We divided the patients with PA into two groups according to the presence of acute kidney injury (AKI). Postoperative AKI was defined as an eGFR decline of >50% from baseline after surgery or an increase in the serum creatinine level of ≥0.3 mg/dL in 48 hours to 7 days, according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [15]. We assessed the incidence of chronic kidney disease (CKD) 6 months after surgery in both groups. We identified independent risk factors for the progression of CKD after excluding patients who had preoperative CKD. In the present study, CKD was defined as eGFR <60 mL/min/1.73 m^2 regardless of the presence or absence of albuminuria before surgery. CKD progression was defined as newly developed CKD after adrenalectomy in patients without CKD preoperatively.

2. Operative technique

All patients underwent laparoscopic adrenalectomy with a lateral or posterior approach. The surgical procedure for lateral and posterior retroperitoneal laparoscopic adrenalectomy was described previously [16,17]. A drainage tube was not routinely placed after the procedure, except in complicated cases or in those involving open conversion, wherein it was removed the day before discharge.

3. Kidney function test and albuminuria

We assessed kidney function based on the eGFR, which was calculated by using the CKD–Epidemiology Collaboration equation (CKD-EPI) formula [18]. Serial kidney function test results were collected at baseline and at 2 days, 1 week, and 3 and 6 months after surgery and analyzed. Albuminuria was defined by an albumin-to-creatinine ratio, and ≥30 mg/g Cr was used as the cutoff in a spot urine test [11].

4. Clinical and biochemical outcomes

The clinical outcome of adrenalectomy for PA was determined according to the consensus criteria of the Primary Aldosteronism Surgical Outcome study [19]. Complete clinical success was defined as normal BP levels, with no need for antihypertensive medications after surgery. Partial clinical success was defined as either a requirement to maintain the preoperative BP levels with a lower DDD or decreased BP levels with the same DDD after surgery. Clinical failure was indicated by increased BP levels, increased DDD, a difference in SBP of ≥20 mmHg or in DBP of ≥10 mmHg, BP levels without a reduction in DDD, or unchanged DDD without a decrease in BP levels. Complete biochemical success was defined as achieving both correction of hypokalemia and normalization of the ARR. Partial biochemical success was defined as the correction of hypokalemia and a high ARR with one or both of the following: 1) a >50% decrease in baseline plasma aldosterone level; and 2) an abnormal but improved postsurgical confirmatory test result. An absence of biochemical success was defined as persistent hypokalemia or a persistent elevated ARR with failure to suppress aldosterone secretion via a postsurgical confirmatory test.

5. Statistical analysis

Continuous variables are expressed as mean±standard deviation and categorical variables as number (%). The chi-squared test was used to compare categorical variables. The Student's t-test or the Mann–Whitney U-test was used to compare the significance of differences between the acute kidney impairment group and the nonimpairment group, as appropriate. Repeated-measures analysis of variance was used to compare the serial eGFR, serum potassium level, and SBP and DBP at each time point in both groups. Univariate and multivariate logistic regression analyses were conducted to identify risk factors for progression to CKD. All statistical analyses were performed using SPSS software (version 25.0 for Windows; IBM Corp., Armonk, NY, USA). Values of $p<0.05$ were considered statistically significant.

RESULTS

1. Baseline characteristics and postoperative clinical outcomes of the study population

The baseline characteristics of the 74 patients who underwent unilateral adrenalectomy for PA are presented in Table 1. The mean patient age was 52.1±11.4 years, and 54.1% of the study population were male. The median follow-up period was 29.5 months. A posterior retroperitoneal approach was used in 69 patients (93.2%). Thirty-two tumors (43.2%) affected the right adrenal gland, and the mean tumor size was 2.7±3.8 cm. Pathologic results showed adrenocortical adenoma in 73 patients (98.6%) and adrenal cortical hyperplasia in only 1 patient (1.4%). The most common reason for performing a PA screening test was uncontrolled hypertension with concomitant hypokalemia. In 5 patients (6.8%), hypertension was newly detected at the time of PA diagnosis. The mean number of antihypertensive medications taken by the patients before surgery was 2.4±1.1, which decreased to 1.0±0.9 postoperatively. The medications are listed in Supplementary Table 1. Complete and partial clinical success after surgery for PA was observed in 23 (31.1%) and 40 (54.1%) patients, respectively.

2. AKI after unilateral adrenalectomy for primary aldosteronism

The patients with PA were divided into two groups according to the presence of AKI after surgery (Table 2). The incidence of postoperative AKI after adrenalectomy was 19/74 (25.7%). Patients with postoperative AKI were more likely to have dyslipidemia (57.9% vs. 30.9%; p=0.036) and LVH (47.4% vs. 21.8%; p=0.033) than were those without AKI. The median ARR was higher in the AKI group than in the non-AKI group (31,888 vs. 8,463; p=0.015). Preoperative serum creatinine, eGFR, and potassium levels did not differ significantly between the AKI and non-AKI groups. Postoperative serum creatinine (1.5±0.6 vs. 1.1±0.4; p=0.005) and potassium (5.2±0.7 vs. 4.7±0.6; p=0.003) levels were higher in the AKI group than in the non-AKI group. There was no significant difference in the progression to CKD at 6 months after surgery according to the presence of postoperative AKI (52.6%

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Table 1. Baseline characteristics and postoperative outcomes of patients with PA

Variable	Value (n=74)
Age (y)	52.1±11.4
Sex, male	40 (54.1)
BMI (kg/m^2)	25.4±3.7
Reason for screening test for PA	
Adrenal incidentaloma	5 (6.8)
Resistant HTN	18 (24.3)
Hypokalemia	10 (13.5)
Symptomatic	6 (8.1)
Adrenal incidentaloma+hypokalemia	1 (1.4)
Uncontrolled HTN+hypokalemia	27 (36.5)
Uncontrolled HTN+symptomatic	3 (4.1)
Hypokalemia+symptomatic	4 (5.4)
Systolic BP (mmHg)	139.9±17.9
Diastolic BP (mmHg)	84.0±13.6
Comorbid diseases	
HTN	
Newly detected HTN	5 (6.8)
Known HTN	69 (93.2)
Duration of HTN (y)	8.8±7.5
DM	16 (21.6)
Dyslipidemia	29 (39.2)
CVD	7 (9.5)
LVH	21 (28.4)
CKD	14 (18.9)
PAC (pg/mL)	134 [195–523]
PRA (ng/mL·h)	0.08 [0.02–0.31]
ARR (pg/mL/ng/mL·h)	3,433 [1,074–11,895]
Serum potassium (mmol/L)	3.3±2.8
Serum creatinine (mg/dL)	1.02±0.43
eGFR (mL/min/1.73 m^2)	81.1±27.6
Albuminuria	15 (20.3)
Operative procedure	
PRLA	69 (93.2)
LRLA	5 (6.8)
Tumor size (cm)	2.7±3.8
Laterality	
Right	32 (43.2)
Left	42 (56.8)
Clinical outcomes	
Complete	23 (31.1)
Partial	40 (54.1)
Absent	11 (14.9)
Biochemical outcome	
Complete	27 (36.5)
Partial	33 (44.6)
Absent	14 (18.9)
Follow-up (mo)	29.5 [14.5–60.3]

Continuous variables are expressed as mean±standard deviation or median [interquartile range]. Categorical variables are expressed as number (%).
PA, primary aldosteronism; BMI, body mass index; HTN, hypertension; BP, blood pressure; DM, diabetes mellitus; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio; eGFR, estimated glomerular filtration rate; PRLA, posterior retroperitoneal laparoscopic adrenalectomy; LRLA, lateral retroperitoneal laparoscopic adrenalectomy.

vs. 32.7%; p=0.123). In the serial analysis during the 6 months after surgery, there was no significant difference in the mean adjusted eGFR, serum potassium level, SBP, or DBP between the AKI and non-AKI groups (Fig. 1). In the multivariate analysis, preoperative ARR and LVH were associated with postoperative AKI (Supplementary Table 2).

3. Progression to chronic kidney disease after unilateral adrenalectomy for primary aldosteronism

The change in the proportion of patients with CKD after adrenalectomy is shown in Fig. 2. The proportion of CKD increased from 18.9% before surgery to 37.8% at 6 months after surgery. Fifteen patients (20.3%) without preoperative CKD showed progression to CKD at 6 months after surgery. Logistic regression analyses were used to identify the risk factors for CKD after adrenalectomy upon excluding the 14 patients who already had preoperative CKD. Univariate regression analysis showed that old age, LVH, preoperative albuminuria, and biochemical outcome were associated with progression to CKD at 6 months after adrenalectomy. In the multivariate analysis, preoperative albuminuria remained statically significant as a risk factor (Table 3).

DISCUSSION

In this study, one-quarter of the patients who underwent unilateral retroperitoneal laparoscopic adrenalectomy for PA had postoperative AKI. However, postoperative AKI was not directly correlated with CKD progression. Preoperative albuminuria was an independent predictor of the progression to CKD after surgery for PA in patients without preoperative CKD.

Lee et al. [20] reported that the incidence of AKI after unilateral adrenalectomy for PA was 27.1%, which was more than twice that in patients with pheochromocytoma. In another study, a more significant postoperative decline in

Table 2. Clinical characteristics of patients with PA who underwent unilateral adrenalectomy according to the presence of postoperative acute renal impairment

Variable	Acute kidney injury (n=19)	No acute kidney injury (n=55)	p-value
Age (y)	52.2±9.6	52.1±12.0	0.978
Sex, male	8 (42.1)	32 (58.2)	0.225
BMI (kg/m^2)	25.2±2.8	25.6±4.0	0.692
Systolic BP (mmHg)	144.7±16.7	138.2±18.1	0.174
Diastolic BP (mmHg)	84.8±14.8	83.4±12.7	0.420
Duration of HTN (y)	9.2±8.2	8.7±7.4	0.810
Number of antihypertensive agents	2.3±1.0	2.4±1.1	0.606
DM	6 (31.6)	10 (18.2)	0.335
Dyslipidemia	11 (57.9)	17 (30.9)	0.036
CVD	0 (0.0)	5 (9.1)	0.319
LVH	9 (47.4)	12 (21.8)	0.033
Albuminuria	6 (31.6)	9 (16.4)	0.190
ARR (pg/mL/ng/mL·h)	31,888 [3,860–50,000]	8,463 [754–44,000]	0.015
Preoperative			
Serum potassium (mmol/L)	3.0±0.4	3.4±3.2	0.574
Serum creatinine (mg/dL)	1.0±0.4	1.0±0.4	0.683
eGFR (mL/min/1.73 m^2)	85.4±30.8	79.7±26.5	0.439
Postoperative (2 weeks)			
Serum potassium (mmol/L)	5.2±0.7	4.7±0.6	0.003
Serum creatinine (mg/dL)	1.5±0.6	1.1±0.4	0.005
eGFR (mL/min/1.73 m^2)	56.5±20.7	70.6±25.4	0.032
CKD 6 months after surgery	10 (52.6)	18 (32.7)	0.123
Clinical outcome			0.015
Complete	3 (15.8)	20 (36.4)	
Partial	10 (52.6)	30 (54.5)	
Absent	6 (31.6)	5 (9.1)	

Continuous variables are expressed as mean±standard deviation or median [interquartile range]. Categorized variables are expressed as number (%).

PA, primary aldosteronism; BMI, body mass index; BP, blood pressure; HTN, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; ARR, aldosterone-to-renin ratio; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

the eGFR was observed in patients with PA than in those with other adrenal diseases after unilateral adrenalectomy. Therefore, this finding shows that excessive aldosterone is more important than unilateral adrenalectomy for kidney outcomes [21]. Previous studies have shown that glomerular hyperfiltration caused by excessive aldosterone levels prevents or conceals kidney damage [1,22]. By controlling the excessive production of aldosterone in PA using adrenalectomy or a mineralocorticoid receptor (MR) antagonist, kidney impairment may worsen or emerge [21,23]. A recent study showed that the initial eGFR decline after adrenalectomy was associated with a long-term decrease in the eGFR in patients with PA taking MR antagonists, whereas this was not observed in patients with PA who underwent adrenalectomy [24]. Patients with PA taking an MR antagonist might still exhibit overproduction of aldosterone. A further decrease in the initial eGFR through more effective aldosterone blockage could be related to the delay in a long-term decline in the eGFR. However, the relationship between postoperative AKI and CKD is still unclear, especially in patients who undergo adrenalectomy for PA. Thus, we investigated whether postoperative AKI progresses to CKD.

An inverse relationship between the plasma aldosterone concentration and kidney function has been demonstrated in the general population. However, excessive aldosterone in patients with PA might ameliorate kidney impairment by glomerular hyperfiltration [25]. Hidden kidney damage can be revealed as a decline in the eGFR when the serum aldosterone level is normalized by PA-specific treatment. Many previous studies have focused on the acute decrease in the eGFR after adrenalectomy. They regarded preoperative albuminuria, serum potassium level, and ARR as possible predictors of postoperative AKI [12,26]. In our study, dyslipidemia, LVH, and high preoperative ARR were more

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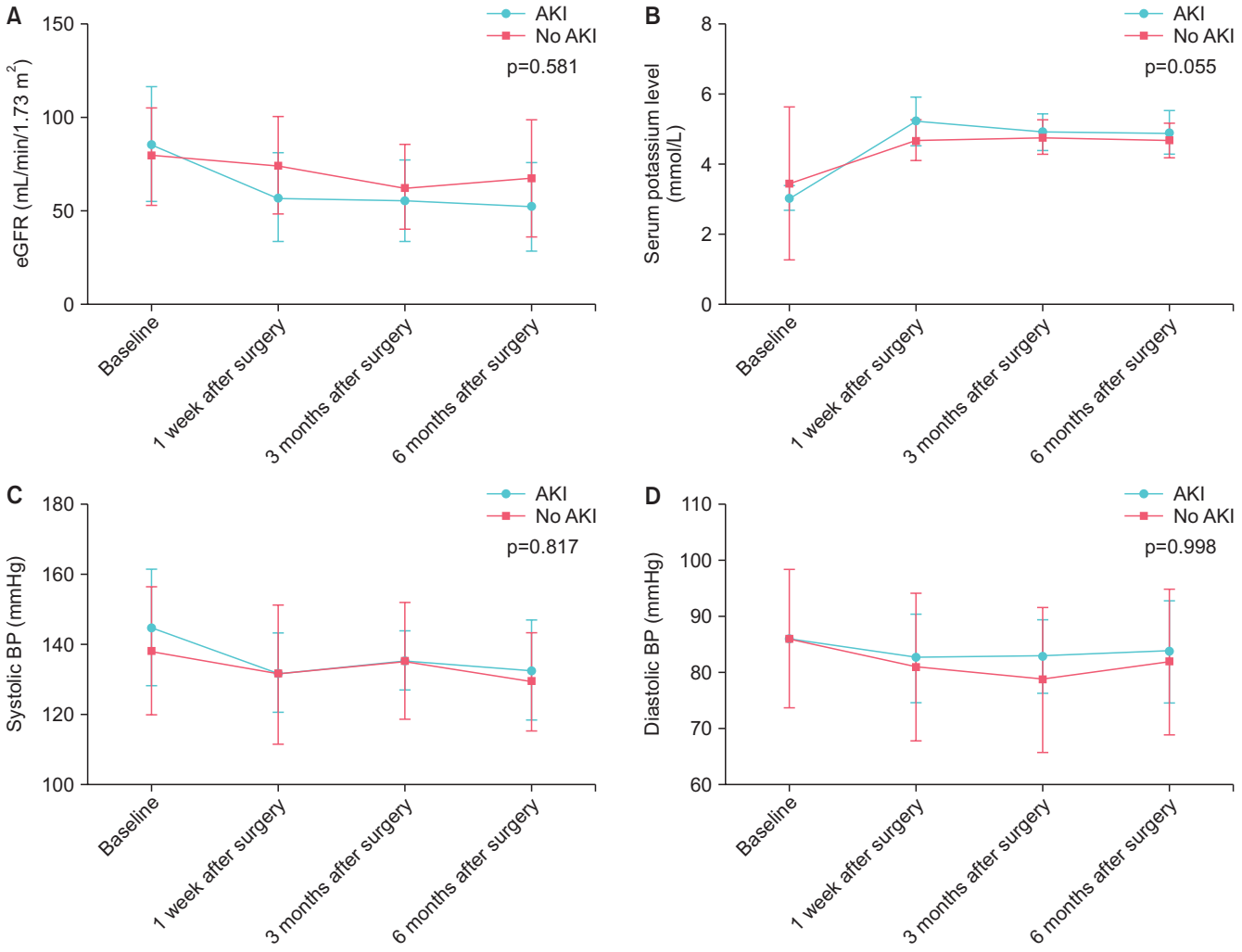

Fig. 1. Mean adjusted (A) eGFR, (B) serum potassium level, (C) systolic BP, and (D) diastolic BP over 6 months after adrenalectomy for PA according to the presence of postoperative AKI. eGFR, estimated glomerular filtration rate; BP, blood pressure; PA, primary aldosteronism; AKI, acute kidney injury.

prevalent in the postoperative AKI group than in the non-AKI group. A higher ARR and LVH reflect overproduction of aldosterone and target organ damage as a cardiovascular complication of long-standing PA, respectively. Excessive aldosterone could be related to increased glomerular infiltration; hence, a sharp reduction in the aldosterone level after adrenalectomy would cause a more prominent decline in the eGFR [24].

Chronic overproduction of aldosterone can lead to renal tubule-interstitial fibrosis and scarring, which can, in turn, induce CKD [27]. The development of CKD is associated with higher rates of cardiovascular events and mortality; thus, early detection and proper management are essential [28]. Similar to previous studies, our results showed that old age, LVH, and albuminuria were associated with progression to CKD, but long-standing hypertension and higher preoperative eGFR were not. In multiple regression analysis, only albuminuria was an independent risk factor for the development of CKD in patients without preoperative CKD. Rossi et al. [29] reported higher urinary albumin excretion in patients with PA than in BP-matched patients with essential hypertension. Long-standing excessive aldosterone-induced structural kidney damage, directly and indirectly, may be associated with glomerular fibrosis and sclerosis, although the underlying mechanism remains unknown [30]. Kobayashi et al. [24] reported no relationship between the initial and the long-term declines in the eGFR in patients with PA treated by adrenalectomy, similar to our study's findings. We determined that postoperative AKI after adrenalectomy for PA was not associated with the development of CKD. A possible explanation for this finding is that the postoperative decline in the eGFR, associated with the elimination of aldosterone-induced glomerular hyperfiltration, is temporary, and the progression of kidney impairment might be attenuated by

well-controlled aldosterone levels, adrenalectomy, and proper postoperative management. However, preexisting structural kidney damage, reflected in albuminuria, is difficult to repair. The median quantitative urinary albumin concentration decreased to 14.1 mg/g (range, 0.0–30.0 mg/g) 6 months after surgery compared with 94.5 mg/g (range, 30.0–122.4 mg/g) preoperatively. However, 11 of the 15 patients (73.3%) who had preoperative albuminuria still had albuminuria 6 months after surgery (data not shown).

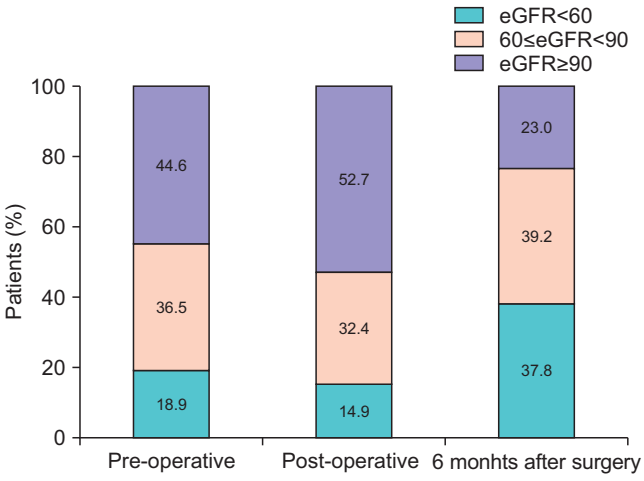

Fig. 2. Changes in the proportions of CKD in patients with PA. CKD, chronic kidney disease; PA, primary aldosteronism; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2).

This study had several limitations inherent to its retrospective design. First, the total sample size was relatively small, particularly for the analysis of other risk factors for the progression to CKD. Second, several parameters, such as mineral bone disorder-related markers, fasting lipid profile, and HbA1c, were unavailable. Furthermore, the follow-up period was relatively short, preventing the investigation of long-term kidney outcomes. Nevertheless, our study results showed that postoperative AKI is not directly associated with postoperative CKD, and albuminuria and low eGFR were independent predictors of CKD in patients with PA treated with laparoscopic surgery. Further large-scale studies with a prospective design are required to determine ways to prevent the development of CKD after adrenalectomy in patients with PA.

CONCLUSIONS

Patients with PA had significant postoperative AKI and showed progression to CKD after laparoscopic adrenalectomy. Preoperative albuminuria was an independent predictor of postoperative CKD; however, postoperative AKI was not directly associated with the progression to CKD. Attentive postoperative management and serial investigation of kidney function are necessary for patients with PA, especially those with preoperative albuminuria.

Table 3. Risk factors for CKD 6 months after adrenalectomy in patients with primary aldosteronism without CKD preoperatively

Variable	Univariate analysis			Multivariate analysis		
	β	SE	p-value	β	SE	p-value
Age (y)	0.093	0.042	0.027	0.045	0.042	0.284
Sex, male	-0.447	0.599	0.455			
BMI (kg/m^2)	-0.067	0.082	0.419			
Duration of hypertension (y)	0.074	0.050	0.135			
Numbers of antihypertensive medications	0.139	0.284	0.625			
Systolic BP	-0.002	0.016	0.922			
Diastolic BP	-0.108	0.093	0.243			
Lowest serum potassium level	-0.127	0.273	0.642			
Preoperative eGFR	-0.025	0.017	0.133			
Preoperative ARR	0.000	0.000	0.193			
DM	0.808	0.731	0.269			
CVD	0.767	0.966	0.427			
Dyslipidemia	0.185	0.658	0.778			
LVH	1.253	0.638	0.049	1.519	0.796	0.056
Albuminuria	2.375	0.907	0.009	3.080	1.133	0.007
Postoperative AKI at 2 weeks	0.981	0.645	0.129			
Clinical outcome	0.606	0.658	0.357			
Biochemical outcome	-1.288	0.630	0.041	-1.284	0.794	0.106

CKD, chronic kidney disease; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; ARR, aldosterone-to-renin ratio; DM, diabetes mellitus; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; AKI, acute kidney injury.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Ho Seok Chung. Data acquisition: Jee Hee Yoon and Ho Seok Chung. Statistical analysis: Jee Hee Yoon and Myung Soo Kim. Data analysis and interpretation: Jee Hee Yoon and Ho Seok Chung. Drafting of the manuscript: Jee Hee Yoon. Critical revision of the manuscript: Jee Hee Yoon and Ho Seok Chung. Obtaining funding: Ho Seok Chung. Supervision: A Ram Hong, Hee Kyung Kim, Eu Chang Hwang, Seung Il Jung, and Kwangsung Park. Approval of the final manuscript: Jee Hee Yoon, Ho Seok Chung, Ho-Cheol Kang, and Dongdeuk Kwon.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20200582.

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