Age-Dependent Progression of Renal Dysfunction After Adrenalectomy for Aldosterone-Producing Adenomas in Japan

Masayuki Yoshioka,[1]* Yasuyo Nakajima,[1]* Tomoko Miyamoto,[1]
Takamichi Igarashi,[2] Koji Sakamaki,[3] Masako Akuzawa,[3] Emi Ishida,[1]
Kazuhiko Horiguchi,[1] Eijiro Yamada,[1] Tsugumichi Saito,[1] Atsushi Ozawa,[1]
Younosuke Shimomura,[3] Isao Kobayashi,[3] Yoshitaka Andou,[3] Ken Shirabe,[2]
and Masanobu Yamada[1]

[1]Department of Internal Medicine, Division of Endocrinology and Metabolism, Gunma University
Graduate School of Medicine, Maebashi 371-8511, Japan; [2]Department of Hepatobiliary and Pancreatic
Surgery, Gunma University Graduate School of Medicine, Maebashi 371-8511, Japan; and [3]Hidaka
Hospital, Takasaki 370-0002, Japan

ORCiD numbers: 0000-0003-2630-2579 (Y. Nakajima).

*M.Y. and Y.N. equally contributed.

Context: In patients with aldosterone-producing adenomas (APAs), adrenalectomy causes a rapid decrease in blood pressure and increase in blood potassium levels; however, the effects of these intensive metabolic changes on kidney function with age have not yet been examined in Japan.

Objective: To investigate factors related to the progression of kidney dysfunction after adrenalectomy in different age groups.

Participants: Fifty Japanese patients with APAs and 27,572 health checkup patients as controls were examined.

Main Outcome Measures: We investigated changes in estimated glomerular filtration rate (eGFR) after adrenalectomy and characterized patients who progressed to chronic kidney disease (CKD).

Results: The postoperative cutoff age of CKD is 50 years and age is a unique factor for the progression of CKD after adrenalectomy. Among preoperative patients, CKD was 6% for those <50 years old and 40% for those ≥50 years old, indicating a higher prevalence of CKD with APAs than in control subjects. Median eGFR <50 mL/min/1.73 m^2 did not significantly change after adrenalectomy but decreased from 67 to 42 mL/min/1.73 m^2 in those with APAs ≥50 years old. Patients with APAs ≥50 years old who progressed to CKD showed higher preoperative aldosterone/renin ratios, lower potassium and chloride levels, lower body mass index, and a higher incidence of a history of cardiovascular events and KCNJ5 mutation rates.

Conclusion: Age is the most important predictor of the progression of kidney dysfunction after adrenalectomy in Japanese patients with APAs, particularly those with a history of cardiovascular events and positivity for KCNJ5 mutations.

Primary aldosteronism (PA) is more strongly associated with cardiovascular complications and organ damage, including kidney dysfunction, than essential hypertension [1–5]. Furthermore, ~6% to 10% of patients with a diagnosis of essential hypertension also have PA [6–10]. However, several differences have been identified in the clinical features of Japanese and Western PA. In Western countries, approximately one-third of patients with PA have aldosterone-producing adenomas (APAs), a small fraction have glucocorticoid-remediable aldosteronism (GRA), and the remainder of APAs are idiopathic [6–10]. In contrast, most Japanese patients with PA (~80%) have APAs [11–13]. Therefore, many cases of PA in Japan are treated by adrenalectomy.

We recently reported a very high frequency (~80%) of somatic mutations in the *KCNJ5* gene in Japanese APAs [14–16]. In contrast, the prevalence of KCNJ5 mutations in APAs was found to be ~40% in Western countries [17]. Patients with KCNJ5 mutations have been reported to be younger, have severe aldosteronism, and have higher blood pressure than those without, suggesting that PA with APAs is more severe in Japan than in Western countries.

PA is more strongly associated with renal dysfunction than essential hypertension. Sechi *et al.* [18] reported that albuminuria was observed at a higher rate in patients with PA than in those with essential hypertension. Reincke *et al.* [19] also demonstrated in a large cohort study that the percentage of patients with a serum creatinine concentration above the normal range was higher in patients with PA than in hypertensive controls. PA is associated with relative renal hyperfiltration caused by excessive aldosterone, a masked kidney dysfunction [19, 20]. Accordingly, adrenalectomy and therapy with spironolactone for PA were associated with a decline in glomerular filtration rate (GFR) in Western countries and Japan; that is, GFR was significantly lower in patients with PA 6 months after treatment than in those with essential hypertension, whereas the rapid decrease in GFR and the deterioration rate of GFR with PA were similar to those in essential hypertension [18, 20–22].

Adrenalectomy causes a rapid decrease in blood pressure and increase in blood potassium levels. However, the effects of these intensive metabolic changes, particularly on kidney damage in patients with APAs, have not yet been examined in detail [20]. PA and kidney dysfunction have not yet been investigated in Japan, where salt intake is high and salt-sensitive hypertension is more common in Western countries [23]. Furthermore, as described above, the epidemiological and genetic backgrounds of APAs in Japan differ from those of Western countries.

In the current study, we examined changes in the estimated glomerular filtration rate (eGFR) before and after adrenalectomy in Japanese patients with APAs and characterized patients who progressed to chronic kidney disease (CKD).

1. Subjects and Methods

A. Subjects

We reviewed the medical records of 50 patients with APAs who were operated on at Gunma University Hospital between 2007 and 2017. The diagnosis of PA was performed as reported previously [6, 15, 24]. As a control, we examined 27,572 health checkup subjects who visited Takasaki Hidaka Hospital between 2003 and 2013 and used a number of parameters, including age, sex, and eGFR. Exclusion criteria were as follows: any history of diseases such as liver cirrhosis and renal failure, the use of medications including insulin and steroid hormones, and missing data.

The mean age of patients with PA was 50 ± 8 years old (mean ± SD) (22 men and 28 women). All patients had a high plasma aldosterone/renin concentration ratio (ARR) and a unilateral adrenal cortical mass evident on CT, and the pathology of all removed tumors confirmed the diagnosis of adrenocortical adenoma. The mean tumor size (maximum diameter) on CT was 17 ± 8 mm. The average follow-up duration for eGFR changes after

adrenalectomy was 14 months (minimum 2 months, 25th percentile 12 months, 75th percentile 17 months, maximum 29 months, median 14 months).

We measured plasma aldosterone levels with the RIA SPAC-S aldosterone kit (TFB Inc., Tokyo, Japan) and plasma renin activity with the RIA Renin IRMA kit "Daiichi" (TFB Inc., Tokyo, Japan).

Serum creatinine values were measured by an enzymatic method, and eGFR was calculated from serum creatinine with equations developed by the Japanese Society of Nephrology [25]. CKD was defined as an eGFR <60 mL/min/1.73 m^2, and CKD was classified based on GFR categories.

A history of cardiovascular events included cerebral infarction, cerebral hemorrhage, atrial fibrillation, myocardial infarction, aortic aneurysm, and aortic valve stenosis.

A-1. Classification of renal dysfunction according to eGFR

The categories of CKD based on eGFR were classified as follows: G1, kidney damage with normal or elevated GFR (>90 mL/min/1.73 m^2); G2, mild reduction in GFR (60 to 89 mL/min/1.73 m^2); G3a, moderate reduction in GFR (45 to 59 mL/min/1.73 m^2); G3b, moderate reduction in GFR (30 to 44 mL/min/1.73 m^2); G4, severe reduction in GFR (15 to 29 mL/min/1.73 m^2); and G5, kidney failure (GFR <15 mL/min/1.73 m^2 or dialysis) [25]. eGFR was calculated with the following formula: $194 \times$ serum creatinine$^{-1.094} \times$ age$^{-0.287} \times$ (0.739 if female). The deterioration of CKD was defined as the progression of the CKD category after adrenalectomy.

A-2. Ethical approval and informed consent

All methods were performed in accordance with the relevant guidelines and regulations including Ethical Guidelines for Medical and Health Research Involving Human Subjects and for human genome and gene analysis research presented by the Ministry of Health, Labour and Welfare in Japan. This study was approved by the ethics committee on human research of Gunma University (approval number 121: Gunma University Human Genome Ethics Committee), and each subject provided written informed consent.

Studies on health checkups as a control were also approved by the ethics committee on human research of Hidaka Hospital (approval number 199: Hidaka Hospital Human Genome Ethics Committee). According to the Ethical Guidelines for Medical and Health Research Involving Human Subjects, written informed consent is not necessarily required in this research design. Therefore, we widely disclosed the outline of our study and provided opportunities for disagreement.

B. RNA Extraction and Detection of Mutations in KCNJ5 and Others cDNA by Direct Sequencing

All APA specimens were placed into liquid nitrogen immediately after removal during surgery. Total RNA was extracted, and cDNA was reverse-transcribed and sequenced with specific primer sets as reported previously [15, 26].

KCNJ5 mutations were observed in 39 out of 50 patients with APAs with KCNJ5 mutations (17 with G151R A/G, 11 with G151RG/C, and 11 with L168R). GNAS mutations (R201C) were also detected in 2 patients with APAs with no KCNJ5 mutations. No mutations were noted in the *ATP1A1, ATP2B3, CACNA1D*, or *PRKACA* genes in any patients examined in the current study.

C. Statistical Analysis

All results are expressed as the mean ± SD for continuous variables and as absolute numbers and relative percentages for categorical variables. Group comparisons were performed with

ANOVA and the Student t test for normally distributed data or the Wilcoxon rank-sum test for nonnormally distributed data for continuous variables. The χ^2 test was used for categorical variables. Receiver operating characteristic (ROC) curves were used to define the most appropriate cutoff age. We used a logistic regression model to evaluate the ROC curve and quantified from area under the curve (AUC).

All tests for significance and the resulting P values were two-sided, with a level of significance of 5%. Statistical analyses were performed with JMP 10.1.2 (SAS Institute Inc., Cary, NC). The sample size was sufficient to evaluate changes in CKD in the older adult group relative to the young group when calculating the setting for α as 0.05 and β as 0.2 (a power of 0.80).

2. Results

A. CKD in the General Population in the Region Close to Our Hospital

We initially examined the prevalence of CKD in local healthy subjects who visited Takasaki Hidaka Hospital for a health checkup between 2003 and 2013; in Gunma Prefecture, salt intake per day is 10.9 g/day for men and 9.3 g/day for women, and this prefecture has the highest number of smokers in Japan [27]. As shown in Fig. 1, eGFR decreased almost linearly with age in men and women; 88 ± 13 mL/min/1.73 m^2 in men <40 years old, 71 ± 14 mL/min/1.73 m^2 in men >60 years old, 90 ± 15 mL/min/1.73 m^2 in women <40 years old, and 74 ± 14 mL/min/1.73 m^2 in women >60 years old. Accordingly, CKD defined by eGFR <60 mL/min/1.73 m^2 significantly increased with age, particularly in men. The rate of CKD was 0.6% in men <40 years old, 4.2% in men aged 41 to 50 years, 8.8% in men aged 51 to 60 years, and 19% in men >60 years old, and 0.6% in women <40 years old, 2.5% in women aged 41 to 50 years, 5.3% in women aged 51 to 60 years, and 13% in women >60 years old.

B. CKD and Age in Patients With PA

We investigated the relationship between eGFR and age in 50 preoperative patients with APAs. Among 50 patients with APAs, 13 were associated with CKD, and these patients were significantly older than the 37 patients without CKD (63 ± 9 vs 47 ± 12 years old, $P < 0.05$).

As shown in Table 1, a univariate analysis between groups with and without CKD revealed that although age, KCNJ5 mutations, diabetes mellitus, systolic blood pressure, and
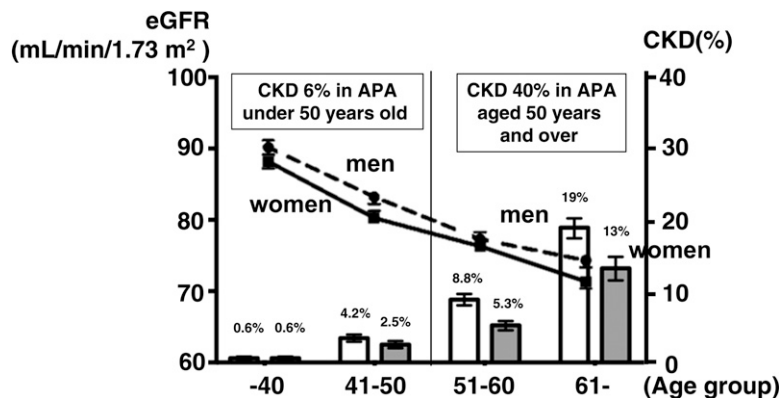

Figure 1. Prevalence of CKD and mean eGFR assessed by sex and age groups in health checkup subjects. We examined the prevalence of CKD in 27,572 local healthy subjects who visited Takasaki Hidaka Hospital for health checkups between 2003 and 2013. The line graphs show the age transition of mean eGFR (dotted line represents men, and the solid line is women). Bar graphs show the age transition in the prevalence of CKD (the white bar is labeled "men" and the gray bar is labeled "women").

midnight cortisol levels were significant, the multivariate analysis identified only age as significant.

In preoperative patients with APAs, a negative correlation was observed between eGFR and age ($r = -0.60$, $P < 0.01$) (Fig. 2A). The cutoff age of CKD after adrenalectomy examined by the ROC analysis was 50 years (sensitivity, 94%; specificity, 65%; AUC, 0.83) (Fig. 2B). Instead of an eGFR cutoff of 60 mL/min/1.73 m^2 after adrenalectomy, we performed a sensitivity analysis by using secondary outcomes, with a 25% decrease in eGFR after adrenalectomy. The cutoff age for a 25% decrease in eGFR after adrenalectomy examined by the ROC analysis was also 50 years (sensitivity, 57%; specificity, 82%; AUC, 0.69) (Fig. 2D). Therefore, comparisons were conducted among patients with APAs who were <50 years old and ≥50 years old.

CKD was identified in 5% of patients with APAs <50 years old and in >40% of those ≥50 years old (Fig. 1, Table 2). As a control, in 27,572 health checkup subjects, as shown in Fig. 1, the prevalence of CKD was 4.2% in men and 2.5% in women aged 41 to 50 years and 18.9% in men and 13.3% in women >61 years old, clearly demonstrating the higher prevalence of CKD in patients with APAs than in healthy subjects, particularly those with APAs ≥50 years old.

C. Clinical Characteristics of Patients With PA <50 and ≥50 Years Old

The prevalence of CKD was higher in patients with APAs, particularly in those ≥50 years old, than in healthy subjects, and we examined clinical characteristics in 30 patients with APAs ≥50 years old and 20 patients <50 years old to examine factors related to the high prevalence of CKD (Table 2). The prevalence of diabetes mellitus was significantly higher in patients with APAs ≥50 years old than in those <50 years old (10% vs 37%, $P < 0.05$), as was that of a history of cardiovascular events (0% vs 30%, $P < 0.01$), including three patients with stroke (two with cerebral hemorrhage and one with cerebral infarction and hemorrhage), four with heart diseases (two with atrial fibrillation, one with aortic aneurysm, and one with aortic valve stenosis), and two with both stroke and atrial fibrillation (one with atrial fibrillation,

Table 1. Comparisons Between CKD and Non-CKD Groups

	CKD −, n = 37	CKD +, n = 13	Univariate, P	Multivariate, P
Age, y	47 ± 21	63 ± 9	<0.01	<0.05
Men, %	43	54	0.51	
BMI, kg/m^2	24 ± 4	24 ± 4	0.87	
Systolic blood pressure, mm Hg	148 ± 17	136 ± 14	<0.05	0.46
Diastolic blood pressure, mm Hg	92 ± 12	85 ± 12	0.13	
Hyperlipidemia, %	35	46	0.48	
Diabetes, %	14	62	<0.01	0.09
Dosage of hypertensive drugs, n	2 ± 1	3 ± 1	0.52	
Serum sodium, mmol/L	143 ± 3	143 ± 3	0.81	
Serum potassium, mmol/L	2.9 ± 0.6	2.9 ± 0.5	0.89	
Serum chloride, mmol/L	103 ± 3	103 ± 5	0.84	
Plasma aldosterone concentration, ng/dL	428 ± 262	620 ± 680	0.91	
PRA, ng/mL/h	0.2 ± 0.2	0.2 ± 0.2	0.91	
ARR	2401 ± 2007	3740 ± 5349	0.95	
Urinary aldosterone, pg/mL	31 ± 23	31 ± 34	0.54	
Midnight serum cortisol level, μg/dL	4.0 ± 2.6	6.8 ± 3.8	<0.01	0.05
ACTH, pg/mL	22 ± 13	29 ± 26	0.85	
Smokers, %	43	42	0.94	
Drinkers, %	40	25	0.35	
Cardiovascular events, %	14	31	0.16	
KCNJ5 mutations, %	83	62	0.09	0.18
Tumor size, mm	16 ± 6	18 ± 10	0.96	

Multivariate P values adjusted for age, systolic blood pressure, diabetes (%), midnight serum cortisol levels, and KCNJ5 mutations (%).
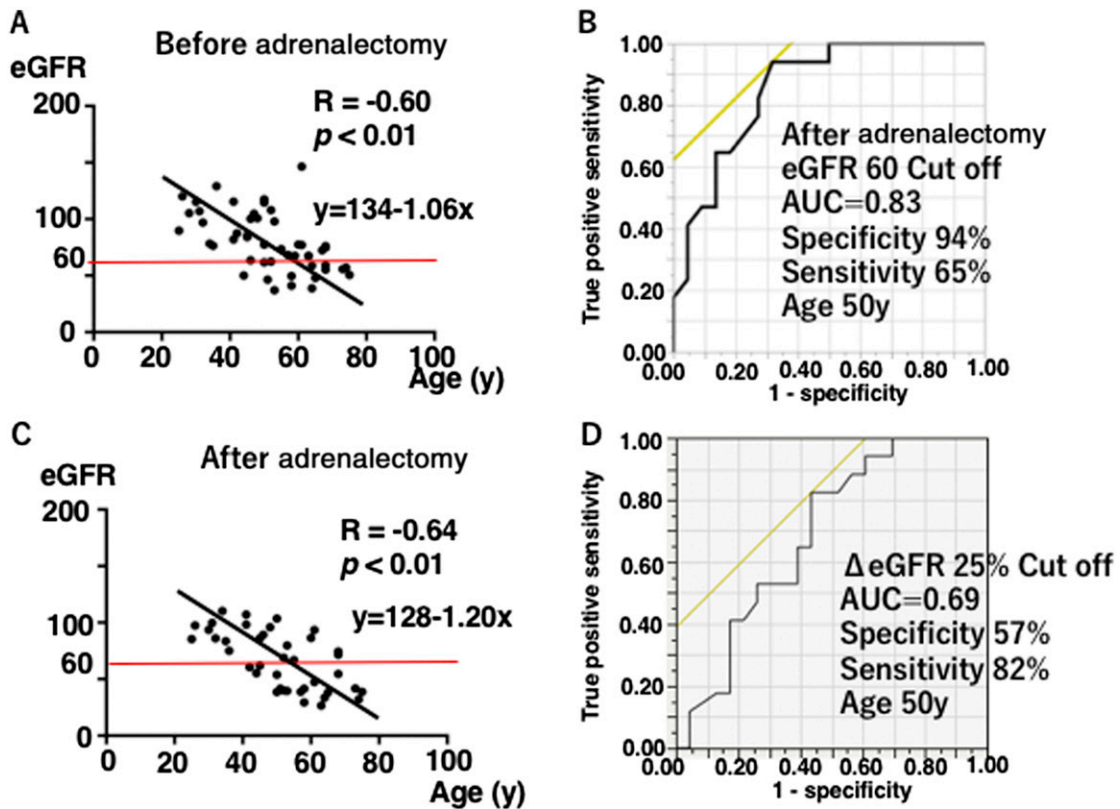
Figure 2. Age and CKD in patients with APAs. Correlations between eGFR and age in patients with APAs (A) before and (C) after adrenalectomy. The cutoff age for postoperative CKD was determined by ROC analysis based on (B) the postoperative level of eGFR ≤60 mL/min/1.73 m^2 and (D) 25% reduction in eGFR.

cerebral infarction, and hemorrhage, and one with cerebral infarction, aortic aneurysm, and atrial fibrillation). Furthermore, systolic blood pressure (95 ± 12 mm Hg vs 87 ± 12 mm Hg, $P < 0.01$), plasma renin assay (PRA) (0.3 ± 0.2 vs 0.2 ± 0.2 pg/mL, $P < 0.05$), urinary aldosterone levels (39 ± 26 vs 25 ± 25 pg/mL, $P < 0.05$), and the rate of KCNJ5 mutations (95% vs 67%, $P < 0.02$) were significantly lower in patients with APAs ≥50 years old than in those <50 years old. In addition, 19 out of 20 patients (95%) with APAs <50 years old had KCNJ5 mutations (seven with G151R A/G, five with G151RG/C, and seven with L168R). In contrast, 20 out of 30 patients (67%) with APAs ≥50 years old had KCNJ5 mutations, including 16 with G151R (10 with G151R A/G and six with G151RG/C) and four with L168R ($P < 0.05$). This is in agreement with evidence that patients with APAs and KCNJ5 mutations are younger and have severe aldosteronism.

D. Differences in Renal Function After Adrenalectomy Between Patients <50 and ≥50 Years Old

We examined changes in eGFR after adrenalectomy. Twenty-four out of the 50 patients with APAs were followed up after adrenalectomy. In patients with APAs after adrenalectomy, a negative correlation was observed between eGFR and age, and correlation curves were similar before and after adrenalectomy ($r = -0.60$, $P < 0.01$ and $r = -0.64$, $P < 0.01$) (Fig. 2A and 2C). In patients with APAs <50 years old, median eGFRs before and after adrenalectomy were 95 mL/min/1.73 m^2 and 88 mL/min/1.73 m^2, respectively, indicating that the percentage of the decrease in eGFR was -7%, which was not significant (paired t test, $P = 0.13$) (Fig. 3A-1). In contrast, in patients with APAs ≥50 years old, median eGFR after adrenalectomy

Table 2. Baseline Characteristics of Patients With PA <50 and >50 Years Old

	Total, n = 50	<50 y, n = 20	>50 y, n = 30	Univariate, P
Age, y	50 ± 8	38 ± 8	60 ± 8	<0.01
Men, %	45	40	50	0.48
BMI, kg/m^2	24 ± 4	24 ± 5	24 ± 4	0.18
Systolic BP, mm Hg	145 ± 17	150 ± 18	141 ± 17	<0.05
Diastolic BP, mm Hg	90 ± 12	95 ± 12	87 ± 12	<0.01
Age of the onset of hypertension, y	42 ± 12	31 ± 6	49 ± 9	<0.01
Duration of hypertension, y	10 ± 9	7 ± 6	12 ± 9	<0.05
Hyperlipidemia, %	36	30	43	0.34
Diabetes, %	29	10	37	<0.05
Dosage of hypertensive drugs, n	2 ± 1	2 ± 1	3 ± 1	0.83
eGFR, mL/min/1.73 m^2	80 ± 26	94 ± 20	70 ± 25	<0.01
CKD, %	26	5	40	<0.01
Serum sodium, mmol/L	143 ± 3	142 ± 2	143 ± 3	0.26
Serum potassium, mmol/L	2.8 ± 0.6	2.9 ± 0.7	2.9 ± 0.5	0.74
Serum chloride, mmol/L	103 ± 3.6	102 ± 3	103 ± 4	0.62
Plasma aldosterone concentration, ng/dL	448 ± 414	438 ± 248	504 ± 497	0.72
PRA, ng/mL/h	0.2 ± 0.2	0.3 ± 0.2	0.2 ± 0.2	<0.05
ARR	2662 ± 3201	2199 ± 2444	3109 ± 3640	0.15
Urinary aldosterone, pg/mL	31 ± 26	39 ± 26	25 ± 25	<0.05
Midnight serum cortisol level, μg/dL	4.6 ± 3.0	3.8 ± 2.2	5.2 ± 3.5	0.19
ACTH, pg/mL	23 ± 17	22 ± 13	25 ± 19	0.92
Smokers, %	37	47	39	0.58
Drinkers, %	38	47	29	0.19
Cardiovascular events, %	18	0	30	<0.01
KCNJ5 mutations, %	78	95	67	<0.05
Tumor size, mm	17 ± 8	17 ± 6	16 ± 8	0.40

decreased to 42 mL/min/1.73 m^2 from 67 mL/min/1.73 m^2 (adjusted by age, paired t test, P = 0.01) (percentage decrease in eGFR, −24%) (Fig. 3A-2).

When we examined preoperative eGFR categories, as described above, the proportion of CKD was significantly higher, at 40%, in patients with APAs ≥50 years old, compared with 6% in those <50 years old. After surgery, the prevalence of CKD remained unchanged at 6% in patients with APAs <50 years old but significantly increased to 67% in those ≥50 years old (Fig. 3A-1 and A-2). CKD categories after adrenalectomy progressed in 19% of patients <50 years old but in 67% of those ≥50 years old (P < 0.01) (Fig. 3B-1 and B-2).

E. Factors Related to Worse CKD Categories After Adrenalectomy in Patients With APAs ≥50 Years Old

To identify the factors causing worse CKD categories in patients with APAs ≥50 years old, we examined the clinical characteristics of those with worse CKD categories after adrenalectomy. Characteristics that were significant in the univariate analysis (P < 0.10) were assessed after adjustments for age and sex (Table 3). A multivariate analysis revealed that patients exhibiting the progression of CKD had significantly higher plasma aldosterone levels (708 ± 604 vs 243 ± 139 pg/mL, P < 0.01), ARRs (4301 ± 4540 vs 1430 ± 1068, P < 0.01), lower serum potassium (3.2 ± 0.6 vs 2.7 ± 0.4 mmol/L, P < 0.01) and chloride levels (105 ± 3 vs 101 ± 4 mmol/L, P < 0.01), and lower body mass index (BMI) (26 ± 2 vs 23 ± 4 kg/m^2, P < 0.05). Furthermore, groups showing the progression of CKD had a significantly higher frequency of a history of cardiovascular events (38% vs 0%, P < 0.05) and KCNJ5 mutation rates (67% vs 33%, P < 0.05; Table 3). Among the 16 patients with APAs ≥50 years old, in whom CKD categories progressed, six (38%) had a history of cardiovascular disorders, including three with stroke (two with cerebral hemorrhage and one with cerebral infarction and cerebral hemorrhage), one with heart disease (one with aortic aneurysm), and two with both stroke and atrial fibrillation (one with atrial fibrillation, cerebral infarction, and
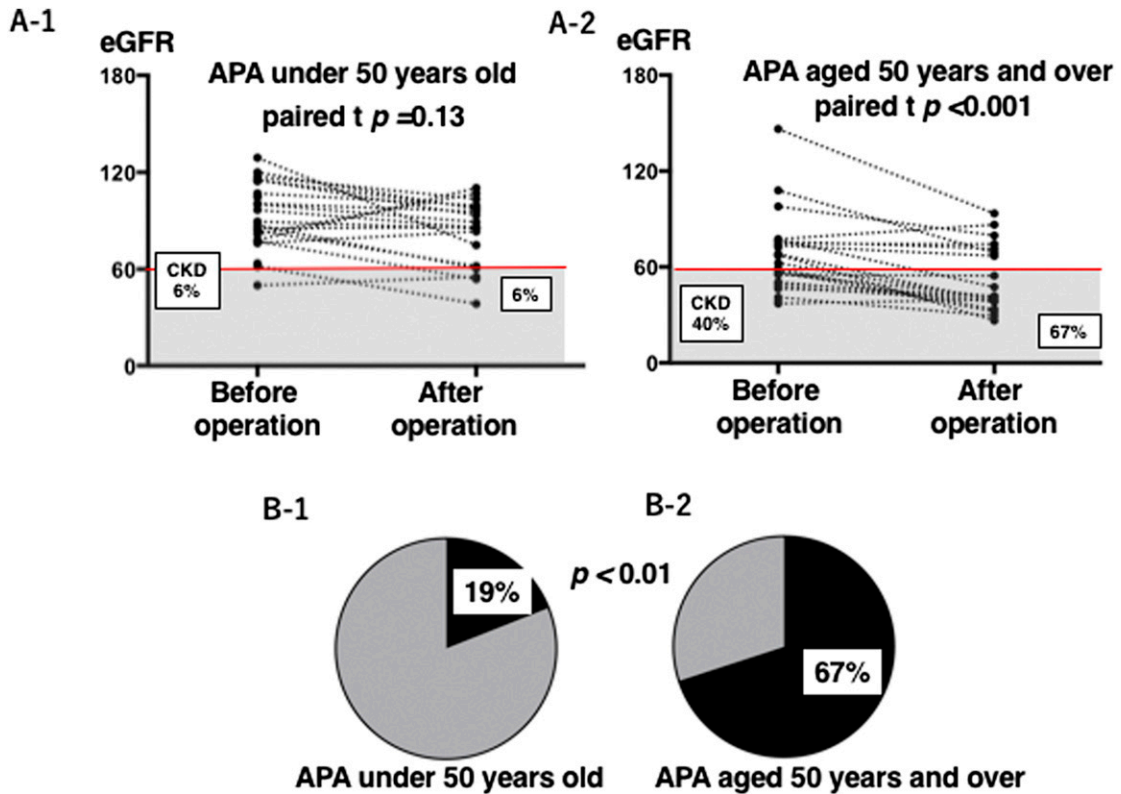
Figure 3. Changes in eGFR after adrenalectomy in patients with APAs. eGFR changes before and after adrenalectomy in patients (A-1) <50 years old and (A-2) ≥50 years. Boxes show the 25th to 75th percentile of values; the median is indicated by a solid line within each box, whiskers show the 0 to 100th percentiles of values. The dotted lines show individual changes before and after adrenalectomy. The proportion of CKD with G3a or worse (eGFR <60 mL/min/1.73 m^2) is shown by the enclosed number. The proportions of patients with APAs showing a progressed eGFR category who were (B-1) <50 years old and (B-2) ≥50 years old. In the pie chart, the worse group is shown in black.

hemorrhage, and one with cerebral infarction, aortic aneurysm, and atrial fibrillation). Among patients who did not show any progression of CKD, only three out of eight (38%) had KCNJ5 mutations (two cases of G151R G/A and one of G151R G/C). In contrast, in patients with progression to CKD 12 out of 16 (75%) had KCNJ5 mutations, including 10 with G151R (7 with G151R A/G and three with G151RG/C), and two with L168R. Furthermore, GNAS mutation (R201C) was found in one out of four cases with no KCNJ5 mutations. No mutations were identified in the *ATP1A1, ATP2B3, CACNA1D,* or *PRKACA* genes.

Collectively, these results demonstrated that severe cases of APAs showed the progression of CKD after adrenalectomy, particularly in patients ≥50 years old.

3. Discussion

We herein demonstrated that age is a unique predictor of progressive renal dysfunction in Japanese patients with PA, particularly after adrenalectomy. In preoperative patients with APAs, age was the sole risk factor for the progression of CKD, eGFR decreased with age, and the percentage of patients <50 years old with CKD was ~6%, and this rate significantly increased to 40% in those ≥50 years old. After surgery, the percentage of patients <50 years old with CKD remained at 6%, increasing to 67% in those ≥50 years old, suggesting that CKD frequently deteriorates in the latter. Reflecting these results, whereas the progression of CKD after surgery was observed in 19% of patients <50 years old, it significantly increased to 67% in those ≥50 years old.

Table 3. Comparisons Between CKD Progressive and Nonprogressive Groups >50 Years Old

	Progression −, n = 8	Progression +, n = 16	Univariate, *P*	Multivariate, *P*
Age, y	60 ± 7	60 ± 9	0.86	
Men, %	38	56	0.39	
BMI, kg/m^2	26 ± 2	23 ± 4	<0.05	<0.05
Follow-up duration for eGFR changes, mo	16 ± 4	14 ± 4	0.23	
Systolic BP, mm Hg	146 ± 19	138 ± 12	0.34	
Diastolic BP, mm Hg	86 ± 12	86 ± 12	0.43	
Age of the onset of hypertension, y	51 ± 7	46 ± 9	0.06	0.14
Duration of hypertension, y	9 ± 7	14 ± 11	0.27	
Hyperlipidemia, %	50	38	0.56	
Diabetes, %	38	44	0.77	
Dosage of hypertensive drugs, n	2 ± 1	3 ± 1	0.06	0.15
eGFR, mL/min/1.73 m^2	82 ± 34	64 ± 18	0.16	
Serum sodium, mmol/L	143 ± 2	143 ± 3	0.88	
Serum potassium, mmol/L	3.2 ± 0.6	2.7 ± 0.4	<0.05	<0.01
Serum chloride mmol/L	105 ± 3	101 ± 4	<0.05	<0.01
PAC, ng/dL	235 ± 130	708 ± 604	<0.05	<0.01
PRA, ng/mL/h	0.2 ± 0.2	0.2 ± 0.2	0.20	
ARR	1430 ± 1068	4301 ± 4540	<0.05	<0.01
Urinary aldosterone, pg/mL	19 ± 17	33 ± 30	0.11	
Midnight serum cortisol level, μg/dL	4.2 ± 3.6	5.8 ± 3.7	0.06	0.27
ACTH, pg/mL	18 ± 8	32 ± 24	0.15	
Smokers, %	50	31	0.37	
Drinkers, %	38	19	0.32	
Cardiovascular events, %	0	38	<0.05	<0.05
KCNJ5 mutations, %	38	75	0.07	<0.05
Tumor size, mm	13 ± 5	18 ± 10	0.16	

Multivariate *P* values adjusted for age and sex.

A. Age and CKD

In healthy subjects, CKD progresses with age. Imai *et al.* [28] reported that the percentage of CKD was <10% in Japanese men and women but 40% in those in their 80s. In the current study, similar results were obtained in healthy subjects: the prevalence of CKD was 4.2% in men and 2.5% in women aged 41 to 50 years old and 18.9% in men and 13.3% in women ≥61 years old. Imai *et al.* also showed a similar decrease in eGFR in CKD and normal subjects.

We herein demonstrated age-dependent increases in the prevalence of CKD in patients with APAs and a higher prevalence of CKD in patients with APAs than in healthy subjects, particularly in those with APAs ≥50 years old. Glomerular hyperfiltration due to long-term hyperaldosteronism may have led to the high prevalence of CKD in patients with APA >50 years old.

B. Age and CKD After Adrenalectomy in Patients With APAs

We showed that the postoperative progression of CKD stages after surgery was 19% in patients <50 years old, and significantly increased to 67% in those ≥50 years old, with 50% reaching CKDG3B or worse, which increased the risk of cardiovascular events. Previous studies reported a similar phenomenon that after treatment of aldosteronism eGFR was reduced, and continued for up to about 1 year, after which it did not change compared with that in essential hypertension [29, 30]. Iwakura *et al.* [20] reported that the prevalence of CKD in APA and bilateral hyperaldosteronism groups significantly increased by ~20% after treatment because of a decrease in eGFR. Their findings suggested that renal damage was initially masked in 20% of patients with PA and that glomerular hyperfiltration may lead to the underestimation of CKD at baseline in patients with PA. They and others reported that

preoperative high urine albumin levels and low serum potassium levels were predictors of decreased eGFR after the treatment of PA [19, 20, 30]. Kim *et al.* [31] reported that age, low serum potassium, low preoperative eGFR, and high serum cholesterol or uric acid were associated with the postoperative development of CKD in Korea. Kramers *et al.* [32] recently identified pretreatment plasma aldosterone, eGFR, plasma renin, and plasma potassium as independent predictors. However, they did not examine patients separately based on age. We also demonstrated that risk factors for the progression of CKD in patients ≥50 years old included a high plasma aldosterone level, high ARR, low potassium level, low chloride level, and low BMI. We did not examine urine albumin levels in the current study. Furthermore, it is important to note that a history of cardiovascular events and a high rate of KCNJ5 mutations were also significant. In addition, a univariate analysis demonstrated that the duration of hypertension and number of antihypertensive medications were higher in the groups showing the progression of CKD than those in nonprogressive groups, suggesting that factors related to atherosclerosis may be risk factors for the postoperative progression of CKD.

Regarding KCNJ5 mutations, we and other groups from Western countries reported that patients with KNCJ5 mutations were younger and had high aldosterone levels [14, 15, 17, 33]. The current study also demonstrated that the mutation rate of the *KCNJ5* gene in patients with APAs was 95% for those <50 years old, and this decreased to 67% in those ≥50 years old. Among patients ≥50 years old, the percentages of KCNJ5 mutations for the postoperative progression and nonprogressive of CKD were 75% and 37%, respectively. Therefore, among patients with PA ≥50 years old, severe aldosteronism was observed in those with KCNJ5 mutations.

The current study also demonstrated that patients with PA and renal dysfunction associated with a low BMI frequently showed worsened relative renal dysfunction after adrenalectomy. A positive correlation has been reported between aldosterone levels and BMI [34, 35]. However, this positive correlation disappeared in patients with PA, and BMI was lower in patients with APAs than in those with idiopathic hyperaldosteronism [20, 36]. The reasons why BMI was lower in patients with PA remain obscure. Hypokalemia has been reported to induce polyurea and myopathy or myolysis [37]. Hypokalemia in patients with PA may also induce similar muscle changes and high creatine phosphokinase levels [38, 39]. Hypokalemia in patients with severe PA may induce dehydration and low BMI induced by muscle weakness. Therefore, a high creatinine level associated with the loss of muscle volume may also be a risk factor for CKD in patients ≥50 years old. A reduced muscle volume in older adults may induce higher eGFR, as assessed by blood creatinine, than real values of eGFR in patients with APAs.

C. Renal Damage by Rapid Reductions in Blood Pressure After Adrenalectomy

Rapid decreases in blood pressure after adrenalectomy may cause cardiovascular and renal damage, particularly in older adults with APAs. The JNC-8 [40] and ESC/ESH2013 [41] guidelines indicated that the target blood pressure for older adults was 150/90 mm Hg, and the Japanese Guidelines for Hypertension 2014 indicated a target blood pressure of 140/90 mm Hg for patients aged 65 to 74 years old with CKD, 150/90 mm Hg for older adults, and 140/90 mm Hg if tolerated for older adults with CKD, which may improve the prognosis of CKD [42]. However, acute lowering or too low blood pressure may result in worse morbidity in older adults. The curve of all causes of death and cardiovascular events against blood pressure in older adults was J-shaped [24]. Imai and Abe [43] reported that dehydration in summer and the excessive lowering of blood pressure increased the risk of acute renal failure in older adults. However, a recent randomized controlled study of older adults demonstrated that the severe control of blood pressure may contribute to the attenuation of cardiovascular events and all causes of death [44]. Therefore, in patients with PA ≥50 years old, adrenalectomy may result in acute lowering of blood pressure and a risk of renal dysfunction; however, in consideration of morbidity, the intensive lowering of blood pressure by

adrenalectomy may be needed. Additional studies are needed to clarify the prognosis of postoperative patients with APAs.

D. Limitations of the Study

The limitations of the current study were that it had a low sample size and was a single-center study of Japanese patients only. The sample size for the multivariate analysis was not sufficient to examine risk factors for CKD.

Many Japanese people have salt-sensitive hypertension and single nucleotide polymorphisms related to salt-sensitive hypertension. More Japanese patients with PA had APAs with KCNJ5 mutations than those in Western countries. Therefore, Japanese patients have the characteristic epidemiology of hypertension or CKD.

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Correspondence: Masanobu Yamada, MD, PhD, Department of Internal Medicine, Division of Endocrinology and Metabolism, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan. E-mail: myamada@gunma-u.ac.jp.

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