

Adrenalectomy Improves the Long-Term Risk of End-Stage Renal Disease and Mortality of Primary Aldosteronism

Ying-Ying Chen,^{1*} You-Hsien Hugo Lin,^{2*} Wei-Chieh Huang,^{3,4,5} Eric Chueh,⁶ Likwang Chen,⁷ Shao-Yu Yang,^{8,9} Po-Chih Lin,^{8,9} Lian-Yu Lin,^{8,9} Yen-Hung Lin,^{8,9} Vin-Cent Wu,^{8,9} Tzong-Shinn Chu^{8,9}, and Kwan Dun Wu^{8,9}

¹Division of Nephrology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan 10491; ²Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan 80145; ³Division of Cardiology, Taipei Veterans General Hospital, Taipei, Taiwan 11217; ⁴School of Medicine, National Yang-Ming University, Taipei, Taiwan 11221; ⁵Division of Cardiology, Department of Internal Medicine, New Taipei City Hospital, New Taipei City, Taiwan 24141; ⁶Case Western Reserve University, Cleveland, Ohio 44106; ⁷Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan 35053; ⁸Division of Nephrology and Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan 10002; and ⁹TAIPAI, Taiwan Primary Aldosteronism Investigator, Taipei, Taiwan 10041

ORCID numbers: 0000-0003-1083-4415 (P.-C. Lin); 0000-0001-7935-0991 (V.-C. Wu); 0000-0002-5291-2509 (T.-S. Chu).

*Y.-H.H.L. and Y.-Y.C. contributed equally to this paper.

Objective: Primary aldosteronism (PA) is a common cause of secondary hypertension, and the long-term effect of excess aldosterone on kidney function is unknown.

Patients and Methods: We used a longitudinal population database from the Taiwan National Health Insurance system and applied a validated algorithm to identify patients with PA diagnosed between 1997 and 2009.

Results: There were 2699 patients with PA recruited, of whom 761 patients with an aldosterone-producing adenoma (APA) were identified. The incidence rate of end-stage renal disease (ESRD) was 3% in patients with PA after targeted treatments and 5.2 years of follow-up, which was comparable to the rate in controls with essential hypertension (EH). However, after taking mortality as a competing risk, we found a significantly lower incidence of ESRD when comparing patients with PA vs EH [subdistribution hazard ratio (sHR), 0.38; $P = 0.007$] and patients with APA vs EH (sHR 0.55; $P = 0.021$) after adrenalectomy; however, we did not see similar results in groups with mineralocorticoid receptor antagonist (MRA)-treated PA vs EH. There was also a significantly lower incidence of mortality in groups with PA and APA who underwent adrenalectomy than among EH controls ($P < 0.001$).

Conclusion: Regarding incident ESRD, patients with PA were comparable to their EH counterparts after treatment. After adrenalectomy, patients with APA had better long-term outcomes regarding progression to ESRD and mortality than hypertensive controls, but MRA treatments did not significantly affect outcome.

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Abbreviations: APA, aldosterone-producing adenoma; DDD, defined daily dose; EH, essential hypertension; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HR, hazard ratio; *ICD-9*, *International Classification of Diseases Ninth Revision*; MRA, mineralocorticoid receptor antagonist; NHI, National Health Insurance; NHIA, National Health Insurance Administration; PA, primary aldosteronism; sHR, subdistribution hazard ratio.

Freeform/Key Words: primary aldosteronism, ESRD, adrenalectomy, spironolactone, TAIPAI, TSA

Primary aldosteronism (PA; *i.e.*, autonomous aldosterone hypersecretion) is noted in 3.9% of patients with stage 1 hypertension, and the proportion increases to 11.8% in patients with stage 3 hypertension [1]. However, a number of cardiovascular and renal sequelae of PA cannot be entirely attributed to the effects of hypertension alone [2]. The reported risk of cardiovascular events was higher in patients with PA, with proinflammatory mediators and oxidative stress affecting multiple organs, than in otherwise similar patients with essential hypertension (EH) [3].

Prolonged aldosterone excess also causes relative kidney hyperfiltration and reversible intrarenal vascular structural changes, which disguise consequent renal injury, including declining glomerular filtration rate (GFR) and proteinuria [4, 5]. Aldosterone has been reported to induce direct glomerular injury and proteinuria independently of its hemodynamic effects [4, 6], such as a high estimated GFR and albuminuria [7]. Hence, PA is associated with higher rates of renal blood flow [8] and, in a previous study, characterized by partially reversible renal dysfunction in which a dynamic, rather than structural, renal defect was demonstrated in a previous study [9].

Although a long-term follow-up study with limited PA patients showed similar therapeutic effects on kidney function [9], adrenalectomy and mineralocorticoid receptor antagonist (MRA) treatments have different short-term clinical impacts with respect to kidney damage, even with a similar blood pressure–lowering effect [4, 7, 10]. In fact, an initial temporary worsening of renal function within 1 month of adrenalectomy has been reported [4, 8, 11], and the decline in renal function could be the result of correction of glomerular hyperfiltration via decreased aldosterone excess–related intrarenal vascular resistance [8] or systemic hemodynamic change [12]. A systemic review supported surgical resection of PA, which can be performed with low morbidity [13]. Adrenalectomy is safe, reverses aldosterone excess, and is effective at normalizing blood pressure and decreasing medication requirements, particularly in younger adults [14]; however, regarding kidney function, the long-term benefit/risk ratio of adrenalectomy compared with MRA treatment is lacking, and additional studies are warranted.

The Taiwan National Health Insurance research database contains records of claims that comprehensively capture information on episodes of care across all hospitals and nearly all health care facilities across Taiwan. Taking advantage of the merits of this database, we examined long-term crucial outcomes of renal events, namely end-stage renal disease (ESRD) and mortality among patients with PA receiving targeted treatment. We scrutinized the effects of different treatment options for PA on ESRD and mortality and subsequently explored the benefits of treatment strategies for reducing long-term ESRD and mortality risk among patients with PA.

1. Materials and Methods

A. Patient Enrollment

This study extracted National Health Insurance (NHI) reimbursement data from 1997 to 2009. The Taiwan government launched the NHI program in 1995. The NHI covers outpatient visits, hospital admissions, prescriptions, and intervention procedures and maintains disease profiles for >99% of the Taiwanese population. The NHI improved access to health care and reduced economic disparity in health care use in the late 1990s. As shown by financial reports from the National Health Insurance Administration (NHIA), the electronic database of NHI claims contains comprehensive information on disease diagnosis and health care use, particularly for cases requiring expensive services. The NHI database has provided research data for various studies on epidemiology, health services research, and clinical

medicine [15]. To detect fraud in the NHI, the NHIA routinely audits data submitted by health care institutions [16]. The NHIA has been the only provider to the NHI, and to avoid NHIA rejection of reimbursement claims, physicians in Taiwan usually follow clinical guidelines. Because the gold standard for diagnosis of PA is still AVS which is costly and invasive, Taiwanese physicians follow the clinical practice guidelines of the Society of Aldosteronism—the Taiwan PA consensus [17, 18]—and focus on performing lateralization tests on patients with a high possibility of PA after a confirmation test [18–22].

B. Algorithms for Identifying PA

We used a validated algorithm to detect patients with PA, recruiting only patients aged ≥ 18 years [*International Classification of Diseases Ninth Revision (ICD-9)* code: 255.1] [15, 23]. We also found an algorithm with a positive predictive value of 0.9 to ensure the reliability of the sample identified by the algorithm to portray clinical outcomes in patients with PA [15]. We enrolled only patients with PA who had used MRA [belonging to anatomical therapeutic chemical (ATC) class C03D] because our main study aim was to construct a reliable PA sample according to our validation [15, 23]. For comparisons between patients with an aldosterone-producing adenoma (APA) treated with surgery vs MRA, patients with PA and the diagnosis of adrenal tumor (*ICD-9* code: 227, 227.0, 239.7) were further classified as having APA. Among patients with PA who underwent adrenalectomy, an adrenal tumor was recorded in 96%. In addition, because patient adherence in taking medication plays a crucial role in successful medical treatment and can affect mortality, we calculated each patient's medication possession ratio for MRA (belonging to ATC class C03D). Adherence was calculated across all disease-modifying drugs for a 12-month postindex date.

We developed additional algorithms to ascertain comorbid conditions among patients with PA. Except for a couple of morbid conditions requiring more detailed *International Classification of Diseases, Ninth Revision, Clinical Modification* coding for confirmation, we used only the first three digits of these codes to identify morbid conditions, rather than more digits [15]. This rule also tended to yield a lower rate of type II error in identifying comorbidities. During review of the NHI data, the identification of a specific morbid condition was based on the criterion of at least one inpatient NHI record or three outpatient records with the corresponding disease diagnosis within 1 year before the time of first PA diagnosis; this method has been well validated [15, 24–27].

In this nested propensity, score-matched, case-control study, patients with EH were ascertained from those with the diagnosis of hypertension and received antihypertensive agents (from ATC) after we excluded patients with secondary hypertension. The duration of hypertension was defined as the period from the first prescription of antihypertension agents to the index date.

C. Outcomes

The outcomes of this study were long-term all-cause mortality and ESRD [28]. We used a subsequent selective period of 90 days to define ESRD because all patients receiving dialysis for more than 90 days in Taiwan can apply for dialysis-related catastrophic cards in the NHI program [29]. Patients with catastrophic illness certification who get care for the illness or related conditions within the certificate's validity period do not need to provide a copayment for outpatient or inpatient care.

D. Statistical Analyses

Student *t* tests and χ^2 tests were used to assess differences between the patients with PA and those with identified EH. We matched patients with PA/APA to patients with EH using a greedy matching algorithm with a caliper width of 0.2 SDs of the log odds of the estimated propensity score. The sampling ratio for patients with PA/patients with EH and for patients with APA/patients with EH was 1:4.

In various subsequent multivariable models for analyzing outcomes, we took into account the propensity score for the PA diagnosis to minimize residual confounding effects in the matching process [23]. To estimate each patient's propensity score for *PA diagnosis*, we fit a separate multivariable logistic regression model with factors predicting *PA* [30]. The caliper distance was 0.25. Multivariable Cox proportional hazard models before and after propensity score matching [23] were applied to estimate hazard ratios (HRs) of study outcomes. The significance level for entry and the significance level for stay were set to 0.15 for conservative purposes. Then, with the aid of substantive knowledge, the best-candidate final Cox model was identified by manually dropping the covariates with *P* value >0.05 one at a time until all regression coefficients were significantly different from 0.

Cox regression models with time-varying covariates accounted for their influence on risk of ESRD or death. Time-varying covariates took the value 0 before the start of MRA or surgical treatment and could switch to 1 at the start of treatment. Additional adjustments in these models included control for direct effects from age, sex, concomitant medications, and the comorbidities listed in Table 1 (and in an online repository [23]). Regarding factors associated with outcomes in further parametric modeling, we adopted three modeling methods: simple Cox regression, multivariable Cox regression, and competing risk regression. We took mortality as competing risk due to the high mortality rate among elderly patients with ESRD, competing-risk regression using the Fine and Gray model with consideration of the subdistribution hazard ratio (sHR) was also performed to show the risk of progression to ESRD. [31].

On the basis of this hazard function, we further simulated and depicted 10-year survival curves for the probability of incident ESRD under different scenarios of treatment with MRA and adrenalectomy among all patients with PA [32, 33]. Specifically, we stratified patients by PA subgroup status including age, sex, urbanization level, monthly income and the comorbidities after targeted treatment and used the mean values of all other covariates for our study patients.

We used R software, version 2.8.1 (Free Software Foundation, Inc., Boston, MA); competing risk analysis was performed with Stata/MP version 12 (Stata Corporation, College Station, TX). A two-sided *P* value <0.05 was considered statistically significant.

2. Results

The process of selecting patients for the newly identified PA and matched EH groups is listed in Fig. 1. Among 4796 patients with an initial diagnosis of PA from the NHRI 1997 to 2009 database, 1571 patients were excluded. As shown, 2699 adults had confirmed PA according to the algorithm; among them, 657 adults underwent adrenalectomy and 2042 patients were administered MRA (Fig. 1).

A. Comparing Adults With EH and Adults With PA

After propensity score matching during index clinical visits [23], 10,796 patients with EH were identified. The mean age of patients at the time of PA diagnosis was 51.6 years, and the proportion of men was 45.6% (Table 1). Likewise, 761 patients with APA (mean age, 48.0 years, 43.2% male) were matched with 3044 EH controls .

B. Comparing the Risk of ESRD Between Patients With PA/APA and Their EH Matches

The incidence rate of ESRD in the EH control group was 5.8 events/1000 person-years, and the PA group had an incidence rate of 5.5 events/1000 person-years after targeted treatment; the APA group had an incidence rate of 2.3 events/1000 person-years (average, 5.2 ± 3.5 years of follow-up) (Table 2). The competing sHR for developing incident ESRD after targeted treatment was 0.96 (*P* = 0.730) among the PA cohort, and 0.50 (*P* = 0.031) among the APA cohort relative to their EH cohort after accounting for mortality in the competing effects.

Table 1. Comparison of Characteristics Between Patients With PA and EH for the Whole PA Cohort and for the APA Subgroup Only

ESRD	Matched EH vs PA			Matched EH vs APA		
	EH (n = 10796)	PA (n = 2699)	P	EH (n = 3044)	APA (n = 761)	P
1997–2009						
Propensity score	−3.9 ± 1.6	−3.9 ± 1.6	0.993	−2.5 ± 0.5	−2.5 ± 0.5	0.999
Sex						
Female	5725 (53.0)	1468 (54.4)	0.211	1763 (57.9)	432 (56.8)	0.566
Male	5071 (47.0)	1231 (45.6)	0.211	1281 (42.1)	329 (43.2)	0.566
Age, y	51.6 ± 14.7	51.6 ± 14.7	0.999	47.8 ± 13.6	48.0 ± 11.5	0.382
Urbanization level						
Urban	4959 (45.9)	1231 (45.6)	0.954	1430 (47.0)	357 (46.9)	0.659
Suburban	2883 (26.7)	724 (26.8)	0.954	802 (26.4)	211 (27.7)	0.659
Rural	2954 (27.4)	744 (27.6)	0.954	812 (26.7)	193 (25.4)	0.659
Monthly income, n (%)						
<USD 640	6391 (59.2)	1621 (60.1)	0.343	1840 (60.5)	458 (60.2)	0.988
≥USD 640	3667 (34.0)	914 (33.9)	0.343	1003 (33.0)	253 (33.3)	0.988
Outpatient visits to specialists, n (%)						
≤5	882 (8.2)	241 (8.9)	0.551	298 (9.8)	72 (9.5)	0.536
5–10	1185 (11.0)	301 (11.2)	0.551	351 (11.5)	76 (10.0)	0.536
10–15	1534 (14.2)	368 (13.6)	0.551	473 (15.5)	113 (14.9)	0.536
≥15	7195 (66.7)	1789 (66.3)	0.551	1922 (63.1)	500 (65.7)	0.536
Comorbidity, n (%)						
Congestive heart failure	420 (3.9)	110 (4.1)	0.658	81 (2.7)	26 (3.4)	0.270
Cerebrovascular disease	794 (7.4)	216 (8.0)	0.252	164 (5.4)	46 (6.0)	0.478
CKD	270 (2.5)	71 (2.63)	0.681	33 (1.1)	10 (1.3)	0.567
COPD	680 (6.3)	179 (6.6)	0.537	109 (3.6)	23 (3.0)	0.507
Coronary artery disease	126 (1.2)	25 (0.9)	0.308	43 (1.4)	6 (0.8)	0.209
Dementia	84 (0.8)	21 (0.8)	0.999	10 (0.3)	1 (0.1)	0.704
Diabetes mellitus	1447 (13.4)	398 (14.8)	0.074	328 (10.8)	83 (10.9)	0.896
Hemiplegia	65 (0.6)	18 (0.7)	0.680	8 (0.3)	5 (0.7)	0.153
Liver disease	657 (6.1)	148 (5.5)	0.256	149 (4.9)	35 (4.6)	0.778
Peptic ulcer	955 (8.9)	235 (8.7)	0.850	194 (6.4)	47 (6.2)	0.934
Peripheral vascular disease	55 (0.5)	10 (0.4)	0.437	15 (0.5)	2 (0.3)	0.550
Rheumatoid arthritis	56 (0.5)	12 (0.4)	0.761	17 (0.6)	1 (0.1)	0.149
Solid tumor	306 (2.8)	66 (2.5)	0.293	46 (1.5)	15 (2.0)	0.338
SLE	12 (0.1)	6 (0.2)	0.232	4 (0.1)	2 (0.3)	0.345
Af	165 (1.5)	38 (1.4)	0.724	41 (1.4)	6 (0.8)	0.271
Dyslipidemia	1602 (14.8)	384 (14.2)	0.430	338 (11.1)	86 (11.3)	0.898
Parkinson disease	72 (0.7)	23 (0.9)	0.304	15 (0.5)	1 (0.1)	0.221
Antihypertensive medication, n (%)						
Alpha-blocker	747 (6.9)	188 (7.0)	0.932	165 (5.4)	54 (7.1)	0.082
ACE-I or ARB	4506 (41.7)	1116 (41.4)	0.727	1308 (43.0)	328 (43.1)	0.967
Beta-blocker	5145 (47.7)	1255 (46.5)	0.291	1518 (49.9)	387 (50.9)	0.656
CCB	6731 (62.4)	1680 (62.3)	0.929	2083 (68.4)	530 (69.7)	0.541
Diuretic	4878 (45.2)	1213 (44.9)	0.829	1175 (38.6)	291 (38.2)	0.868
Other medication, n (%)						
Aspirin	728 (6.7)	193 (7.2)	0.443	192 (6.3)	50 (6.6)	0.803
Clopidogrel	177 (1.6)	49 (1.8)	0.503	65 (2.1)	15 (2.0)	0.888
Ticlopidine	112 (1.0)	30 (1.1)	0.752	21 (0.7)	3 (0.4)	0.451
Warfarin	103 (1.0)	29 (1.1)	0.584	24 (0.8)	6 (0.8)	1.000

(Continued)

Table 1. Comparison of Characteristics Between Patients With PA and EH for the Whole PA Cohort and for the APA Subgroup Only (Continued)

ESRD	Matched EH vs PA			Matched EH vs APA		
	EH (n = 10796)	PA (n = 2699)	P	EH (n = 3044)	APA (n = 761)	P
1997–2009						
PPI	437 (4.1)	117 (4.3)	0.515	88 (2.9)	21 (2.8)	0.904
H ₂ blocker	1076 (10.0)	271 (10.0)	0.914	260 (8.5)	64 (8.4)	0.942
Statin	961 (8.9)	244 (9.0)	0.821	222 (7.3)	53 (7.0)	0.814
NSAID	5345 (49.5)	1333 (49.4)	0.914	1471 (48.3)	358 (47.0)	0.543
Steroid	1006 (9.3)	277 (10.3)	0.142	238 (7.8)	57 (7.5)	0.820
SSRI	306 (2.8)	72 (2.7)	0.696	73 (2.4)	17 (2.2)	0.894
Nitrate	28 (0.3)	9 (0.3)	0.536	8 (0.3)	0 (0.0)	0.370
Outcome, n (%)						
ESRD	322 (3.0)	80 (3.0)	0.999	84 (2.8)	11 (1.5)	0.037
Mortality	1641 (15.2)	366 (13.6)	0.032	375 (12.3)	40 (5.1)	<0.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; Af, atrial fibrillation; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; H₂, histamine type 2; N, number; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SLE, systemic lupus erythematosus; SSRI, selective serotonin reuptake inhibitor; USD, United States dollar.

C. Comparing the Risk of ESRD and Mortality Between Patients With PA/APA and Their EH Matches

Table 3 shows that the risks of mortality (adjusted HR, 0.22; $P < 0.001$), ESRD (sHR, 0.38; $P = 0.007$), and ESRD with mortality (adjusted HR, 0.26; $P < 0.001$) among patients with PA who underwent adrenalectomy were all significantly decreased compared with those of EH controls. In an additional analysis, patients with APA who underwent adrenalectomy

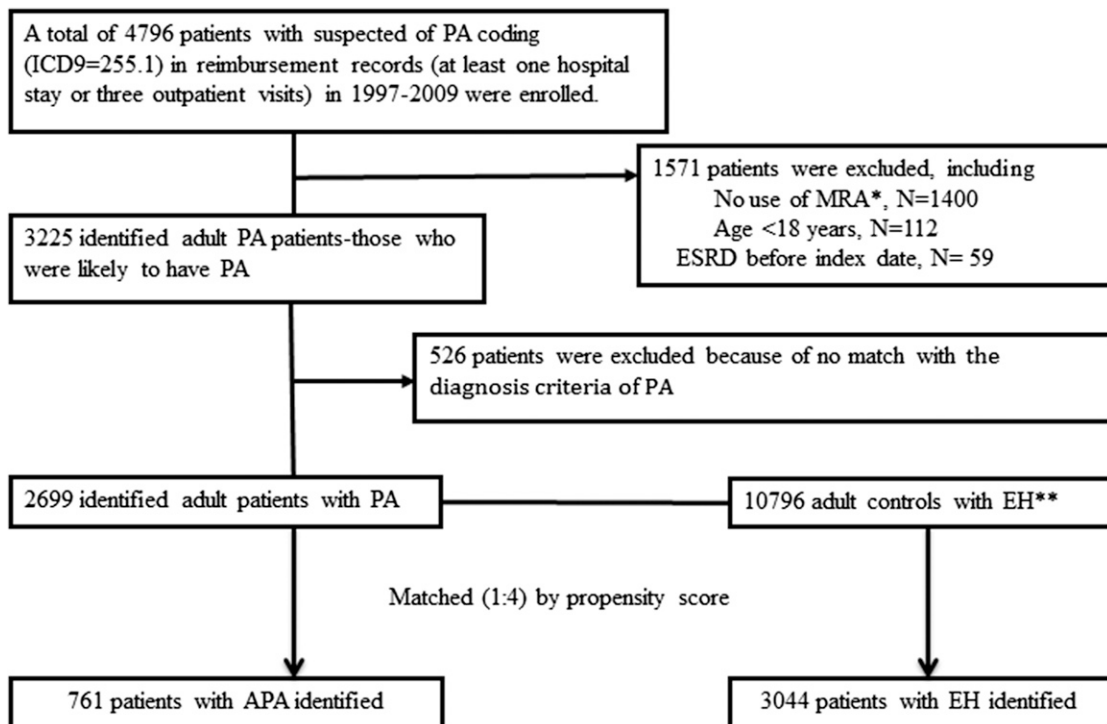


Figure 1. Flowchart of the participants in the cohort (PA/APA cohort and essential hypertension cohort). *Patients who did not use MRA during the year before or 2 year after the first PA coding. **Secondary hypertension excluded.

had decreased incidences of ESRD (sHR, 0.55; $P = 0.021$), mortality (adjusted HR, 0.31; $P < 0.001$), and ESRD with mortality (adjusted HR, 0.35; $P < 0.001$) compared with EH controls. However, patients with PA who underwent MRA treatment had a risk of incident ESRD similar to that of EH controls (sHR, 1.08; $P = 0.570$). Similarly, there was no significant difference in the risk of incident ESRD between APA and EH groups when MRA treatment was used (sHR, 0.39; $P = 0.100$) (Table 3).

In the subgroup analysis, there were no significant differences in incident ESRD among patients with PA after targeted treatment vs patients with EH (Fig. 2a). In terms of undergoing adrenalectomy, there was a significantly lower incidence of ESRD among patients with a Charlson score >0 (HR, 0.18; 95% CI: 0.04 to 0.71) (Fig. 2b)

Using the Cox regression model, we further assessed incident ESRD for patients with PA who were given MRA or adrenalectomy, with EH as the control and mortality as a competing risk (Fig. 3). A longer period of hypertension led to a similar cumulative proportion of ESRD for those given MRA ($P = 0.100$); however, there was a smaller cumulative proportion of ESRD for those who underwent adrenalectomy ($P = 0.021$) compared with patients with EH.

D. Comparison of the Effect of Adrenalectomy on the Long-Term Risk of Incident ESRD Under the Framework of a Subgroup Analysis

To investigate the consistency of the beneficial effect of adrenalectomy among different groups of PA patients, we conducted a subgroup analysis with respect to baseline comorbidity that further adjusted for age and sex. Our simulation results (Fig. 4) showed the beneficial effect of adrenalectomy among different treatments in patients with PA for the entire period (estimated 10 years) after index diagnosis. We found that adrenalectomy was consistently associated with a much lower long-term risk of ESRD, especially in those without residual hypertension after adrenalectomy. Patients with PA who received MRA had the highest incidence of ESRD.

E. Dose-Response Relationship Between Spironolactone and the Probability of Developing Incident ESRD

We further evaluated the dose-response relationship between MRA and ESRD. Targeting MRA users, we found the HR was 0.82 (95% CI, 0.67 to 0.96; $P < 0.001$) per defined daily dose (DDD) of MRA after adjustment for age, comorbidities, and influential drugs (c statistic 0.85; adjusted R^2 , 0.31). However, the GAM plot showed that the dose-response curve was non-linear (Fig. 5). One-half to one DDD of MRA was sufficient to prevent the initiation of long-term dialysis. This favorable effect increased in a dose-response manner up to one DDD, at which point a ceiling effect was reached.

3. Discussion

A. Main Findings

Regarding incident ESRD, patients with PA were comparable to those with EH after targeted treatment. We further demonstrated significantly lower incidences of ESRD and mortality in patients with PA who underwent adrenalectomy than in EH controls; no differences were seen in ESRD and mortality rates in patients with PA receiving MRA management compared with EH controls. According to our plot of 10-year probability of freedom from dialysis, prolonged duration of hypertension will increase the episode of incident ESRD. Our results show that patients with PA have a decreased incidence of ESRD after undergoing adrenalectomy, implying the importance of early diagnosis of APA and advising adrenalectomy for patients with APA and acceptable surgical risk.

To the best of our knowledge, the incidence of ESRD among patients with PA has not been reported. Our report details information regarding the association between different kinds of targeted PA treatments and the incidence of ESRD (*i.e.*, 3% as EH, with an average 5.2 years of follow-up). Coincidentally, in one retrospective study of 11,912 veterans with hypertension

Table 3. Comparison of Risks of ESRD and Death Between Patients With PA and Their EH Matches for the Whole PA Cohort and the APA Subgroup Only by Targeted Treatments

Therapeutic Option	Adrenalectomy						MRA					
	Crude Hazard Ratio (95% CI)		Adjusted Hazard Ratio (95% CI)		Competing Hazard Ratio (95% CI)		Crude Hazard Ratio (95% CI)		Adjusted Hazard Ratio (95% CI)		Competing Hazard Ratio (95% CI)	
	P		P		P		P		P		P	
ESRD Mortality	0.46 (0.23, 0.92)	0.028	0.46 (0.23, 0.93)	0.031	0.38 (0.19, 0.76)	0.007	1.09 (0.85, 1.41)	0.492	0.93 (0.72, 1.20)	0.567	1.08 (0.83, 1.39)	0.570
	0.22 (0.15, 0.34)	<0.001	0.22 (0.15, 0.34)	<0.001	NA	NA	1.05 (0.94, 1.18)	0.381	1.05 (0.94, 1.18)	0.380	NA	NA
	0.26 (0.18, 0.38)	<0.001	0.26 [0.18, 0.37]	<0.001	NA	NA	1.08 (0.97, 1.20)	0.175	1.08 (0.97, 1.20)	0.178	NA	NA
ESRD + mortality	0.53 (0.26, 1.11)	0.092	0.43 (0.21, 0.89)	0.024	0.55 (0.27, 0.89]	0.021	0.39 (0.12, 1.25)	0.113	0.31 (0.10, 1.03)	0.080	0.39 (0.12, 1.22)	0.100
	0.30 (0.19, 0.46)	<0.001	0.31 (0.20, 0.47)	<0.001	NA	NA	0.67 (0.42, 1.07)	0.095	0.61 (0.38, 0.99)	0.045	NA	NA
	0.34 (0.23, 0.50)	<0.001	0.35 (0.24, 0.52)	<0.001	NA	NA	0.65 (0.42, 1.00)	0.051	0.61 (0.39, 0.94)	0.027	NA	NA

Abbreviation: NA, not available.

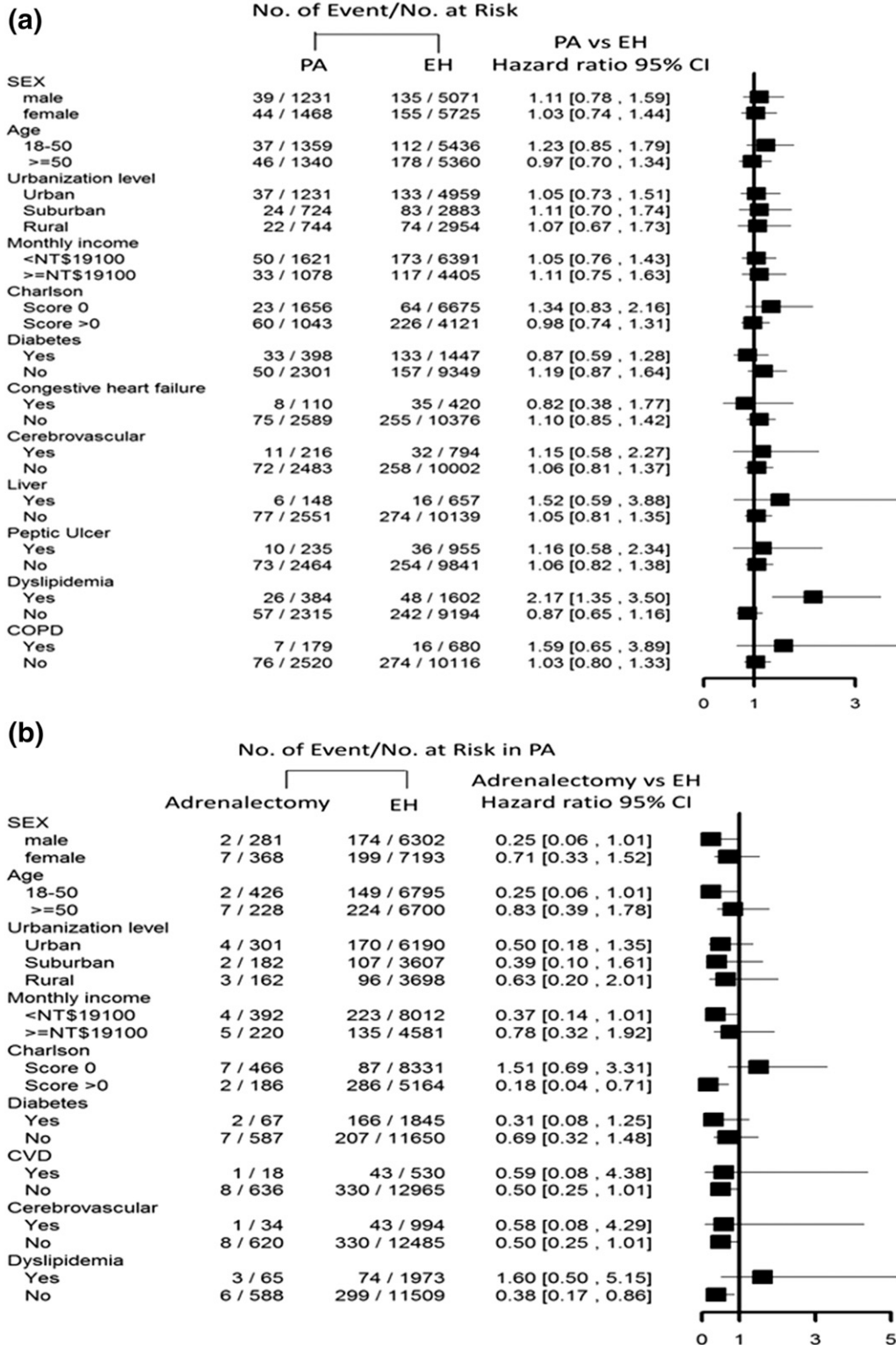


Figure 2. (a) Risk of incident ESRD between patients with PA and EH controls and (b) between patients with PA and adrenalectomy and their EH controls by participant characteristics. CVD, cardiovascular disease, NT\$, New Taiwan dollar.

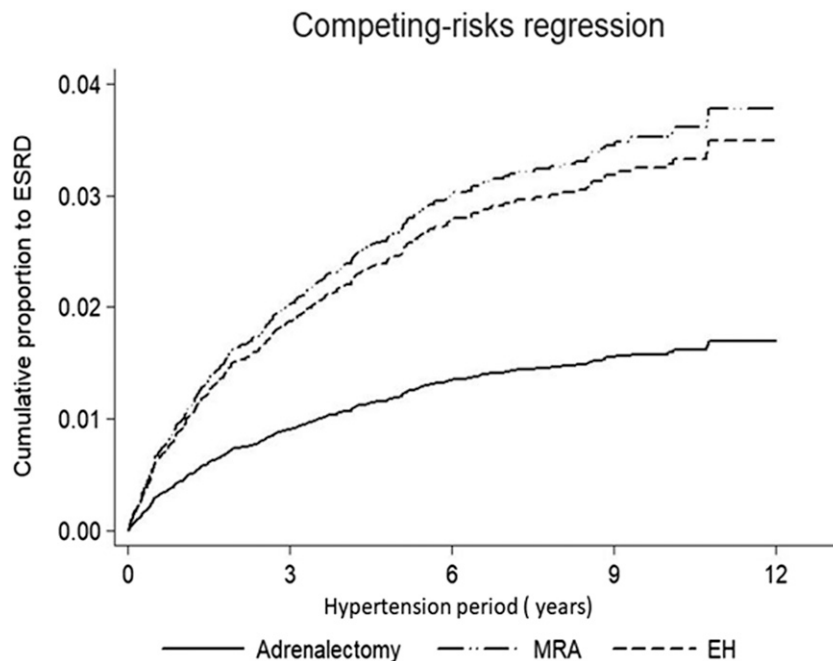


Figure 3. Cox regression model comparing incident ESRD in patients with adrenalectomy ($P = 0.021$), MRA ($P = 0.100$) treatment, and EH during the follow-up period with mortality taken as a competing risk.

who were followed up for an average of 9.8 years, the estimated cumulative ESRD rate was 2.8% [34].

A-1. Kidney function in aldosteronism

Persistent hypertension and electrolyte imbalance are not the only effects of PA; a proinflammatory effect causing end-organ damage has also been observed [3, 15]. The glomerular hemodynamic situation in PA also occurs in intraglomerular hypertension and excessive proximal tubular sodium reabsorption, which may trigger tubuloglomerular feedback and glomerular hyperfiltration via mineralocorticoid receptor activation in macula densa cells [35]. These data do not necessarily contradict the findings of our current study. Sodium retention-induced hypertension results in an augmented GFR and subsequent pressure natriuresis and nephropathy [36], despite the potential initial adaptive value of resetting of tubuloglomerular feedback in offsetting the renal sodium-retaining actions of aldosterone for tubular injuries [10]. Moreover, long-term excessive aldosterone concentrations have caused enduring hypertension due to increased arterial stiffness [37]. Growing evidence supports the idea that the nonhemodynamic actions of aldosterone are responsible for small- and medium-sized arterial injuries and nephropathy [6], as well as interstitial and renal vascular damage [38].

The hypertensive duration of PA is associated with heavy proteinuria and an increased renal resistance index [4]. The activation of mineralocorticoid receptors injures podocytes and disrupts the glomerular filtration barrier, leading to proteinuria and the progression of chronic kidney disease [39]. These findings raise the ultimate issues of early diagnosis and targeted treatment of PA with respect to kidney function.

A-2. Outcome in patients with PA/APA who underwent adrenalectomy or MRA treatment

Previous reports with a limited number of patients with PA showed that the subsequent rate of decline in glomerular filtration was comparable in PA and EH, whereas albuminuria did

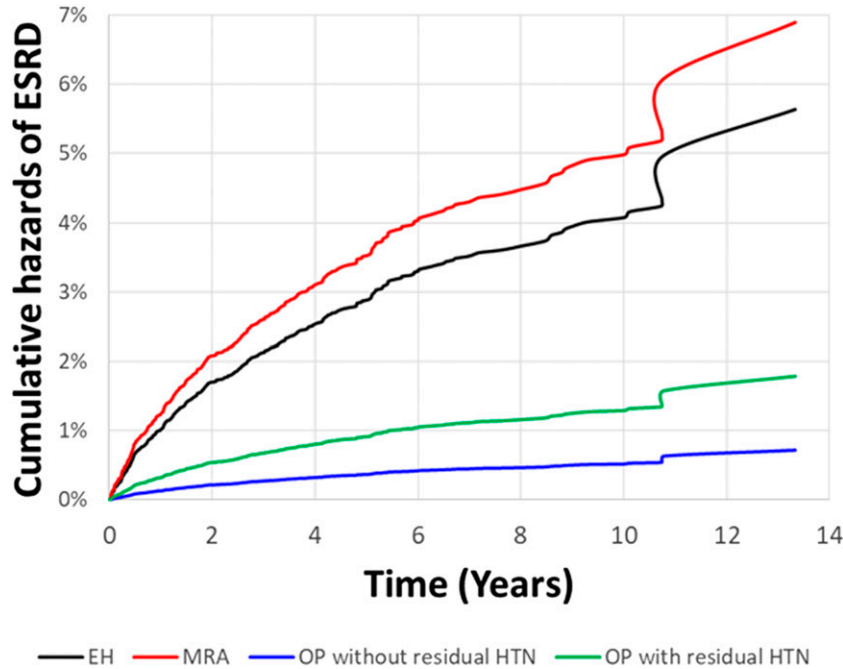


Figure 4. Future 10-y probability of freedom from ESRD events. The simulation curves were based on different scenarios of targeted treatment with MRA and adrenalectomy stratified by subsequent blood pressure. The incident ESRD was lower among patients with PA who underwent adrenalectomy, especially those without residual hypertension after adrenalectomy during follow-up. IHA, idiopathic hyperaldosteronism; OP.

not progress in the remainder of the follow-up period [9]. Adrenalectomy not only corrects high blood pressure and biochemical parameters but also reverses adverse vascular changes in patients with APA [40]. This finding is also supported by the observation in a recent study that patients with PA who underwent adrenalectomy had reduced risk of mortality and lower blood pressure levels than their matched EH controls [33].

In our analysis, the long-term solid outcome of ESRD rate decreased after surgical intervention compared with MRA treatment alone in patients with EH or PA, although decreased short-term kidney function was found in patients with APA after adrenalectomy [4]. Improvements in renal function include microalbuminuria due to the resolution of glomerular hyperfiltration in PA after adrenalectomy [9, 41]. Our results suggest that patients with APA who respond to adrenalectomy demonstrate better outcomes in 10-year probability of incident ESRD than those receiving MRA alone (Fig. 3). Furthermore, in patients with PA who respond to adrenalectomy, the absence of residual hypertension is less likely to lead to ESRD.

MRA treatment may induce an increase in aldosterone level and subsequently trigger a vicious cycle that leads to the insufficient effect of prescribed MRA on blocking mineralocorticoid receptors activated by the high plasma aldosterone level. On the other hand, it is likely that glucocorticoid cosecretion exists in patients with PA and at least partially contributes to associated adverse metabolic risks, including insulin resistance, type 2 diabetes mellitus, and osteoporosis [42–45]. In recent studies, adrenalectomy in patients with APA decreased glucocorticoid secretion, restored osteoporosis, attenuated adverse metabolic risks, and improved quality of life [42, 44–46], findings attributed to decreased glucocorticoid levels in addition to mineralocorticoid excess. The previously mentioned studies indicate that glucocorticoid cosecretion in PA may relate to systemic effects, which could further explain the benefits of adrenalectomy relative to MRA treatment.

Our study also revealed the importance of performing a dose-response analysis of MRA use, incident ESRD, and mortality. Further concerns about MRA prescription, such as drug adherence with an inadequate dose (Fig. 4), also exist. Our additional analysis of the DDD of

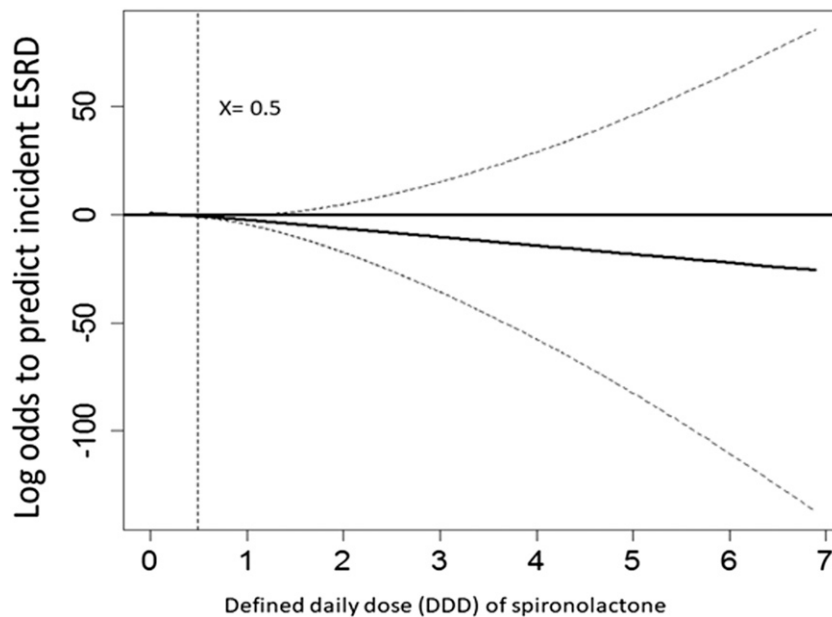


Figure 5. The dose-response relationship between spironolactone and the probability of developing incident ESRD using generalized additive modeling. The defined daily dose (DDD) of MRA = 0.5 is equal to a daily dose of 37.5 mg.

MRA on ESRD incidence also showed that only patients with PA who were exposed to a dose-dependent DDD >0.5 (dose equal to 37.5 mg of spironolactone) experienced decreased long-term ESRD. Dysmenorrhea and gynecomastia, presenting as adverse effects of anti-androgens, can result from spironolactone treatment, particularly in a dose-dependent relationship [47, 48]. These phenomena suggest that the usual doses of MRA in clinical practice may be too low; this problem warrants more attention.

A-3. Hypertensive duration and outcome in patients with PA

Our findings support the notion that adrenalectomy attenuates incident ESRD risk more than in patients with PA receiving MRA and in patients with EH. Patients with PA benefit from decreased blood pressure levels and use of fewer antihypertensive drugs after surgical management [49]. Hypertension in patients with PA can decrease within 1 year after surgery; sometimes it resolves generally or improves between 1 and 6 months after adrenalectomy [50]. As demonstrated by a prospective study, proteinuria and cystatin C (a marker of kidney function) dropped off soon after adrenalectomy but still failed to significantly decrease 1 year after the initiation of MRA treatment [4]. Given that adrenalectomy eliminates the source of aldosterone hypersecretion on the cardiovascular system, cerebrovascular system, and kidneys, it has been fully delineated that surgery successfully improves electrolyte levels and normalizes hypertension [51, 52]. According to the Primary Aldosteronism Surgical Outcome study, rates of partial to complete clinical success ranged from 37% to 47% [53]. Regarding to the incidence of ESRD, our study established the evidence that adrenalectomy decreased the risk in patients with major comorbidity, and the risk could be reduced up to 82% in those Charlsons score >0 . Our result disclosed the great benefit of patients with PA and major comorbidities who receive adrenalectomy when compared with patients with EH. (Fig. 2).

A-4. Strengths and limitations

This study has some limitations. This was a retrospective cohort study, and some biochemical data could not be obtained. Because of characteristics of the NHI database of Taiwan, several

potential confounders were lacking, including blood pressure, detailed renal function, proteinuria, and serum potassium, aldosterone, and renin levels, which are associated with response to treatment. This indeed limited our study, and further studies are needed to measure these effects. In addition, we focused on progression to ESRD after two different therapies as the renal outcome, rather than on developing or worsening of chronic kidney disease. Therefore, the absence of data such as estimated glomerular filtration rate (eGFR) and proteinuria level did not affect the renal outcome, as the registration of ESRD in the NHI database in Taiwan is credible and officially certified [54]. Moreover, we could not identify patients with PA and bilateral adenomas or unilateral hyperplasia, as the difference between them was ambiguous and always confused by micronodules. In fact, the incidence of the two subgroups is relatively low, and our results were robust across the different models, strengthening our conclusions. The diagnostic reliability of PA and its comorbidities was validated in detail in our cohort. Moreover, our analysis considered time-varying covariates, including MRA treatment and cumulative doses of MRA as a dose-dependent covariate in the model, ensuring that patients were at risk only when they had used these drugs.

Of note, the data retrieved and examined in this study came from health insurance registrations, for which diagnostic tests were not controlled as ideally as some single or multicenter clinical studies could have easily achieved. Nevertheless, these are real-life data with completed medical records that allowed us to scrutinize some large-scale, long-term follow-up outcomes in patients with PA among a population of 23 million people, according to *ICD-9* diagnostic and current procedural terminology (CPT) coding. We believe this big data approach offers important insights into the understanding of PA, which has not been examined and could not be offered with smaller-scale multicenter studies. Further prospective trials are warranted to confirm the significantly beneficial effect of adrenalectomy on incident ESRD among patients with PA.

4. Conclusion

Although patients with PA had an incidence of ESRD compatible with that of patients with EH after targeted treatment, our results highlight the importance of early diagnosis of PA and appropriate adrenalectomy for patients who are suitable for surgery to lower the risk of long-term incident ESRD and improve survival. MRA management did not provide comparable renal function and survival advantages. Further prospective studies are necessary to confirm our results.

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Correspondence: Vin-Cent Wu, MD, Room 1555, Clinical Research Building, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan. E-mail: q91421028@ntu.edu.tw.

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