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Risk of severe erectile dysfunction in primary hyperaldosteronism: A population-based propensity score matching cohort study ☆

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ABSTRACT

Background: An elevated plasma aldosterone level has been reported as an independent risk factor for severe erectile dysfunction in men. The aim of this study was to explore whether primary hyperaldosteronism patients experience erectile dysfunction after targeted treatment.

Methods: We conducted a population-based cohort study of men with newly identified primary hyperaldosteronism/aldosterone-producing adenoma from January 1, 1997, to December 31, 2009. Men with essential hypertension and normotension were matched to the primary hyperaldosteronism group according to propensity score matching.

Results: We identified 1,067 men with primary hyperaldosteronism (mean age, 46.7 ± 12.8 years) and matched them with the same number of men with essential hypertension or normotension. During the mean follow-up interval of 5.4 years, the incident rates of total erectile dysfunction were 5.7, 3.9, and 3.1 per 1,000 person-years for the primary hyperaldosteronism, essential hypertension, and normotension groups, respectively. Men with primary hyperaldosteronism exhibited a higher risk of erectile dysfunction compared with men with normotension (competing risks hazard ratio, 1.83), and no difference was seen in comparison with men who have essential hypertension. After adrenalectomy, men who have primary hyperaldosteronism had a higher risk of exhibiting severe erectile dysfunction compared with men who have essential hypertension (competing risks hazard ratio, 2.44) or normotension (competing risks hazard ratio, 2.90).

Conclusion: Men with primary hyperaldosteronism reported a higher incidence of severe erectile dysfunction than normotension controls despite targeted treatment. The risk of severe erectile dysfunction increased after men who have primary hyperaldosteronism underwent adrenalectomy. This result raises

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the possibility of severe erectile dysfunction after adrenalectomy and calls for a prospective large-scale study of men who have aldosterone-producing adenoma regarding their erectile function both before and after adrenalectomy.

Introduction

Primary hyperaldosteronism (PH) is one of the most common variants of endocrine hypertension, originating from pathologically high aldosterone levels.[1–3] Aldosterone enhances sodium retention, resulting in fluid accumulation, potassium excretion, poorly controlled hypertension, and hypokalemia.[1,4] In the resistant hypertensive population, the prevalence of PH is reported to be 17%–23%.[1] Regarding targeted treatment, adrenalectomy for aldosterone-producing adenoma (APA) and mineralocorticoid receptor antagonist (MRA) therapy for idiopathic hyperplasia of the adrenal glands could effectively improve patient outcomes.

Severe erectile dysfunction (ED) is the most common sexual problem in men. Severe ED is defined as a consistent or recurrent inability to acquire or sustain an erection of sufficient rigidity and duration for sexual intercourse.[5,6] In a Canadian study, the prevalence of ED was 16% among men from 20 to 75 years old.[7] Based on a Taiwanese study, the prevalence was 29% among those older than 40 years.[8] Furthermore, accumulated evidence shows a significant association between ED and cardiovascular disease (CVD).[9–11]

Antihypertensive drugs, psychosocial conditions, trauma, metabolic syndrome, diabetes mellitus, and endocrine disorders[12,13] could contribute to ED in PH patients. Higher plasma aldosterone concentrations were linked to ED in a recent report.[5] Aldosterone enhances the affinity of the α-receptors for noradrenaline in human penile corpus cavernsum tissue, harboring of mineralocorticoid receptors,[14,15] which promotes noradrenaline-induced contraction and thereby could result in ED.[14,15] In fact, patients with pheochromocytoma are at a higher risk of ED[16] and patients with Cushing's syndrome also suffer from reduced libido and ED.[17] The risk of incidence of ED in PH has not been well studied.

Our previous study reported on two men with APA, suffering from new-onset persistent ED after unilateral adrenalectomy.[18] After this study, we conducted a population-based propensity-matched cohort study using comprehensive information from Taiwan's National Health Insurance Research Database (NHIRD) to evaluate the association between PH and incident severe ED events after targeted treatment. We scrutinized the effects of various treatment options for PH on the risk of severe ED.

Methods

Data sources

The study database was obtained from the National Health Research Institutes (NHRI, Taipei,Taiwan) from the original Taiwan National Health Insurance (TNHI) data (23.12 million insured people), including outpatient visits, hospital admissions, prescriptions, intervention procedures, and disease profiles for more than 99% of the population in Taiwan.[19] To detect fraud in the National Health Insurance (NHI), the National Health Insurance Administration has been routinely auditing data submitted by health care institutions.[20] We used a validated algorithm to identify diagnosed PH patients and enrolled patients aged $\geq$ 18 years at the time of PH identification (Fig 1).[21]

Because our main study purpose was to construct a reliable PH sample, we aimed to have high values for both sensitivity and specificity. We also intended to find an algorithm with a positive predictive value of 0.9 to ensure the reliability of using the sample identified by the algorithm to portray PH patient clinical outcomes.[21]

For personal privacy, the identification numbers of all enrollees in the database were encrypted. This study was approved by the institutional review board of the NHRI (EC1011006-E).[9–16]

Study sample

To ensure clear identification, patients who had an earlier diagnosis of ED before the PH diagnosis or index date of control enrollment were excluded. Essential hypertension (EH) and normotension (NT) patients were matched to the PH group in a 1:1 ratio individually according to propensity score matching. The propensity scores were calculated from the risk factors presented in Table 1. The outcome of interest was severe ED as defined by 9th edition of the International Classification of Diseases, ICD-9 codes: 607.84 and 302.72, that recorded at least one inpatient NHI record or three outpatient records.[6] The ICD-9 code has been well-validated (supplementary methods). We defined severe ED based on International Index of Erectile Function (IIEF-5) scores less than 8 points and those recorded by ICD-9 code had a positive predictive value of 88.9%, a negative predictive value of 87.1%, a sensitivity of 80% and a specificity of 93.9%.

Identification of PH or APA patients receiving targeted treatment with adrenalectomy or MRA

APA patients were defined as PH patients with an ICD-9 record of an adrenal tumor. There was a very high positive predictive value (96%) for APA.[19] We confirmed the delivery of MRA medication and adrenalectomy by referring to reliable TNHI data on medication/surgical procedure codings, which were tied to reimbursement. Because adrenalectomy, MRA prescription, and potassium supplements (belonging to the ATC class A12B) for hypokalemia are the main treatments after a PH diagnosis, we used a Cox proportional hazards model with time-varying covariates to account for their influences on the risk of incident ED. Each patient was followed from the date of PH diagnosis to new onset of ED, death, or the end of the study (December 31, 2011), whichever occurred first. We compared the subgroup of patients with APA and without ED at the time of adrenalectomy, as well as control groups of EH and NT without ED at the time of matching from our time-varying analysis.

Comorbidities

The identification of a specific morbid condition from reviewing the NHI data was based on the criterion that there was at least one inpatient NHI record or three outpatient records with the corresponding disease diagnosis in the year before the time of first PH diagnosis and was well-validated.[21–26] The composite outcome was defined as all ED or death, whichever occurred first.

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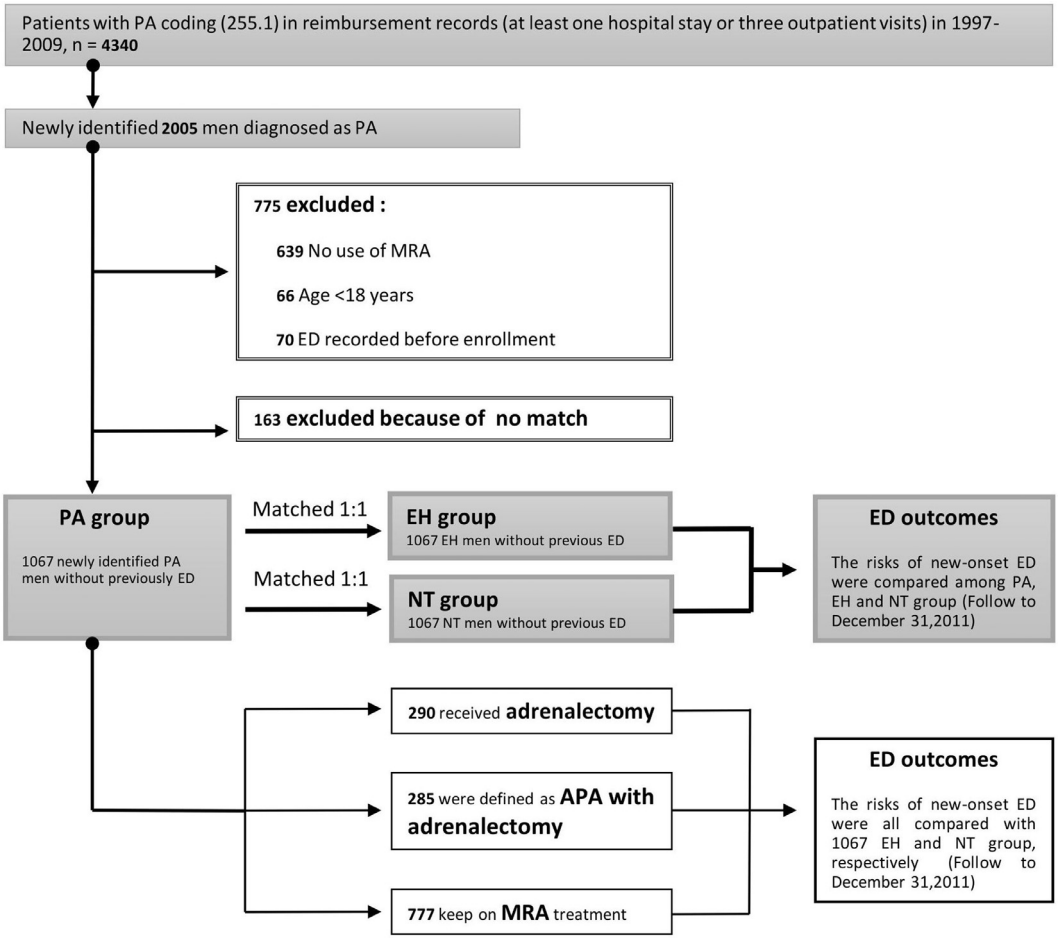

Fig. 1. The flowchart of inclusion and exclusion criteria in this study.
APA, aldosterone-producing adenoma; *ED*, severe erectile dysfunction; *EH*, essential hypertension; *MRA*, mineralocorticoid receptor antagonist; *NT*, normotension; *PH*, primary hyperaldosteronism.

Statistical analysis

Continuous variables are described as mean ± SD. Categorical variables are reported as counts or percentages. The propensity score was used for individual matching between the PH group and the ET or NT groups. We matched PH patients to EH patients using a greedy matching algorithm with a caliper width of 0.2 SD of the log odds of the estimated propensity score. We used the time-varying Cox proportional hazards model with targeted treatment as varying risks to evaluate the crude and adjusted hazard ratios (HRs) of ED.[9–12]

In further parametric modeling with regard to factors associated with outcomes, we adopted three modeling methods: simple Cox regression, multivariable Cox regression, and competing risk regression. Because of the high mortality rate among end-stage renal disease patients of advanced age, competing-risk regression was performed using the Fine and Gray model by considering the subdistribution hazard.[27]

We used R software, v 2.8.1 (Free Software Foundation, Inc, Boston, MA). The competing risk analysis was performed with Stata/MP v 12 (Stata Corporation, College Station, TX).

Results

We identified 1,067 qualified PH men (mean age, 46.7 ± 12.8 years) during the study period. There were 1,067 matched EH patients (mean age, 47.8 ± 14.1 years) and 1,067 matched NT patients (mean age, 46.7 ± 12.8 years) according to the propensity score at the same index time. Table 1 summarizes the enrollee characteristics. The groups of PH, EH, and NT patients shared similar propensity scores, age, and duration of hypertension. Baseline comorbidities were well matched among the three groups. All antihypertensive medications had similar proportions. The doctor visiting times and administration of various types of medication were similar between groups. In the comparison of all-cause mortality, APA patients had a lower mortality rate than EH or NT patients. Regarding incidence of severe ED, there was no significant difference between the PH and EH groups. The men in the PH group had a significantly higher rate of severe ED incidence than those in the NT group ($P = .046$). The comparisons between PH or APA and NT patients are presented in Supplemental Table I.

Table 2 presents the association between PH and the risk of incidents of severe ED. During the mean follow-up interval of 5.4 years, the total incident rates of severe ED were 5.7, 3.9, and 3.1 per 1,000 person-years for the PH, EH, and NT groups, respectively. The mean year to ED after adrenalectomy was 2.8 ± 1.8 years. The PH patients exhibited a higher risk of incidents of severe ED compared with the NT patients (competing risks HR 1.83, taking account of mortality), and no difference was noted in the comparison with EH patients.

Table 3 demonstrates the risk of incidents of severe ED associated with PH patients after stratifying by targeted treatment (ie, unilateral adrenalectomy or MRA). There were 13 ED events in 285 APA patients after adrenalectomy, over 5.4 years. The incidence

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Table 1
Comparison of characteristics between PA or APA and EH patients from 1997 to 2009 after propensity score matching

	Matched PA/EH		SD	Matched APA/EH		SD
	EH ($n=1,067$)	PA ($n=1,067$)		EH ($n=322$)	APA ($n=322$)	
Variables						
Propensity score	−3.88 ± 1.83	−3.88 ± 1.83	0.000	−1.09 ± 0.43	−1.09 ± 0.43	0.000
Age (y)	47.8 ± 14.1	46.7 ± 12.8	0.082	45.4 ± 13.54	46.07 ±10.78	−0.055
Baseline comorbidity						
CHF	3 (0.28%)	2 (0.19%)	−0.019	0 (0.00%)	1 (0.31%)	0.079
CVD	36 (3.37%)	30 (2.81%)	−0.032	5 (1.55%)	10 (3.11%)	0.103
CKD	22 (2.06%)	21 (1.97%)	−0.007	2 (0.62%)	2 (0.62%)	0.000
COPD	15 (1.41%)	28 (2.62%)	0.087	4 (1.24%)	5 (1.55%)	0.026
CAD	6 (0.56%)	3 (0.28%)	−0.043	4 (1.24%)	1 (0.31%)	−0.106
Dementia	7 (0.66%)	4 (0.37%)	−0.039	1 (0.31%)	2 (0.62%)	0.046
Diabetes Mellitus	111 (10.40%)	98 (9.18%)	−0.041	35 (10.87%)	33 (10.25%)	−0.020
Hemiplegia	5 (0.47%)	3 (0.28%)	−0.031	2 (0.62%)	2 (0.62%)	0.000
Liver disease	44 (4.12%)	57 (5.34%)	0.057	16 (4.97%)	16 (4.97%)	0.000
Peptic ulcer	57 (5.34%)	49 (4.59%)	−0.035	12 (3.73%)	13 (4.04%)	0.016
PVD	9 (0.84%)	5 (0.47%)	−0.046	4 (1.24%)	1 (0.31%)	−0.106
RA	3 (0.28%)	2 (0.19%)	−0.019	1 (0.31%)	0 (0.00%)	−0.079
Solid tumor	10 (0.94%)	12 (1.12%)	0.019	2 (0.62%)	0 (0.00%)	−0.112
SLE	5 (0.47%)	0 (0.00%)	−0.097	4 (1.24%)	0 (0.00%)	−0.159
Af	9 (0.84%)	4 (0.37%)	−0.060	2 (0.62%)	2 (0.62%)	0.000
Dyslipidemia	108 (10.12%)	117 (10.97%)	0.027	44 (13.66%)	31 (9.63%)	−0.126
Alzheimer	0 (0.00%)	1 (0.09%)	0.043	0 (0.00%)	1 (0.31%)	0.079
Parkinson	7 (0.66%)	2 (0.19%)	−0.072	0 (0.00%)	1 (0.31%)	0.079
BPH	22 (2.06%)	17 (1.59%)	−0.035	2 (0.62%)	2 (0.62%)	0.000
Urinary incontinence	5 (0.47%)	2 (0.19%)	−0.049	0 (0.00%)	0 (0.00%)	
Nocturia	0 (0.00%)	1 (0.09%)	0.043	0 (0.00%)	1 (0.31%)	0.079
Urinary calculi	34 (3.19%)	39 (3.66%)	0.026	10 (3.11%)	12 (3.73%)	0.034
Prostate cancer	2 (0.19%)	2 (0.19%)	0.000	1 (0.31%)	0 (0.00%)	−0.079
Antihypertensive medications						
Alpha-blocker	115 (10.78%)	117 (10.97%)	0.00602	41 (12.73%)	40 (12.42%)	−0.0094
Beta-blocker	495 (46.39%)	483 (45.27%)	−0.0226	176 (54.66%)	174 (54.04%)	−0.0125
ACEI or ARB	511 (47.89%)	512 (47.99%)	0.00188	170 (52.80%)	180 (55.90%)	0.06237
CCB	712 (66.73%)	700 (65.60%)	−0.0238	252 (78.26%)	253 (78.57%)	0.00755
Diuretic	524 (49.11%)	488 (45.74%)	−0.0676	165 (51.24%)	153 (47.52%)	−0.0745
MRA	86 (8.06%)	304 (28.49%)	0.54816	26 (8.07%)	90 (27.95%)	0.53541
Outcomes						
ED	21 (1.97%)	33 (3.09%)	0.072	10 (3.11%)	15 (4.66%)	0.080

ACEI, angiotensin-converting-enzyme inhibitors; *Af*, atrial fibrillation; *ARB*, angiotensin II receptor blockers; *BPH*, benign prostate hypertrophy; *CAD*, coronary artery disease; *CCB*, calcium-channel blocker; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CVD*, cerebrovascular disease; *ED*, erectile dysfunction; *EH*, essential hypertension; *MRA*, mineralocorticoid receptor antagonist; *NT*, normotension; *PA*, primary aldosteronism; *PVD*, peripheral vascular disease; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *SDf*, standardized difference.

rate of severe ED is 7.3 per 1,000 person-years. There were 20 severe ED events in 777 PH patients with MRA. The incidence rate of ED is 4.1 per 1,000 person-years. A significant trend toward higher ED risk was noted in PH patients after adrenalectomy; this was higher than that in the EH (competing risks HR, 2.44; $P=.011$) and NT patients (competing risks HR, 2.90; $P=.003$). However, there was no difference in incidence of ED between PH patients who had MRA treatment, and the EH or NT groups. Defined APA patients showed a similar risk of incidents of severe ED as PH patients receiving adrenalectomy. Using MRA alone did not increase the risk of incidence of severe ED in APA patients, when compared with the EH or NT group.

Figure 2 presents the conditional effect on the log odds ratio to predict ED with spline age, grouped by PH patients with adrenalectomy, EH patients, and NT patients. The conditional effect plot shows that the slope of the response function was highest in patients treated by adrenalectomy. Moreover, the oldest men had the highest risk of severe ED.

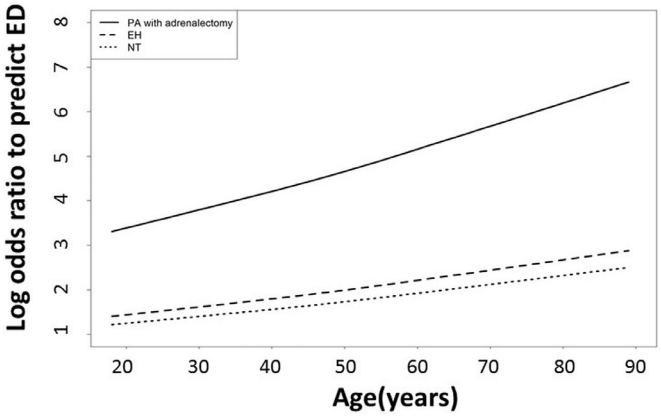

Fig. 2. The conditional effect plot shows the relationship of log odds ratio to predict ED with spline age, grouped by PH patients with adrenalectomy and EH and NT patients. The slope of the response function is the highest in PH patients with adrenalectomy and the oldest ages also have the most response to ED.
ED, severe erectile dysfunction; *EH*, essential hypertension; *NT*, normotension; *PH*, primary hyperaldosteronism.

Discussion

This is the first population-based cohort study to explore the association between PH and the risk of incidence of severe ED, particularly including the effects of targeted treatment on the severe ED rate. The present study highlights a crucial result, showing that PH men who underwent unilateral adrenalectomy had a higher risk of incidence of severe ED than the EH controls, and

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Table 2
Incidence and risks of ED in PA patients compared with matched EH and NT patients

							Crude		Adjust*		Competing risks†	
	Events	Person-years	Incidence rate per 1,000 person-years	Events	Person-years	Incidence rate per 1,000 person-years	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
	EH			PA			PA versus EH					
ED	21	5,377	3.9	33	5,759	5.7	1.47 (0.85, 2.54)	.167	1.49 (0.86, 2.57)	.156	1.52 (0.88, 2.63)	.130
	NT			PA			PA versus NT					
ED	18	5,742	3.1	33	5,759	5.7	1.84 (1.04, 3.27)	.037‡	1.83 (1.03, 3.25)	.039‡	1.83 (1.03, 3.25)	.038‡

PA, primary aldosteronism; *ED*, erectile dysfunction; *EH*, essential hypertension; *NT*, normotension.
* Stepwise all variables in Table 1, adrenalectomy, steroid and potassium supplement for hypokalemia as time varying risks.
† Adjusted with age, sex, and propensity score.
‡ $P < .05$.

Table 3
Incidence and risks of ED in PA and APA patients compared with matched EH and NT patients according to target treatments

	Adrenalectomy						MRA					
	Crude Hazard ratio (95% CI)	*P*	Adjust* Hazard ratio (95% CI)	*P*	Competing† Hazard ratio (95% CI)	*P*	Crude Hazard ratio (95% CI)	*P*	Adjust* Hazard ratio (95% CI)	*P*	Competing† Hazard ratio (95% CI)	*P*
PA versus EH												
ED	2.21 (1.10, 4.43)	.030‡	2.35 (1.16, 4.76)	.017‡	2.44 (1.23, 4.86)	.011‡	1.21 (0.66, 2.23)	.540	1.20 (0.65, 2.22)	.550	1.18 (0.64, 2.17)	.610
APA versus EH												
ED	2.28 (1.13, 4.62)	.022‡	2.37 (1.16, 4.86)	.018‡	2.45 (1.23, 4.86)	.011‡	0.92 (0.21, 3.97)	.909	0.92 (0.21, 3.99)	.913	0.72 (0.17, 3.07)	.660
PA versus NT												
ED	2.85 (1.39, 5.85)	.004§	2.84 (1.38, 5.81)	.004§	2.90 (1.43, 5.90)	.003§	1.50 (0.79, 2.83)	.220	1.49 (0.78, 2.81)	.220	1.49 (0.78, 2.81)	.220
APA versus NT												
ED	3.03 (1.47, 6.28)	.003§	3.01 (1.46, 6.24)	.003§	3.01 (1.49, 6.11)	.002§	1.06 (0.24, 4.69)	.935	1.11 (0.25, 4.88)	.894	1.01 (0.24, 4.29)	.990

APA, aldosterone-producing adenoma; *CI*, confidence interval; *ED*, erectile dysfunction; *EH*, essential hypertension; MRA, mineralocorticoid receptor antagonist; *PA*, primary aldosteronism.
* Stepwise all variables in Table 1, steroid and potassium supplement for hypokalemia as time varying risks.
† Adjusted with age, sex, and propensity score.
‡ $P < .05$.
§ $P < .01$.

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those receiving MRA treatment did not. The time-varying Cox proportional hazards model for the analysis of HR supported the risk of unilateral adrenalectomy on incidence of severe ED. Based on the conditional effect plot, this result also provides evidence that older PH men and the PH men with adrenalectomy have a higher risk of severe ED compared to EH or NT controls. The standard targeted treatment for APA men deserves further discussions according to our findings.

Long-term exposure to excess aldosterone has been documented as causing damage to the cardiovascular system. Increased left ventricular mass, greater carotid intima-media thickness, arterial stiffness, and reduced endothelial function could result in worse cardiovascular complications.[28–31] Targeted treatments, including adrenalectomy and MRA treatment, can reverse cardiovascular morbidity in PH patients. Strauch et al[46] and Lin et al[47] both reported improved adrenalectomy arterial stiffness in PH patients. MRA, an aldosterone receptor blocker, was effective at reducing blood pressure in PH patients and resulted in a significant decrease in biomarkers of collagen synthesis, left atrial dimension, left ventricular wall thickness and mass.[32,33] In view of this, early detection of PH is necessary because effective targeted treatment could affect hypertension-related outcomes. Considerable evidence has shown that ED is significantly associated with CVD and subsequent all-cause mortality.[9,34,35] However, there are few reports regarding ED in APA men undergoing adrenalectomy and their subsequent risk of CVD. More attention in clinical practice should be exerted to follow APA men undergoing adrenalectomy for incidence of ED and associated CVD events.

The effect of aldosterone on erectile function is controversial. Wu et al[5] concluded that elevated plasma aldosterone is an independent risk factor for ED. Muguruma et al[15] suggested that aldosterone acts to enhance noradrenaline-induced contraction of human penile corpus cavernosum tissue and is one of the restraining factors for human penile erection. Furthermore, endothelial cells produce nitric oxide (NO), which is a strong trigger of vessel dilation and erectile function. In view of results showing that aldosterone infusion induces endothelial dysfunction in rats,[5] it is possible that aldosterone impairs human erectile function because of abnormal NO production. On the contrary, a few studies have shown that aldosterone deficiency plays a role in the pathogenesis of ED. In a rat model, penile NO synthesis activity was significantly decreased in the bilateral adrenalectomized group compared with the intact group.[36] Impaired erectile response in animals that had undergone adrenalectomy could be restored with the administration of hydrocortisone and aldosterone.[37] In clinical studies, sexual dysfunction in men has been observed at the onset of autoimmune Addison's disease. However, after adrenal cortical hormone replacement, sexual dysfunction was reversible.[37] Cortisol and aldosterone deficiency may both play important roles in ED. According to this evidence, the overproduction of or a deficiency in adrenal cortical hormones may both result in ED.

The crucial effect of the renin-angiotensin system (RAS) on erectile function had been widely discussed.[38] As an endocrine system, RAS is upregulated according to blood volume and renal perfusion.[39,40] Dehydration induces renin secretion from juxtaglomerular cells in the kidney. Subsequently, angiotensin made in the liver is cleaved by renin into angiotensin I (Ang I). Then, angiotensin-converting enzyme (ACE) promotes the conversion of Ang I into angiotensin II (Ang II), which stimulates aldosterone production. Accumulated evidence has revealed that elevated Ang II levels contribute to the development of ED in humans and different animal models. RAS blockers may be beneficial in patients with ED.[38] In our study, restored plasma renin activity (PRA) and Ang II levels after unilateral adrenalectomy may explain why PH patients who underwent unilateral adrenalectomy had a higher risk of incidence ED than EH patients. This probably occurred because long-term exposure to excess aldosterone suppresses PRA and Ang II. With the recovery of PRA and Ang II, the associated vasoconstriction and changes in endothelial function may lead to ED. Other possible mechanisms of postadrenalectomy ED include insufficient androgen of adrenal origin, impaired NOS activity after adrenalectomy, and postoperative normalization of blood pressure actually resulting in relative hypotension (in comparison with blood pressure before surgery). These factors may contribute to hypoperfusion of the penis during an erection.[18]

MRA is known to exert serious organic side-effects, including ED, gynecomastia, and mastodynia in men.[12] The possible mechanisms are based on the effect of MRA on both gonadal and adrenal steroidogenesis and as an antiandrogen at the target tissue level.[41] Notably, side effects of spironolactone are dose dependent.[1] Our results demonstrate that PH patients receiving MRA treatment did not have an increased risk of incidence of ED compared with EH or NT patients in this population-based cohort. According to a previous study, renin values remain low during MRA therapy in selected PH patients.[42] Persistent low PRA and Ang II levels may not be contributory to ED, which may explain the absence of increased ED risk in PH patients receiving MRA treatment compared with EH or NT patients. Another rational cause is that clinicians prefer to prescribe low-dose spironolactone to PH men rather than moderate or high doses, if hypertension is under control, because of the well-known ED side effect of spironolactone.

Several limitations should be addressed in this study. First, the diagnosis of PH, ED, and other comorbidities depended on administrative claims data and misclassification cannot be ruled out. Despite this, based on previous studies using the NHIRD, the identification of PH patients was highly reliable.[6,43–45] We have further validated the ICD-9 coding from real-world practice and focused on severe ED because the identification has high positive predictive value. Some serious deficiencies should be considered. Design of the study makes it impossible to identify the actual diagnostic criteria used to make a diagnosis of ED, and variable definitions may be another source of variability, rather than true difference in the incidence. Because the diagnosis of ED relies on the patient's subjective self-reported complaint and there are no routine objective laboratory or imaging tests to prove or document the diagnosis, there is a relatively high probability of response or reporting biases. Second, laboratory data, physical examination, and lifestyle data could not be obtained from the NHIRD. Thus, potential confounders, such as plasma aldosterone concentration, plasma renin activity, body mass index, or psychologic performance could not be adjusted. Cosecretion from an adrenal adenoma could not have been identified in this study. Third, it is a concern that the event rate is quite low and just a handful of patients reporting or not reporting mild ED could drastically alter our analysis, therefore we focused on patients with severe ED. Fourth, healthy-user (ascertainment) bias was possible, meaning that patients on medication may have changed to healthier behaviors to improve the outcomes. Therefore, to reduce this bias, we also identified the number of outpatient visits before the index date. We used doctor visiting times and different types of medication as a proxy to adjust for the socioeconomic status and frequency of health care utilization–seeking behavior. The unmeasured health behaviors associated with PA/APA would not be different from EH because the frequency of all medications and the intensity of health care resource usage, after matching at the index date, were similar for the two groups. Fifth, although we matched HA patients with their controls with propensity scores with compatible comorbidities, some confounding risks could not be adjusted. However, we adjusted for the most severe morbidities. From the competing risk analysis, taking mortality of risk, patients who received adrenalectomy were more likely to have ED. Finally, because of the limitations of our study, we were unable to determine whether the ED is

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transient, like some other postadrenalectomy phenomena (eg, relative hypotension, hyperkalemia) or it tends to be prolonged.

In conclusion, PH men had a higher incidence of severe ED than normotensive controls. Our study found that the risk of ED increased among PH men who underwent adrenalectomy, and those receiving MRA treatment did not differ from the controls. Most important, our results call for a further prospective large-scale study to investigate the influence of adrenalectomy on men with APA.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.08.020.

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