Title: Long-term Mortality and Cardiac Outcomes in Patients with Clinical Aldosterone Producing Adenomas after Target Treatments
Brief title: Clinical APAs after Target Treatments

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Research in context

Evidence before this study

We did a systematic review of studies that focused on the long-term mortality, cardiovascular events, targeted treatments, and complete clinical success in patients with clinical aldosterone producing adenoma (cAPA). Major electronic databases (including, but not limited to, PubMed, Embase, medRXIV, and Web of Science without language restriction) were searched for articles published by Dec, 2020. This search was complemented by interrogation of grey literature and manual searching of reference lists. The review was done in accordance with PRISMA guidelines. We noticed that there was no prospective or retrospective cohort report specifically focused on APA patients and their related long-term outcomes of interest. A previous systematic review focusing on primary aldosteronism (PA) patients showed that both surgery and medical treatments are of considerable value to clinical outcome improvement (2019). Several subgroup analyses of APA patients based on population databases from the health insurance registry showed that adrenalectomy could decrease mortality (2016, 2018) and the incidence of congestive heart failure (CHF) (2019) and stroke (2020), but were not focused on clinical success after adrenalectomy. On the contrary, a cohort study showed that adrenalectomized cAPA patients have a similar survival rate as compared to that of optimally treated essential hypertensive (EH) patients (2018).

Added value of this study

The incidence rate of all-cause mortality was 0.76 per 1000 person-years of all cAPAs after targeted treatments. Both HTN-remission and non-cured hypertension (defined by the Primary Aldosteronism Surgical Outcome criteria, PASO) after adrenalectomy could attenuate all-cause mortality of cAPA patients compared to that of the EH controls, while non-cured hypertension after adrenalectomy could not decrease the risk of incident major cardiac events (MACE) relative to that of EH controls. Adrenalectomy, in comparison to mineralocorticoid receptor antagonist (MRA) treatment for cAPA patients, led to lower incidence of long-term mortality, and incident MACE and CHF, but similar incident atrial fibrillation (Af). Plasma aldosterone concentration (PAC) of more than 27 ng/dL after adrenalectomy or plasma renin activity (PRA) of less than 0.6 ng/mL/hr after MRA treatment could be associated with higher risks of mortality or MACE.

Implications of all the available evidence

Our study found that cAPA patients would have lower long-term risk of death after adrenalectomy, regardless of whether the surgery resolved their hypertension or not, implicating the importance of early diagnosis of cAPA and advising adrenalectomy as an optimal treatment for cAPA patients. However, postoperative non-cured hypertension and MRA therapy could still be associated with higher risks of MACE than that of EH controls in cAPA patients.

The risks of MACE, CHF, and Af could not be attenuated in cAPA patients taking MRA as opposed to those of the EH controls. Monitoring post-operative PAC and post-MRA treatment PRA in the cAPA patients could forecast future mortality or MACE.

Abstract

Background

There is no good long-term mortality and cardiac outcome study of clinical aldosterone producing adenoma (cAPA) patients after various treatments. This study reports long-term cardiac and mortality outcomes of cAPA patients who underwent medical therapy or adrenalectomy, against those with essential hypertension (EH).

Methods

Using an inception observational cohort, we examined longitudinal outcomes for 858 cAPA patients among 1220 primary aldosteronism (PA) patients and another 1210 EH controls patients diagnosed throughout 2007-2017. cAPA patients underwent unilateral adrenalectomy or mineralocorticoid receptor antagonist (MRA) therapy as opposed to standard medical treatment for EH. Operated cAPA patients were grouped via 1-year post-therapy statuses according to the Primary Aldosteronism Surgical Outcome (PASO) criteria.

Long-term all-cause mortality was the primary outcome. Secondary outcomes were incident major cardiovascular events (MACE), atrial fibrillation (Af) or congestive heart failure (CHF) after the PA confirmatory diagnosis.

Findings

272 (49.9%) of 545 surgically-treated cAPA patients achieved PASO clinical complete success (hypertension-remission). After follow-up of 6.3±4.0 years, both hypertension-remissive (HR, 0.54, p< 0.001) and non-cured (HR, 0.61, p< 0.001) groups of these cAPA patients showed lower all-cause mortality thanEH controls, whereas the non-cured group had a higher risk of incident MACE (sub-hazard ratio (sHR), 1.41, p= 0.037). MRA-treated cAPA patients had a higher risk of MACE (sHR, 1.38, p= 0.033), Af (sHR,1.62, p= 0.049) and CHF (sHR, 1.44, p= 0.048) than those of EH controls, with mortality as a competing risk. Using inverse probability of treatment-weighted matching and counting adrenalectomy as a time-varying factor, treatment with adrenalectomy was associated with lower all-cause mortality (HR 0.57; p= 0.035), MACE (HR 0.67; p= 0.037) and CHF (HR 0.49; p= 0.005) relative to MRA therapy. Plasma aldosterone concentration > 27 ng/dL after adrenalectomy or plasma renin activity < 0.6 ng/mL/hr after MRA treatment could be associated with higher risks of mortality or MACE.

Interpretation

Adrenalectomy, independent of post-surgical hypertension-remission, was associated with lower all-cause mortality of cAPA patients. However, post-adrenalectomy non-cured hypertension and/or MRA therapy in cAPA patients could still have higher MACE risk than EH controls. We further documented a more beneficial effect of adrenalectomy over MRA treatment on long-term mortality, MACE, and CHF in cAPA patients. (NCT00917345)

Key words: Primary aldosteronism, mortality, adrenalectomy, mineralocorticoid receptor antagonist, TAIPAI

Abbreviations list:
Af: atrial fibrillation

AVS: adrenal venous sampling
cAPA: clinical aldosterone-producing-adenoma
CHF: congestive heart failure
EH: essential hypertension
HR: hazard ratio
IHA: idiopathic hyperplasia of adrenal glands
MRA: mineralocorticoid receptor antagonist
MACE: major cardiovascular events
MAPM: multiple aldosterone-producing micronodules
PA: Primary Aldosteronism
PASO: Primary Aldosteronism Surgical Outcome
PAC: Plasma aldosterone concentration
PRA: Plasma renin activity
sHR: sub-hazard ratio

INTRODUCTION

Although the role of primary aldosteronism (PA) in increasing cardiovascular risks is well-known, along with the potential of targeted therapies for PA,[1,2] it is still unclear whether pharmacological or surgical targeted treatment [3] for clinical aldosterone producing adenoma (cAPA) could yield better complete hypertension-remission, as defined by recent Primary Aldosteronism Surgical Outcome (PASO) criteria.[4] Therefore, which PASO status could be translated into lower long-term mortality, major adverse cardiovascular events (MACE), and/or other cardiac outcomes remains unknown.[5]

A systematic review indicated that clinical outcomes were similar in PA patients treated with mineralocorticoid receptor antagonist (MRA) or adrenalectomy.[6] However, since patients with idiopathic adrenal hyperplasia (IHA) bear significantly different genotypes and heterogeneous phenotypic characteristics compared to cAPA patients,[7,8] optimal treatment options for cAPA patients to achieve better long-term outcomes remains unknown.

A long-term research registry cohort reported higher risks of cardiometabolic events and death among PA patients after MRA treatment (non-surgical group) than their essential hypertension (EH) counterparts.[9] In another cohort of PA patients, surgical or medical treatment had long-term cardiovascular outcomes comparable to EH controls.[10] While we have shown via subgroup analyses from a population insurance database that adrenalectomy was associated with lower long-term all-cause mortality (independent of hypertension-remission) in PA patients, whether MRA treatment could lead to similar beneficial effects regarding prevention of MACE or other cardiac issues and/or survival advantage among cAPA patients is still uncertain.[11,12]

We aimed to investigate the long-term outcomes, especially mortality, MACE, atrial fibrillation (Af), and congestive heart failure (CHF) of the cAPA patients who underwent medicinally- or surgically-targeted treatment relative to the EH controls, and to focus on the association of outcomes with the statuses of post-treatment hypertension-remission.

Methods

Patients

This is a prospectively designed inception observational cohort. The Taiwan Primary Aldosteronism Investigation (TAIPAI) group enrolled possible PA patients who first had their aldosterone-to-renin ratio (ARR) screened for PA case detection and were followed-up thereafter. We analyzed all patients prospectively registered in the TAIPAI database [5,13-18] from 2007-2017.

We enrolled 1220 patients diagnosed with PA and another 1231 patients with EH; EH patients were screened negative for secondary hypertension during the study period. Demographic and clinical characteristics of all PA and EH patients at their diagnosis confirmatory stage were recorded. Patients were followed-up from the date of PA diagnosis to either death or the end of the study (December 31, 2017).

Diagnosis and further lateralization of clinical APA

Screening, confirmation, and subtype identification of PA were performed in hypertensive patients according to the standard TAIPAI protocol and aldosteronism consensus [5,19] (referring to online-only Supplement). cAPA was identified on the basis of the following criteria[20]: (1) autonomous excess aldosterone production evidenced with ARR > 35 ng/dL per ng/ml/hr, TAIPAI score > 60%, [16] and seated post-saline

loading plasma aldosterone concentration (PAC) > 16 ng/dL; (2) unilateral adrenal adenoma evidenced with a CT scan; (3) lateralization of aldosterone hypersecretion on the ipsilateral side of the adrenal adenoma via adrenal vein sampling (AVS) or dexamethasone-suppression radioiodinated I-6-B-iodomethyl-19-norcholesterol NP-59 SPECT/CT scan ; and (4; only for cAPA after adrenalectomy) pathologically proven positive CYP11B2-staining adenoma or multiple aldosterone-producing micronodules (MAPM) via immunohistochemistry (IHC). [21 20]

Exposure

Main target treatments following cAPA diagnosis were either adrenalectomy or MRA prescription. After PA diagnosis was ruled out, EH controls were treated with standard anti-hypertensive medications and monitored clinically according to best practices.

Outcomes of interest

All-cause mortality was the primary outcome; secondary outcome was *de-novo* (incident) MACE, Af and/or CHF after the index date of PA confirmation. MACE included the incidence of coronary events including non-fatal myocardial infarction (MI), coronary artery bypass graft (CABG), stroke, and coronary angiography. To corroborate long-term outcome events, we have validated TAIPAI records with the Taiwan National Health Insurance Research Database (referring to Supplement).

Ethical considerations

Ethical approval (approval number: 201801049RIND, NCT00917345) was obtained from the institutional review board of the National Taiwan University Hospital. Written informed consent for clinical data collection and research use was obtained from participants at study enrollment. All methods were carried out in accordance with approved guidelines.

Clinical success after unilateral adrenalectomy

Patients were evaluated monthly during the first 3 months post-operatively and every 3 months thereafter. This cohort followed up patients' blood pressure and biochemistry under a standard protocol at one year after adrenalectomy. cAPA patients who underwent MRA therapy were followed-up every 3 months. *De-novo* events of mortality and MACE, Af, and CHF were recorded. At 12 months, for those who underwent adrenalectomy, complete clinical success (hypertension-remission) was defined as normal blood pressure without usage of anti-hypertensives[6] according to the PASO criteria on clinical consensus.[4]

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as percentages. As adrenalectomy and MRA prescription are main target treatments following cAPA diagnosis, we used a Cox proportional hazards model with time-varying covariates to account for healthy survivor bias on outcomes of interest. Time-varying covariates took the value 0 before the beginning of treatments and could switch to 1 at the start of treatment. Each patient was followed from the date of the PA diagnosis to death or the end of the study (December 31, 2017), whichever occurred first.

To obtain unbiased estimates of average treatment effects comparing adrenalectomy and non-adrenalectomy groups, the inverse probability of treatment weighted (IPTW) method was used. The IPTW method with propensity score was applied to correct biases in basic characteristics and outcomes and has the effect of creating a pseudo-population with a covariate distribution of the individual treatment groups similar to that of the overall study population. Covariate balance was assessed

by examining the magnitude of any weighted residual differences between treatment groups. (Figure S1) Taking mortality as a competing risk, we drew Cox survival curves separately for patients receiving/not receiving adrenalectomy and conducted the log-rank test to compare risk of death among the patient groups. Significance levels for entry (SLE) and for stay (SLS) were conservatively set to 0.15.

To indicate the implications of post-operative plasma aldosterone concentration (PAC), plasma renin activity (PRA) and serum potassium levels in individual patients, a generalized additive model (GAM) (with spline) incorporating subject-specific (longitudinal) random effects was plotted and adjusted for other clinical parameters to predict outcomes of interest.[22] We defined the optimal PAC or PRA cut-off value as log odd ratio equaling to zero. (Figure S2)

Finally, to assess whether observed associations between adrenalectomy or MRA therapy and the end points of interest were attributable to different health statuses, we further compared the risks of gastrointestinal bleeding, an outcome believed to be unaffected by the choice of treatments, as a specificity test (negative control outcome). Bleeding was ascertained from emergency department visits and hospitalization episodes. All analyses were performed using SAS 9.2 (SAS Institute Inc.), R software, version 3.4.2 (Free Software Foundation, Inc., Boston, MA) and Stata/MP version 12 (Stata Corporation, TX) for data analysis and figure plotting. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

After excluding 303 patients with IHA or bilateral APA, 59 with pre-existing cardiovascular disorders, a total of 858 cAPA patients, along with another 1210 EH

controls, were enrolled based on our diagnosis algorithm **(Figure 1)**.

Table 1 summarized demographic and clinical characteristics of cAPA patients and EH patients as control by their treatment modalities and statuses. After confirmation of cAPA diagnosis, 545 patients (63.5%) underwent adrenalectomy. The other 313 cAPA patients electing not to have adrenalectomy were kept on MRA.

At 12 months after adrenalectomy, 272 (49.9%) cAPA patients achieved complete clinical success (hypertension-remission without medications). Hypertension duration was longer in cAPA patients than in EH controls (all $p< 0.05$, **Table 1**).

Post-operatively, the hypertension-remissive group had lower PAC and blood pressure yet similar PRA and serum potassium levels as the non-cured group (**Table 1**).

Outcomes of interest

After a follow-up of 6.29±3.97 years, 43 patients (5.0%) died with an incidence rate of 0.76 per 1000 person-years of all cAPAs. cAPA patients who underwent adrenalectomy had a lower all-cause mortality than those without operation (3.7% v.s. 7.4%, $p= 0.017$), and also had a lower incidence rate of incident MACE (15.0% v.s. 21.4%, $p= 0.018$) and CHF (7.0% v.s. 14.1%, $p< 0.001$) yet similar incidence rate of Af (6.4 % v.s. 8.6%, $p= 0.230$) compared with MRA use (Table 1) (Table s1-4)

In the Cox proportional hazard model, all cAPA patients after adrenalectomy in either hypertension-remissive (HR, 0.54, $p< 0.01$) or non-cured groups (HR, 0.61, $p< 0.01$) were associated with lower all-cause mortality, compared with that of EH controls. However, patients who were treated with MRA could not mitigate their mortality ($p= 0.52$)(Table 2).

We further took mortality as a competing risk and found that cAPA patients who underwent adrenalectomy, either in remission or uncured of their hypertension, had

similar risks of incident Af and CHF as those of their EH controls, whereas those who had non-cured hypertension had higher risk of MACE(sHR, 1.41, p= 0.037).

Clinical APA Patients matched via IPTW and their outcomes after targeted treatments

Because the MRA-treated patients could be sicker with chronic comorbidities at cAPA diagnosis, we performed IPTW-matching to balance out pre-existing comorbidities. Our logistic regression model of IPTW identified several factors predicting adrenalectomy (r^2= 0.81, p= 0.68 for the Hosmer-Lemeshow goodness of fit test; **Table S5**). Comparison between these 545 cAPA patients who underwent adrenalectomy and their adjusted counterparts indicated adequate comparability between the two groups, with similar characteristics in gender, age, blood pressure, premorbid risks, baseline biochemistry data and anti-hypertensive drugs used at diagnosis. **(Figure S1).** Results from the alternative Cox proportional hazards model, inverse-probability weighted and taking adrenalectomy as a time-varying factor, depicted that adrenalectomy for cAPA could mitigate all-cause mortality (HR 0.57; p= 0.035; **Figure 3),** MACE (HR 0.67; p= 0.037; **Figure 3**) and CHF (HR, 0.49; p= 0.005) better than those treated medically with MRA. (**Table 2**) (Table S6-9)

Negative control analysis

To resolve concern of possible health indication bias or unobserved confounders, we examined and compared the risk of new onset gastrointestinal bleeding. cAPA patients who underwent adrenalectomy or MRA use had similar risks of gastrointestinal bleeding by Cox regression using adrenalectomy as a time-varying risk (HR, 0.95, 95% CI, 0.84-1.07, p= 0.421).

Biochemistry cure and prognosis-significant biochemical parameters

The post-adrenalectomy PAC level was plotted against the log odds ratio of predicting all-cause mortality or MACE for cAPA patients who underwent adrenalectomy via a GAM model. PAC > 27 ng/dL, but not renin or potassium level, was found to be an independent risk factor predicting long-term mortality or MACE, after adjusting for the nonlinear effects of age, comorbidities and influential drugs (sFigure 2). Cox proportional hazard regression analysis revealed that patients undergoing adrenalectomy who displayed higher PAC (>27 ng/dL) had a higher mortality or MACE during the follow-up period with an adjusted HR of 1.79 (95% CI, 1.03 -3.10; p= 0.038) as compared with cAPA patients with lower post-adrenalectomy PAC **(Fig 4A).**

Additionally, in cAPA patients who underwent MRA treatment, a PRA level < 0.6 ng/mL/hr, identified via a GAM model, showed higher long-term risk of mortality and MACE (HR, 3.85, 95% CI, 1.04- 13.7; p= 0.038) as compared with patients with higher PRA values by Cox analysis **(Fig 4B)**.

Discussion

The incidence rate of all-cause mortality was 0.76 per 1000 person-years for all cAPA patients after targeted treatments. Based on the widely-accepted outcome criteria set by PASO,[4] either status of clinical remission or non-cured hypertension after adrenalectomy was associated with attenuated all-cause mortality in our cAPA patients, while those with non-cured hypertension did not have reduced risk of incident MACE than that of EH controls. We show here unprecedentedly that unilateral adrenalectomy, relative to MRA treatment, led to lower long-term mortality, and MACE/CHF incidence by taking adrenalectomy as a time-varying factor. Additionally, we also demonstrated that PAC > 27 ng/dL after adrenalectomy and PRA < 0.6 ng/mL/hr after MRA treatment could be associated with higher risks of mortality or MACE.

Clinical Cure of hypertension and subsequent outcomes (Table 2)

Half of our cAPA patients achieved complete hypertension-remission at one year after adrenalectomy, similar to previous observations.[3] Moreover, we found that adrenalectomized cAPA patients would have lower long-term mortality risk, regardless of any existence of residual hypertension. This result is different from a previous study that focused on all PA (including IHA) patients and concluded that both adrenalectomy and MRA treatment led to similar mortality rates as those in EH[3]. Taking mortality as a competing risk, we further revealed that either MRA treatment or non-cured hypertension after adrenalectomy in the cAPA patients was associated with higher long-term incident MACE risk than that of the controls- an observation different from heterogeneous MACE risks among various subtypes of PA patients after different targeted treatments. [10,23]

Adrenalectomy versus MRA (Table 3)

cAPA patients treated with MRA had higher risk to subsequent MACE, CHF and all-

cause mortality compared to those who underwent adrenalectomy even after our IPTW-adjusted time-varying analysis. These findings are consistent with a report of a German cohort with only univariate analyses and a population study using all subgroups of PA patients.[11] A Japanese nationwide study reported a better effect of adrenalectomy than pharmacological treatment on improving hypertension and hypokalemia in all PA patients.[24] Studies consistently reveal more reduction in blood pressure and hyperaldosteronism status after adrenalectomy, which abrogated detrimental genomic and nongenomic effects of excessive PAC exposure.[25] Adrenalectomy might also lead to a therapeutic effect more rapidly,[5] whereas longer MRA administration could lead to poor drug compliance.

MRA led to less improvement on the left ventricle mass index (LVMI) than adrenalectomy.[26,27] The percent alleviation of LVMI, in-part by the aldosterone effect, and more reversal of collagen content in the myocardium, was more prominent in adrenalectomized cAPA patients.[27] MRA treatment may result in increased PAC, suppressed PRA and subsequent cardiovascular events. Cortisol can exert its effects in the ischemic striatum via forming glucocorticoid-MR complexes [28] to attenuate the vascular protective effect of spironolactone in PA patients.

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<u>Biochemistry levels affecting outcomes after adrenalectomy or MRA therapy in cAPA</u>

We propose that higher PAC after adrenalectomy could be a signal heralding a higher mortality in regard to the cut-off levels of biochemistry cure. This hypothesis led us to further conduct a dose-response analysis regarding the association of post-surgical PAC, serum potassium level and PRA versus long term mortality.

We identified that a PAC level > 27 ng/dL, but not PRA, among the patients who underwent adrenalectomy was associated with higher long-term mortality or MACE during further follow-up. Our findings further suggest that persistent post-operative high PAC could be as fatal as subsequent MACE, and this deserves more attention during post-operative follow-up visits. We speculate that post-adrenalectomy cAPA patients could have an increased mortality risk in those with higher PAC levels, either with or without hypertension-remission.

Furthermore, after MRA therapy, the increase in PRA has previously been shown to be associated with a lower risk for MI, stroke, heart failure and death[9]. Here in our multivariate analysis, a PRA level < 0.6 ng/mL/hr at one year after MRA treatment could be related to higher risks of long-term incident MACE or mortality. Our result was based on a prospective follow-up cAPA cohort checking biochemistry data under a standard protocol, which made it significantly different from those prior reports from insurance claim data in PA patients. We unprecedentedly report the implications of these critical cut-off levels of aldosterone or renin activity defining clinical biochemistry success after the targeted treatment; further verifications from future larger cohorts or multi-center prospective studies are needed to validate their usefulness.

Study limitations

Even though we performed extensive collections of high-quality detailed biochemical and clinical data correlations among 858 cAPA patients (out of 1220 PA patients) and their 1210 EH controls in this long-term cohort, this is still a local multi-center series with relatively limited case numbers. Most of the engaged hospitals were referred medical centers, therefore the ratio of APA is high in our cohort. The incidences of the outcome events were relatively low and the follow-up duration was less than 10

years, although our findings were robust and consistent across various models for a long-term follow-up of more than 6 years, hinting that some significant separation of the survival curves may happen only after 5 years of follow-up. This is the first report of clinical outcomes from a quality observational cAPA cohort with trustily identified EH controls, which distinguishes it from other reports using population or insurance databases. A concordant finding was observed in a previous German PA long-term study.

As a placebo-controlled randomized clinical trial regarding the effectiveness of MRA versus adrenalectomy for cAPA patients over as many years as ours is neither practically possible nor ethically acceptable to conduct, our prospective inception observational cohort with comorbidities adjusted via IPTW provided a valid and feasible alternative.

Our results must still be interpreted within the limitations of observational studies. The retrospective comparison of cAPA patients undergoing adrenalectomy versus MRA therapy will always be confounded by possible biases. We did not record exactly why the patients opted for MRA treatment; it could be patients' preference, advanced age, or higher surgical risks. We avoided indication bias by matching surgically- versus medically-treated cAPA patients with IPTW.[29] Moreover, A specificity test evaluating new onset events of gastrointestinal bleeding was not different between patients who underwent adrenalectomy or MRA therapy in our negative control analysis, so we concluded that the indication bias about health statuses was not significant.

In order to address the delay between diagnosis and adrenalectomy or if adrenalectomy was chosen as a starting time for survival analyses, we addressed the potential immortal time bias via our time-varying model adjustment. [30] Furthermore,

co-interventional proficiency biases in patients with adrenalectomy (i.e.: more followed-up than those with MRA therapy) was attenuated by our cross check-up with a population-based health-insurance database.

Finally, we also adjusted the possible over-estimation from mortality as a competing risk to avoid confounding the exposure-primary outcome and the exposure-competing outcome effect. [31]

Conclusions

Our comparison of the effect of adrenalectomy versus MRA on long-term risks of mortality and cardiovascular events in cAPA patients showed that adrenalectomy could ameliorate all-cause mortality, compared with that of EH controls, and such effect is independent of post-operative hypertension-remission. However, post-adrenalectomy non-cured hypertension and MRA therapy could still be associated with higher risks of MACE than that of EH controls in cAPA patients. We further matched the cAPA patients in regard to their targeted treatments, and suggested an obvious beneficial effect of adrenalectomy over MRA therapy on long-term mortality, MACE, and CHF. Our study generated the first in-depth analysis on the more favorable effects of adrenalectomy over MRA treatment on the survival and cardiovascular benefits among cAPA patients in the long run.

Taken together, our data supports the concept that adrenalectomy is advantageous through not only alleviating hyper-aldosteronism, hypo-renin, hypokalemia, obesity, and comorbidities, but also plays a key role in abrogating hypertension. Our results support adrenalectomy to be an optimal treatment for feasible cAPA patients.

Prospective

COMPETENCY IN MEDICAL KNOWLEDGE: cAPA patients, compared to EH controls, would have lower long-term mortality risk after adrenalectomy, regardless of the status of post-operative hypertension-remission. Unilateral adrenalectomy, in comparison to MRA treatment for cAPA patients, led to lower long-term mortality, incident MACE and CHF, but similar incident Af. These findings implicate the importance of early diagnosis of cAPA and advise adrenalectomy as an optimal treatment for cAPA patients. However, postoperative non-cure of hypertension in cAPA patients were associated with higher risks of MACE than that of EH controls. The risks of MACE, CHF, and Af could not be attenuated in cAPA patients taking MRA than those of the EH controls. To monitor post-operative PAC and post-MRA treatment PRA in the cAPA patients could forecast future mortality or MACE.

TRANSLATIONAL OUTLOOK: Further studies are needed to differentiate the long-term cardiovascular effects of clinical partial success (partial hypertension-remission) versus persistent hypertension after adrenalectomy, and to identify the predictors of treatment success, in order to fine-tune the algorithm of individually tailored intervention due to the wide inter-patient variability of the disease, along with various medical comorbidities in each patient.

Contributors

VCW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: VCW, JSC
Acquisition of data: JSC, CCC
Analysis and interpretation of data: SMW, CCC
Drafting of the manuscript: VCW, JSC

Critical revision of the manuscript for important intellectual content: SMW, KHW, JSC
Statistical analysis: VCW
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Supplementary Data

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Table 1. The characteristics of enrollees

Pre-treatment characteristics							
Baseline characteristics	**s/p HTN-Remission**	**s/p HTN no - Cured**	**MRA**	**EH**	**s/p HTN-Remission vs EH¶**	**s/p HTN no - Cured vs EH¶**	**MRA vs EH¶**
No of patients	272	273	313	1210			
Age (years)	49.53±11.35	52.04±10.72	58.09±13.32	49.89±15.33	1.00	0.13	<0.01
Sex, Male (%)	104(38.24)	134(49.08)	145(46.33)	635(52.48)	<0.01	0.31	0.05
Body weight (kg)	65.06±13.33	71.37±15.67	67.06±13.47	68.47±14.54	0.00	0.02	0.76
Body mass index (kg/m^2)	24.62±3.83	26.61±4.57	25.46±3.80	25.45±4.24	0.02	0.00	1.00
Visit, n (%)					0.02	0.37	0.26
0	183(67.28)	173 (63.36)	184(58.79)	704(58.18)			
1-6	62(22.79)	66(24.17)	62(19.81)	312(25.79)			
7-12	21(7.72)	26(9.52)	45(14.38)	144(11.90)			
>12	6(2.21)	8(2.93)	22(7.03)	50(4.13)			
Monthly income (USD)					0.17	0.26	<0.01
<600	56(20.59%)	56(20.51%)	97(30.99%)	254(20.99%)			
600-1,300	94(34.56%)	123(45.06%)	109(34.82%)	483(39.92%)			
≧1,300	122(44.85%)	94(34.43%)	107(34.19%)	473(39.09%)			
Hypertension duration (years)	5.96±6.05	9.44±7.77	8.20±9.02	4.72±6.69	0.06	<0.01	<0.01
Smoking (%)	41(15.07)	37(13.55)	22(7.03)	130(10.74)	0.04	0.19	0.05
Charlson comorbidity index	0.97±1.19	1.42±1.35	2.12±1.84	1.22±1.45	0.06	0.23	<0.01
DM (%)	29(10.66)	55(20.15)	52(16.61)	135(11.16)	0.81	<0.01	0.01
CKD (%)	32(11.76)	54(19.78)	80(25.56)	383(31.65)	<0.01	<0.01	0.04
Dyslipidemia (%)	43(15.81)	59(21.61)	66(21.09)	240(19.83)	0.13	0.51	0.62

CAD (%)	16(5.88)	30(10.99)	53(16.93)	113(9.34)	0.07	0.40	<0.01
Anti-hypertension drug class (%)							
Alpha-blocker	40(14.71%)	87(31.87%)	57(18.21%)	111(9.17%)	0.01	<0.01	<0.01
ACEI or ARB	18(6.62%)	37(13.55%)	40(12.78%)	71(5.87%)	0.41	0.08	0.88
Beta-blocker	101(37.13%)	130(47.62%)	126(40.26%)	245(20.25%)	<0.01	<0.01	<0.01
Calcium-channel Blocker	167(61.40%)	205(75.09%)	182(58.15%)	590(48.76%)	<0.01	<0.01	<0.01
Diuretics	87(31.99%)	110(40.29%)	107(34.19%)	419(34.63%)	0.64	<0.01	<0.01
Plasma aldosterone level (ng/dL) †	50.32±35.96	42.20±26.17	47.94±31.85	37.42±25.59	<0.01	0.67	<0.01
Plasma renin activity (ng/mL/hr) †	0.97±3.62	0.90±2.38	1.08±3.62	3.84±6.46	0.50	0.43	<0.01
Log ARR (ng/dL per ng/ml/hr)	5.28±1.94	5.14±1.79	5.04±1.78	3.18±1.72	<0.01	<0.01	<0.01
Creatinine (mg/dL)	0.90±0.51	1.02±0.45	1.17±1.13	1.00±0.65	0.28	1.00	<0.01
SBP (mm Hg)	151.5±23.9	159.9±19.6	150.00±23.7	145.0±20.3	<0.01	<0.01	<0.01
DBP (mm Hg)	91.0±14.4	95.0±14.0	88.22±14.5	86.3±13.3	<0.01	<0.01	0.17
K(mg/dl)	3.41±0.72	3.51±0.71	3.79±0.62	4.15±0.45	<0.01	<0.01	<0.01
eGFR (mL/min/1.73m2)	91.25±27.45	81.18±25.22	80.07±29.87	83.65±25.23	<0.01	1.00	0.24

Post-treatment characteristics (according to PASO)

	s/p HTN-Remission	s/p HTN no - Cured	MRA	EH	s/p HTN-Remission vs s/p HTN no - Cured¶	s/p HTN-Remission vs MRA¶	s/p HTN no - Cured vs MRA¶
Plasma aldosterone level (ng/dL) †	27.83±18.28	33.67±21.46	61.10±44.96	N/A	0.02#	<0.01‡	1.00§
Plasma renin activity (ng/mL/hr) †	3.13±5.49	3.39±7.72	2.94±6.43	N/A	1.00#	1.00‡	1.00§
K (mg/dl)	4.34±0.39	4.32±0.51	4.27±0.58	N/A	0.22#	<0.01‡	<0.01§
SBP (mm Hg)	124.84±10.9	147.14±17.4	147.22±20.9	N/A	<0.01#	1.00‡	<0.01§
DBP (mm Hg)	78.56±7.9	89.62±11.8	86.48±11.9	N/A	<0.01#	<0.01‡	0.01§
Biochemistry (%)					0.29#		
Complete	209(76.8%)	204(74.7%)	N/A	N/A	N/A	N/A	N/A
Partial	26 (9.5%)	36(13.1%)	N/A	N/A	N/A	N/A	N/A
Absent	6 (2.2%)	10(3.6%)	N/A	N/A	N/A	N/A	N/A
Long-term outcomes of interest							
Outcomes	**s/p HTN-Remission**	**s/p HTN no - Cured**	**MRA**	**EH**	**s/p HTN-Remission vs EH**	**s/p HTN- no Cured vs EH**	**MRA vs EH**
Mortality (%)	7(2.57%)	13(4.73%)	23(7.35%)	65(5.37%)	0.05	0.67	0.18

MACE (%)	32(11.76%)	50(18.32%)	67(21.41%)	161(13.31%)	0.50	0.03	<0.01
Af (%)	15(5.51%)	20(7.33%)		55(4.55%)	0.50	0.06	<0.01
CHF (%)	14(5.15%)	24(8.79%)		99(8.18%)	0.09	0.74	<0.01

Abbreviations: ACEI/ARB, angiotensin converting enzyme inhibitors and angiotensin-receptor blockers; Af, atrial fibrillation; ARR, aldosterone to renin ratio; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; dBP, diastolic blood pressure; DM, diabetic mellitus; eGFR, estimated Glomerular filtration rate; HTN, hypertension; K, potassium; MACE, major cardiovascular event; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism; Primary Aldosteronism Surgical Outcome (PASO) criteria; sBP, systemic blood pressure; s/p, post-adrenalectomy.

†Obtained after hold drug that will interfere the renin-angiotensin system.
Laboratory values at confirmation stage.

SI conversion factors: To convert creatinine to millimoles per liter, multiply by 88.4; estimated glomerular filtration rate to milliliters per second, multiply by 0.0167; hemoglobin to grams per liter, multiple by 10.0; potassium to millimoles per liter, multiply by 1.0.

s/p HTN-Remission vs s/p HTN no -Cured
‡ s/p HTN-Remission vs MRA
§ s/p HTN no -Cured vs MRA
¶post-hoc analysis consisted of paired t-tests with Bonferroni correction.

Table 2. Incidence and risks for outcomes of interest of enrollee after treatments

Classified by clinical complete remission of HTN†† and various target treatments of cAPA and essential HTN									
Incidence				**Crude**		**Adjusted***		**Competing risk****	
	Events	Person-Years	Incidence Rate per 1000 Person-Years	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	p	subHazard Ratio (95% CI)	p
	EH								
All-cause mortality	65	7538.41	0.86	N/A	N/A	N/A	N/A	N/A	N/A
MACE	161	6939.13	2.32	N/A	N/A	N/A	N/A	N/A	N/A
Af	55	7612.01	0.72	N/A	N/A	N/A	N/A	N/A	N/A
CHF	99	7433.60	1.33	N/A	N/A	N/A	N/A	N/A	N/A
s/p Remission of HTN††				s/p Remission of HTN vs EH					
All-cause Mortality	7	1786.41	0.39	0.75[0.65,0.87]*	<0.01	0.54[0.43,0.66]*	<0.01	N/A	N/A
MACE	32	1610.26	1.99	0.75[0.64,0.87]*	<0.01	0.57[0.46,0.72]*	<0.01	0.61[0.29,1.28]	0.77
Af	15	1761.12	0.85	0.71[0.61,0.82]*	<0.01	0.50[0.40,0.62]*	<0.01	0.86[0.46,1.61]	0.64
CHF	14	1752.33	0.80	0.72[0.62,0.83]*	<0.01	0.47[0.38,0.59]*	<0.01	0.79[0.38,1.66]	0.40
s/p HTN No -cured				**s/p HTN No -cured vs EH**					
All-cause Mortality	13	1936.02	0.67	0.69[0.60,0.80]*	<0.01	0.61[0.49,0.76]*	<0.01	N/A	N/A
MACE	50	1681.76	2.97	0.66[0.56,0.77]*	<0.01	0.59[0.46,0.75]*	<0.01	1.41[1.02,1.94]*	0.04
Af	20	1852.52	1.08	0.67[0.58,0.78]*	<0.01	0.56[0.44,0.70]*	<0.01	1.67[0.97,2.90]	0.07
CHF	24	1805.99	1.33	0.69[0.60,0.81]*	<0.01	0.53[0.42,0.68]*	<0.01	1.05[0.66,1.60]	0.89
MRA				MRA vs EH					
All-cause Mortality	23	1921.16	1.20	0.86[0.76,0.99]*	0.03	0.95[0.80,1.12]	0.52	N/A	N/A
MACE	67	1603.97	4.18	0.88[0.76,1.02]	0.09	1.07[0.89,1.28]	0.48	1.38[1.03,1.84]*	0.03
Af	27	1844.99	1.46	0.90[0.79,1.03]	0.11	1.10[0.92,1.31]	0.29	1.62[1.00,2.63]*	0.05
CHF	44	1790.12	2.46	0.88[0.76,1.00]	0.06	1.04[0.87,1.25]	0.65	1.44[1.00,2.07]*	0.05

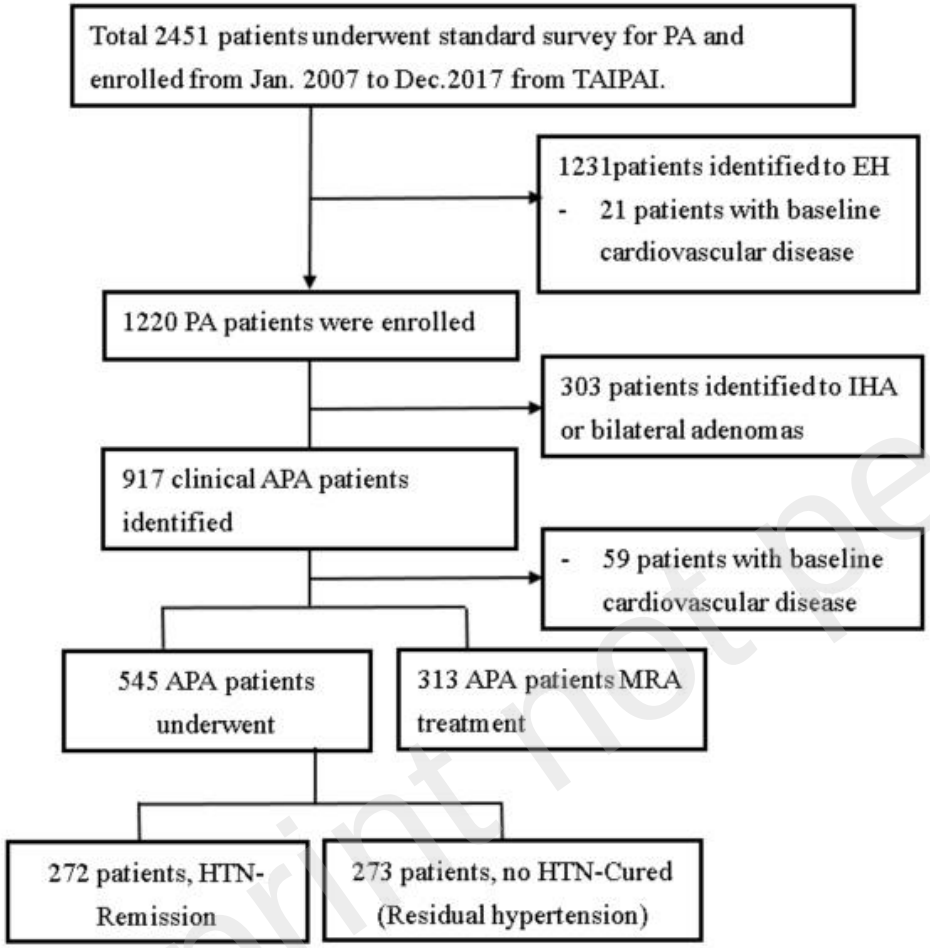
cAPA patients who underwent adrenalectomy or MRA treatment.

Incidence			**Crude**	**IPTW Adjust§**		**IPTW and Time Varying ‖**			
	Events	Person-Years	**Incidence Rate per 1000 Person-Years**	**Hazard Ratio (95% CI)**	p	**Hazard Ratio (95% CI)**	p	Hazard Ratio (95% CI)	p
	Adrenalectomy			Adrenalectomy vs MRA					
All-cause Mortality	20	3722.43	0.54	0.75[0.62,0.91]*	<0.01	0.67[0.59,0.77]*	<0.01	0.57[0.34,0.96]*	0.04
MACE	82	3292.01	2.49	0.80[0.65,0.98]*	0.03	0.75[0.66,0.86]*	<0.01	0.67[0.46,0.98]*	0.04
Af	35	3613.65	9.7	0.70[0.57,0.85]*	<0.01	0.60[0.53,0.69]*	<0.01	0.64[0.36,1.15]	0.14
CHF	38	3558.32	1.07	0.75[0.62,0.92]*	<0.01	0.65[0.57,0.75]*	<0.01	0.49[0.30,0.81]*	<0.01

*Adjust with the baseline characteristics listed in table 1
** **t**aking mortality as a competing risk.
Abbreviations: Af, atrial fibrillation; CHF, congestive heart failure; CI, confidence interval; EH, essential hypertension; HR, hazard ratio; HTN, hypertension; IPTW (inverse probability of treatment weighting), K, potassium; MACE, major cardiovascular event; MRA, mineralocorticoid receptor antagonist.

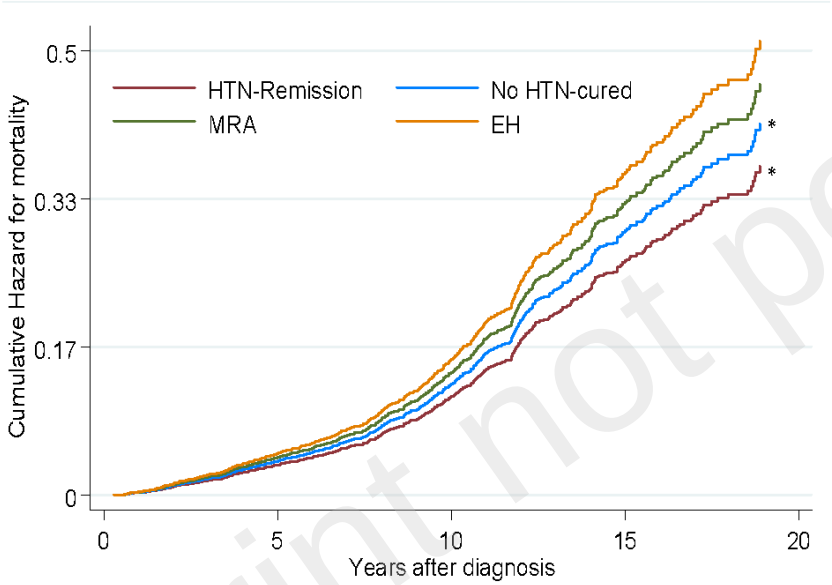
†† Cure of HTN was defined by complete clinical success in term of normal blood pressure without the use of antihypertensives at 12 months postoperatively according to the PASO criteria .
§Adjusted with age, sex, BMI and IPTW propensity score
‖ Adjusted with age, sex, BMI and IPTW propensity score, antihypertensive drugs, systemic blood pressure, diastolic blood pressure, aldosterone, PRA, potassium level and taking adrenalectomy as a time dependent variable.

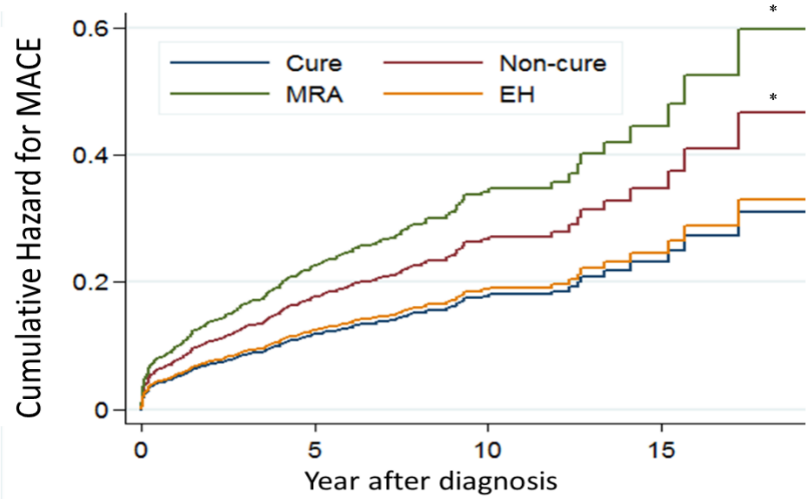
Figure 1. Flowchart diagram of selecting study subjects.



Abbreviations: APA, aldosterone producing adenoma; ARR, aldosterone to renin ratio; EH, essential hypertension; TAPAI, Taiwan Primary Aldosteronism investigator ; PA, primary aldosteronism; MRA, mineralocorticoid receptor antagonist; primary aldosteronism.

Figure 2. Proportional curve for (A) all-cause mortality, and (B)MACE, taking mortality as a competing risk in cAPA patients with adrenalectomy (sub-classified as hypertension-remissive versus hypertension-non-cured groups) or MRA treatment group versus that of EH controls. * compared with EH.





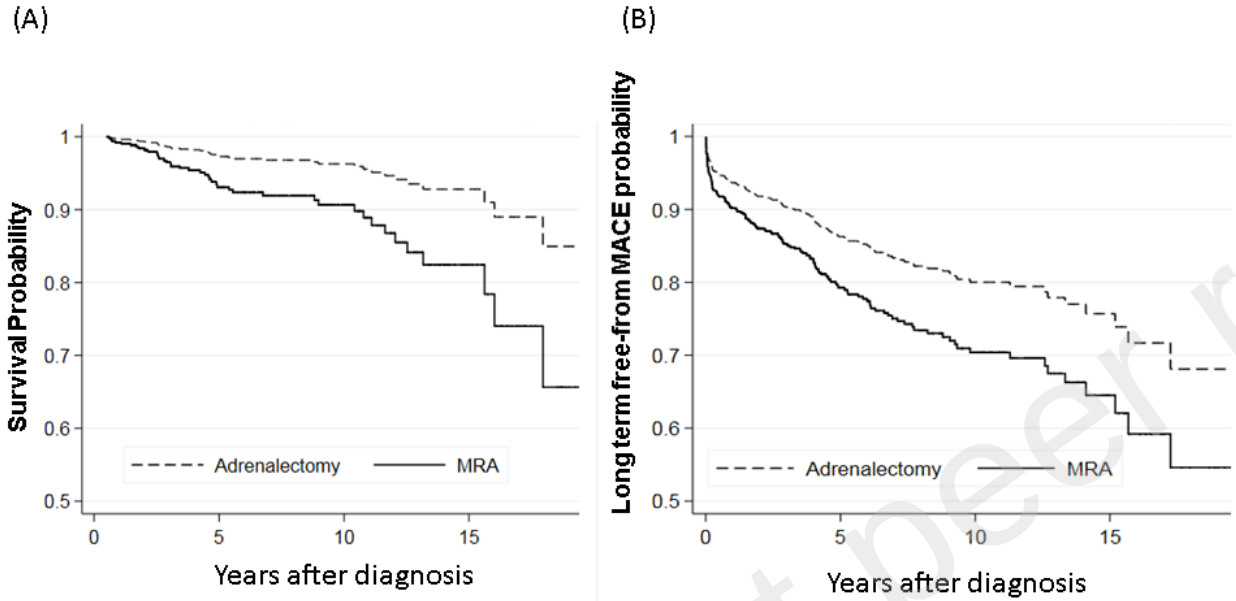
Abbreviations: EH, essential hypertension; MACE, major cardiovascular events; MRA, mineralocorticoid receptor antagonist;

.

¶ Adjust with the baseline characteristics listed in table 1

***p <0.05**

Figure 3. Probability of (A) all-cause mortality, and (B) MACE, adjusted with inverse probability of treatment weighting in cAPA patients after target treatments. ¶ The *p* value in both Cox regression model were <0.05.



Abbreviations:

¶ Adjusted with age, sex, Charlson comorbidity index, BMI and IPTW propensity score, antihypertensive drugs, systemic blood pressure, diastolic blood pressure, aldosterone, PRA, potassium level and taking adrenalectomy as a time dependent variable.

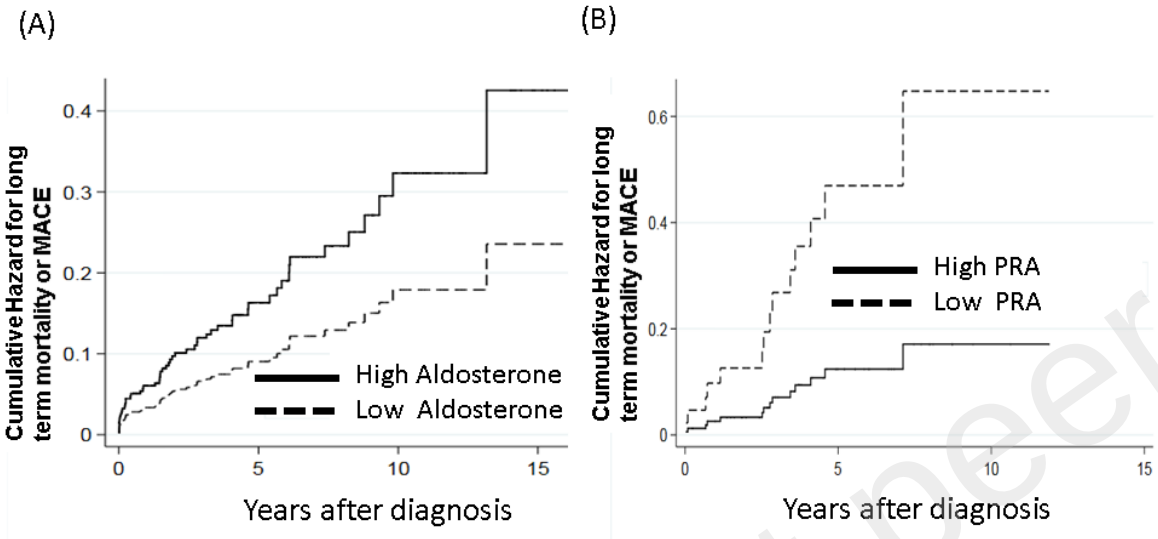
Figure 4

Cumulative hazard to all-cause mortality or MACE in cAPA patients after target treatments.¶

(A) Plasma aldosterone concentration higher than 27ng/dL (High aldosterone) was an independent factor predicting long term all-cause mortality or MACE after adrenalectomy.

(B) Plasma renin activity less than 0.6 ng/mL/hr (Low PRA) after MRA treatment was an independent risk for all-cause mortality or MACE.

*The p value in both Cox regression model were $p<0.05$.



¶ Adjusted with age, sex, Charlson comorbidity index, BMI and, antihypertensive drugs, systemic blood pressure, diastolic blood pressure, and potassium level.