RESEARCH

Autonomous cortisol secretion in patients with primary aldosteronism: prevalence and implications on cardiometabolic profile and on surgical outcomes

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Abstract

Purpose: The aim of this study was to evaluate the prevalence of autonomous cortisol secretion (ACS) in patients with primary aldosteronism (PA) and its implications on cardiometabolic and surgical outcomes.

Methods: This is a retrospective multicenter study of PA patients who underwent 1 mg dexamethasone-suppression test (DST) during diagnostic workup in 21 Spanish tertiary hospitals. ACS was defined as a cortisol post-DST >1.8 µg/dL (confirmed ACS if >5 µg/dL and possible ACS if 1.8–5 µg/dL) in the absence of specific clinical features of hypercortisolism. The cardiometabolic profile was compared with a control group with ACS without PA (ACS group) matched for age and DST levels.

Results: The prevalence of ACS in the global cohort of patients with PA (*n* = 176) was 29% (ACS–PA; *n* = 51). Ten patients had confirmed ACS and 41 possible ACS. The cardiometabolic profile of ACS–PA and PA-only patients was similar, except for older age and larger tumor size of the adrenal lesion in the ACS–PA group. When comparing the ACS–PA group (*n* = 51) and the ACS group (*n* = 78), the prevalence of hypertension (OR 7.7 (2.64–22.32)) and cardiovascular events (OR 5.0 (2.29–11.07)) was higher in ACS–PA patients than in ACS patients. The coexistence of ACS in patients with PA did not affect the surgical outcomes, the proportion of biochemical cure and clinical cure being similar between ACS–PA and PA-only groups.

Conclusion: Co-secretion of cortisol and aldosterone affects almost one-third of patients with PA. Its occurrence is more frequent in patients with larger tumors and advanced age. However, the cardiometabolic and surgical outcomes of patients with ACS–PA and PA-only are similar.

Key Words

- primary aldosteronism
- autonomous cortisol secretion
- dexamethasone suppression test
- cardiometabolic profile

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Introduction

Primary aldosteronism (PA) is the most common cause of secondary hypertension, with a prevalence of close to 10% in all hypertensive patients, and 20% in the setting of resistant hypertension (1). Excess aldosterone in PA is associated with increased cardiovascular morbidity and mortality compared to patients with essential hypertension (EHT) (2). On the other hand, autonomous cortisol secretion (ACS) is a well-known condition linked to a detrimental cardiometabolic profile, leading to an increased risk of diabetes mellitus, hypertension, osteoporosis, cardiovascular events, and global mortality. Therefore, its correct identification is also of great relevance (3). Recently, an association of PA with mild ACS – the Connshing syndrome (4) – has been reported in several studies (5, 6, 7, 8, 9), and the coexistence of both conditions can be expected to result in a particularly unfavorable cardiometabolic profile. In this regard, a higher prevalence of impaired glucose metabolism (8), a greater incidence of cardiovascular events (7) and renal complications (9), and worse arterial stiffness and vascular remodeling (5) have been described in patients with both hormonal excesses compared to patients with PA without associated glucocorticoid hypersecretion (PA-only). Nevertheless, the studies investigating this aspect are scarce and most of them included a limited number of patients or had been performed in a single center. In addition, the definition of ACS is widely variable among these studies: some used a threshold of 1.8 µg/dL in the 1 mg dexamethasone-suppression test (DST) to define hypercortisolism (5), others selected the cutoff point of 3 µg/dL for this test (10), and others considered a combination of different tests (either elevated DST, late-night salivary cortisol, or 24 h urinary free cortisol (11)) for the diagnosis of ACS. This heterogeneity may explain, at least in part, the variability in the reported coexistence of ACS in patients with PA, ranging from 13% (10) to 78% (11). Besides, it should be also taken into account that some cases of Connshing syndrome may be of familial origin (nonglucocorticoid-remediable aldosteronism (12)).

Moreover, to the best of our knowledge, no previous study has compared the cardiometabolic profiles between patients with PA and ACS (ACS–PA) and patients with ACS in whom PA was ruled out.

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Furthermore, although it is known that cortisol co-secretion can lead to misinterpretation of non-ACTH-stimulated adrenal venous sampling (AVS) (13, 14), the impact of simultaneous autonomous aldosterone and cortisol production on surgical and postoperative outcomes has been poorly investigated (15). Another important point to consider is that the finding of an aldosterone- and cortisol-co-secreting tumor also has an impact on the therapy and the postoperative management, so that adrenal crises may occur after surgery (14).

Our study aimed to assess the prevalence of mild ACS – including confirmed and possible ACS – using the current recommended definition proposed by the European Society of Endocrinology Clinical and European Network for the Study of Adrenal Tumors guidelines (16) in patients with PA and its impact on the cardiometabolic profile. Additionally, we compared the differences among the cardiometabolic profiles of patients with ACS–PA, patients with PA without ACS (PA-only group) and those with ACS without PA (ACS group). Finally, we investigated the impact of the co-secretion of cortisol and aldosterone on surgical and postsurgical outcomes.

Methods

Study population and definitions

Patients with PA in follow-up between January 2018 and December 2022 were enrolled in 27 Spanish tertiary hospitals (SPAIN-ALDO registry). At the time of the analysis (December 28, 2022), 696 patients had been included**.** For the study, the 176 cases with available results in the DST at the time of diagnosis of PA were included (evaluated in 21 Spanish hospitals). A control group of ACS without PA or other hormonal hypersecretion (pheochromocytoma or sexual steroids) was included to compare the cardiometabolic profile with that of the ACS–PA group (Fig. 1). As we have previously described (17), the clinical data of the patients were entered into an electronic database (REDCap® database) (18, 19) after pseudonymization using an identification number (record_Id). The study was approved by the Ethics committee of the Ramón y Cajal Hospital, Madrid.

The SPAIN-ALDO registry includes data on demographic characteristics, comorbidities, biochemical, and radiological parameters, as well as information on physical evaluation and treatments for PA, as we have previously mentioned (20). All variables were measured in the outpatient clinic, and data were collected from the time PA was diagnosed until the last available visit during follow-up, including postsurgical information in those who underwent adrenalectomy. PA diagnosis was established according to the criteria proposed by the last clinical European guidelines of PA (21, 22): 123 were confirmed using dynamic test and 53 met criteria of overt PA (spontaneous hypokalemia, plasma renin activity or concentration below detection levels, plasma aldosterone concentration (PAC) >20 ng/dL, and a pathological plasma aldosterone/renin ratio). Regarding subtyping, 65 underwent AVS, being informative of laterality in 35 patients. Unilateral PA ($n=23$) based on AVS was defined by a lateralization index >2 or >3 (depending on the cutoff established in the centre of study) without ACTH or >4 with ACTH stimulation. A total of 59 cases underwent laparoscopic adrenalectomy. The definitions of biochemical and clinical cure for PA after adrenalectomy were based on the PASO classification system (23).

Regarding cardiometabolic profile, cardiovascular disease was defined as any of the following: ischemic heart disease, hypertensive heart disease, heart failure, ventricular arrhythmias, atrial fibrillation, and valvular heart disease; cerebrovascular disease included ischemic and hemorrhagic stroke, and transient ischemic attack. Type 2 diabetes, dyslipidemia, and obesity were defined

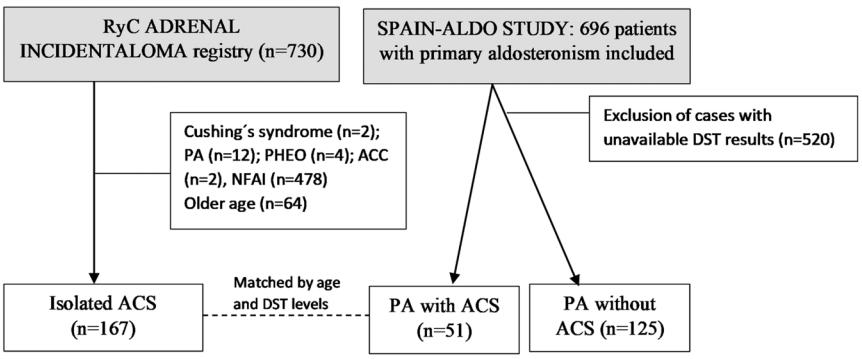

Figure 1
Study population. ACS, autonomous cortisol secretion; ACC, adrenocortical carcinoma; DST, dexamethasone suppression test; NFAI, nonfunctioning adrenal incidentalomas; PHEO, pheochromocytoma; PA, primary aldosteronism; RyC, Ramón y Cajal Hospital.

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as previously described (17) and chronic kidney disease as a glomerular filtration rate (GFR) <60 mL/min/1.73m^2 (GFR was estimated with the modification of diet in renal disease formula (MDRD-4)) for a period exceeding 3 months (24)).

ACS was defined by a cortisol post-1 mg dexamethasone above 1.8 µg/dL in the absence of specific clinical data of overt Cushing's syndrome (3), with confirmed ACS considered when it was greater than 5 µg/dL and possible ACS if it was between 1.8 and 5 µg/dL.

Hormonal and biochemical evaluation

During the initial diagnostic workup, all the included patients underwent at least one DST. At the discretion of the patient's physician, the study was completed by measuring urinary cortisol levels, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulfate (DHEA-S) and night-time salivary cortisol. In addition, all patients underwent routine biochemical profile testing after an overnight fast, both during their initial evaluation and at their last follow-up visit. The profile included fasting plasma glucose (FPG), total cholesterol, LDL-C, HDL-C, and triglycerides. HbA1c was also measured in some patients.

Statistical analysis

All statistical analyses were conducted with STATA.15. Shapiro–Wilk's test was used to assess the normality of continuous variables. All data are expressed as the mean and S.D. for normally distributed variables and the median (25th–75th percentile) for non-normally distributed variables. Student's *t*-test was used to compare quantitative variables and the X^2 test for comparing qualitative variables between the two groups. Lineal correlation between continuous parameters was determined by Pearson's correlation coefficient (*r*). In all cases, a two-tailed *P*-value <0.05 was considered statistically significant.

Results

Differences in the cardiometabolic profile between ACS–PA and PA groups

The prevalence of ACS (ACS–PA) in the overall cohort of patients with PA ($n=176$) was 29.0% ($n=51$). In 10 patients, DST was >5 µg/dL and in the remaining 41 patients, it was between 1.8 and 5 µg/dL. The mean DST levels in the global cohort were of 2.0 ± 2.65 µg/dL. A strong positive correlation was found between DST and ACTH ($r=0.71$, $P < 0.001$) but not with DHEA–S levels ($r = -0.3$, $P=0.901$) in patients with PA–ACS. No correlation was observed between these parameters and cardiovascular outcomes ($P > 0.05$). Nevertheless, the prevalence of cardiovascular events tended to be higher in patients with ACS–PA with ACTH levels ≤10 pg/mL than in those ACS–PA with ACTH >10 pg/mL (41.7% vs 22.2%, $P=0.194$), but no relevant differences were detected in the prevalence of other comorbidities ($P > 0.05$).

The cardiometabolic profiles of patients with ACS–PA and PA were similar, except for older age and a larger tumor size of the adrenal lesion in the ACS–PA group than in the PA-only group. Additionally, as it would be expected, in ACS–PA patients, cortisol post-DST was higher and ACTH levels lower than in the PA group (Table 1). In the global cohort ($n=156$), tumor size was positively correlated with PAC levels at diagnosis ($r = 0.21$, $P=0.016$) but not with cortisol post-DST levels ($r = 0.04$, $P=0.61$).

Differences in the cardiometabolic profile between ACS–PA and ACS groups

The 51 patients with ACS–PA were compared to 167 patients matched by age and cortisol levels after DST who had isolated ACS. As expected, the ACS–PA group had higher levels of aldosterone and lower levels of renin and potassium. The prevalence of hypertension was significantly higher in patients with ACS–PA than in those with ACS-only (OR 7.7 (2.64–22.32)), and patients with ACS–PA had a five-fold higher risk of having experienced a cardiovascular event than those with ACS-only (OR 5.0 (2.29–11.07)). However, patients with isolated ACS had higher HbA1c levels than patients with ACS–PA (Table 2).

Impact of coexistence of ACS on surgical outcomes in patients with PA

Fifty-nine of the 176 patients in the PA cohort underwent adrenalectomy: 20 in the ACS–PA group and 39 in the PA-only group. Biochemical cure was achieved in 94.9%, cure of hypertension in 37.3%, and improvement of hypertension in 54.3%. Of the 31 cases with ACS who did not undergo surgery, 3 had an AVS indicating bilateral

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Table 1 Differences in clinical and hormonal data between PA patients with and without ACS.

	ACS–PA group ($n = 51$)	**PA-only group** ($n = 125$)	***P***
Age (years)	59.3 ± 11.22	55.5 ± 11.87	0.049[a]
Male sex	56.9% ($n = 29$)	41.3% ($n = 78$)	0.49
Number of antihypertensives	2.6 ± 1.5	2.8 ± 1.4	0.36
Hypertension grade ≥2 ($n = 159$)	63.6% ($n = 28/44$)	65.2% ($n = 75/115$)	0.85
Hypertension duration (years) ($n = 155$)	13.6 ± 10.8	10.8 ± 9.4	0.15
Dyslipidemia	45.1% ($n = 23$)	45.6% ($n = 57$)	0.95
Type 2 diabetes	17.7% ($n = 9$)	20.8% ($n = 26$)	0.63
Cardiovascular events	33.3% ($n = 17$)	23.2% ($n = 29$)	0.16
Left ventricular hypertrophy ($n = 323$)	51.9% ($n = 14/27$)	58.5% ($n = 38/65$)	0.56
Cerebrovascular events	5.9% ($n = 3$)	9.6% ($n = 12$)	0.42
Chronic kidney disease	11.8% ($n = 6$)	9.6% ($n = 12/125$)	0.67
Sleep apnea syndrome ($n = 170$)	6.3% ($n = 3/48$)	16.4% ($n = 20/122$)	0.08
Active smoking ($n = 173$)	26.5% ($n = 13/49$)	14.5% ($n = 18/124$)	0.06
Hypokalemia at any time	52.9% ($n = 27$)	50.4% ($n = 63$)	0.76
Obesity	42.0% ($n = 21$)	54.1% ($n = 66$)	0.15
Body mass index (kg/m^2)	29.2 ± 4.5	31.0 ± 6.0	0.06
Systolic blood pressure (mmHg)	147.0 ± 18.4	152.6 ± 23.1	0.13
Diastolic blood pressure (mmHg)	88.8±12.9	91.4 ± 12.9	0.24
Fasting plasma glucose (mg/dL)	104.1 ± 20.8	103.7 ± 19.7	0.92
HbA1c (%) ($n = 103$)	5.8 ± 0.8	5.9 ± 1.0	0.66
Serum potassium (mEq/mL)	3.9 ± 0. 7	3.8 ± 0.6	0.79
LDL-C (mg/dL) ($n = 140$)	109.0 ± 32.9	106.9 ± 36.7	0.77
HDL-C (mg/dL) ($n = 140$)	55.7 ± 20.0	50.1 ± 15.7	0.08
Triglycerides (mg/dL) ($n = 151$)	107.5 ± 56.2	121.8 ± 71.2	0.24
PAC (ng/dL)	33.0 ± 37.0	32.4 ± 23.3	0.9
PRA (ng/mL/h) ($n = 114$)	0.3 ± 0.3	0.4 ± 0.8	0.29
PRC (µU/mL) ($n = 91$)	2.7 ± 2.8	2.6 ± 5.2	0.95
DST (µg/dL)	4.1 ± 4.2	1.1 ± 0.4	<0.001
ACTH (pg/mL) ($n = 83$)	15.0 ± 10.97	20.2 ± 10.55	0.03
DHEAS (µg/dL) ($n = 48$)	147.9 ± 294.23	126.4 ± 211.89	0.771
Maximum tumor size (mm)	24.4 ± 14.01	17.3 ± 6.84	<0.001
Unilateral lesion >2 cm in CT/MRI	37.3% ($n = 19$)	17.6% ($n = 22$)	0.005
Unilateral lesion >4 cm in CT/MRI	7.8% ($n = 4$)	0%	0.002
Unilateral PA based on AVS ($n = 35$)	75.0% ($n = 9/12$)	60.9% ($n = 14/23$)	0.4

DST, dexamethasone suppression test; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC,plasma renin concentration.

PA, 10 had no ACS-related comorbidities other than hypertension and no available AVS, and in the other 18 cases, the reasons why surgery was not performed is not available. After surgery, hypercortisolism was reevaluated only in 3 of the 20 operated patients, with confirmed resolution in 2 out of these 3 cases (DST <1.8 µg/dL).

Overall, no differences in surgical outcomes were observed between the ACS–PA and PA-only groups (Table 3). After a median follow-up of 13.4 months (IQR 12-28.5), no differences were evident in the evolution of cardiometabolic parameters (BMI, glycemic and lipidic profile). The incidence of type 2 diabetes (0% vs 9.4%, $P = 0.193$), obesity (0% vs 13.3%, $P = 0.229$), dyslipidemia (7.7% vs 22.2%, $P = 0.257$), cardiovascular events (7.7% vs 0%, $P = 0.137$), and cerebrovascular events (5.9% vs 0%, $P = 0.153$) did not differ between ACS–PA and ACS-only. No differences in the evolution of the cardiometabolic parameters (glycemic and lipidic profile) were observed when we compared patients (ACS–PA and PA-only, $n = 22$) who had hypertension cured after surgery with those patients without cure ($n = 37$) neither. When comparing ACS–PA patients undergoing adrenalectomy ($n = 20$) and those treated medically ($n = 31$), there were no differences in the evolution of the cardiometabolic profile between the two groups, but surgery led to a greater increase in serum potassium levels (Table 4).

We also compared the improvement in the cardiometabolic profile between patients with ACS–PA who underwent surgery ($n = 20$) and those medically treated ($n = 31$): although all the evaluated parameters (reduction in systolic and diastolic pressure, decrease in the number of antihypertensive agents, serum potassium, fasting glucose, HbA1c, and LDL-C) had a better outcome in the surgical group, only the difference in serum potassium increase reached statistical significance (Table 4).

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Table 2 Differences in clinical and hormonal data between ACS–PA and ACS groups.

	ACS–PA group ($n = 51$)	**ACS group** ($n = 167$)	***P*-value**
Age (years)	59.3 ± 11.22	60.1 ± 7.73	0.57
Male sex	56.9% ($n = 29$)	41.3% ($n = 69$)	0.05
Hypertension	92.2% ($n = 47$)	60.5% ($n = 101$)	<0.001
Dyslipidemia	45.1% ($n = 23$)	53.9% ($n = 90$)	0.27
Type 2 diabetes	17.7% ($n = 9$)	28.7% ($n = 48$)	0.11
Cardiovascular events	33.3% ($n = 17$)	9.04% ($n = 15$)	<0.001[a]
Cerebrovascular events	5.9% ($n = 3$)	1.8% ($n = 3$)	0.12
Chronic kidney disease	11.8% ($n = 6$)	6.0% ($n = 10$)	0.17
Obesity	42.0% ($n = 21$)	33.6% ($n = 56$)	0.27
Body mass index (kg/m^2)	29.2 ± 4.5	29.8 ± 6.8	0.53
Systolic blood pressure (mmHg)	147.0 ± 18.4	136.4 ± 18.3	<0.001
Diastolic blood pressure (mmHg)	88.8 ± 12.9	79.9 ± 10.7	<0.001
Fasting plasma glucose (mg/dL)	104.1 ± 20.8	112.5 ± 35.2	0.12
HbA1c (%) ($n = 103$)	5.8 ± 0.8	6.5 ± 1.5	0.024
Serum potassium (mEq/mL)	3.9 ± 0.7	4.3 ± 0.4	<0.001
LDL-C (mg/dL) ($n = 140$)	109.0 ± 32.9	122.6 ± 37.7	0.048
HDL-C (mg/dL) ($n = 140$)	55.7 ± 20.0	51.6 ± 15.8	0.19
Triglycerides (mg/dL) ($n = 151$)	107.5 ± 56.2	121.9 ± 64.5	0.18
PAC (ng/dL)	33.0 ± 37.0	15.3 ± 17.3	<0.001
PRA (ng/mL/h) ($n = 114$)	0.3 ± 0.3	1.8 ± 3.3	0.028
PRC (µU/mL) ($n = 91$)	2.7 ± 2.8	70.7 ± 156.3	0.012
DST (µg/dL)	4.1 ± 4.2	3.8 ± 3.0	0.56
DST >5 µg/dL	19.6% ($n = 10$)	18.6% ($n = 31$)	0.87
ACTH (pg/mL) ($n = 83$)	15.0 ± 11.0	12.8 ± 9.1	0.22

DST, dexamethasone suppression test; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration.

Table 3 Differences in surgical outcomes between ACS–PA and PA groups.

	Operated ACS–PA ($n = 20$)	**Operated PA-only** ($n = 39$)	***p***
Before surgery			
Age (years)	54.6 ± 11.6	51.6 ± 9.2	0.326
Male sex	50.0% ($n = 10$)	53.9% ($n = 21$)	0.779
Number antihypertensives	2.7 ± 1.4	2.7 ± 1.4	0.726
Hypertension grade ≥2 ($n = 159$)	72.2% ($n = 13/18$)	69.4% ($n = 25/36$)	0.833
Hypertension duration (years) ($n = 53$)	10.5 ± 12.4	7.9 ± 8.3	0.368
Obesity	40.0% ($n = 8$)	56.8% ($n = 21$)	0.227
BMI (kg/m^2)	29.4 ± 4.3	30.8 ± 6.0	0.349
Systolic BP (mmHg)	154.1 ± 19.2	159.1 ± 30.0	0.506
Diastolic BP (mmHg)	92.9 ± 10.8	94.7 ± 13.4	0.606
Serum potassium (mEq/mL)	3.7 ± 0.7	3.7 ± 0.6	0.697
PAC (ng/dL)	41.8 ± 55.7	35.4 ± 20.6	0.536
DST (µg/dL)	4.3 ± 3.27	1.2 ± 0.40	<0.0001
After surgery			
Biochemical cure	100% ($n = 20$)	92.3% ($n = 36$)	0.203
Hypertension resolution	45.0% ($n = 9$)	33.3% ($n = 13$)	0.380
Hypertension cure	55.0% ($n = 11$)	53.9% ($n = 21$)	0.933
ΔSBP (mmHg)	−22.1 ± 29.4	−27.7 ± 29.2	0.520
ΔDBP (mmHg)	−14.8 ± 18.4	−15.7 ± 15.0	0.851
ΔSerum potassium (mEq/mL)	1.0 ± 0.9	0.9 ± 0.7	0.692
Δnumber of antihypertensive drugs	−0.7 ± 1.1	−1.1 ± 1.4	0.372
ΔFasting plasma glucose (mg/dL)	1.4 ± 10.6	2.1 ± 35.2	0.944
ΔHbA1c (%)	−0.3 ± 1.0	0.4 ± 0.6	0.095
ΔLDL-C (mg/dl)	−32.1 ± 36.5	−3.1 ± 37.1	0.084
PAC (ng/dL)	11.2 ± 7.24	22.8 ± 28.54	0.218
DST (µg/dL) ($n = 10$)	1.5 ± 1.11	0.9 ± 0.45	0.230

BP, blood pressure; BMI, body mass index; DBP, diastolic blood pressure; DST, dexamethasone suppression test; PAC, plasma aldosterone concentration; SBP, systolic blood pressure.

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Table 4 Differences in the evolution of the cardiometabolic profile between ACS–PA who underwent surgery and those medically treated.

	Operated ACS–A ($n = 20$)	**Medically treated ACS–PA** ($n = 31$)	***P*-value**
ΔSPB (mmHg)	−22.1 ± 29.40	−10.2 ± 18.4	0.11
ΔDBP (mmHg)	−14.8 ± 18.4	−5.8 ± 13.4	0.07
ΔSerum potassium (mEq/mL)	1.0 ± 0.9	0.1 ± 0.84	0.006
ΔNumber of antihypertensive drugs	−0.7 ± 1.1	−0.1 ± 1.4	0.14
ΔFasting plasma glucose (mg/dL)	1.4 ± 10.6	0.1 ± 21.54	0.71
ΔHbA1c (%)	−0.3 ± 1.0	0.1 ± 0.5	0.24
ΔLDL-C (mg/dL)	−32.1 ± 36.5	−7.6 ± 27.1	0.10

DBP, diastolic blood pressure; SBP, systolic blood pressure.

In addition, after a mean follow-up of 27.2 ± 34.52 months, when a whole cohort of patients with PA–ACS (surgically and medically treated, $n = 51$) were compared to the whole cohort of patients with PA only ($n = 125$), no differences were detected in clinical and analytical outcomes (Table 5).

Table 5 Differences in the evolution of the cardiometabolic profile between ACS–PA and PA only.

	ACS–PA ($n = 51$)	**PA only** ($n = 125$)	***P*-value**
ΔSBP (mmHg)	−14.9 ± 23.78	−10.8 ± 27.53	0.701
ΔDBP (mmHg)	−9.3 ± 15.99	−8.6 ± 14.31	0.785
ΔBMI (kg/m2)	−0.3 ± 2.48	−0.5 ± 2.77	0.792
ΔSerum potassium (mEq/mL)	0.5 ± 0.96	0.6 ± 0.71	0.367
ΔNumber of antihypertensive drugs	−0.3 ± 1.29	−0.6 ± 1.36	0.404
New cases of diabetes	2.6%	7.3%	0.308
New cases of dyslipidemia	12.0%	14.0%	0.803
New cases of obesity	12.5%	14.3%	0.835
New cardiovascular events	12.5%	10.1%	0.715
New cerebrovascular events	2.4%	0%	0.123
ΔFasting plasma glucose (mg/dL)	−0.1 ± 18.19	2.0 ± 27.12	0.659
ΔHbA1c (%)	−0.0 ± 0.65	0.1 ± 1.07	0.860
ΔLDL-C (mg/dL)	−15.8 ± 31.91	−4.9 ± 35.47	0.207

BMI, body mass index; DBP, diastolic blood pressure; PAC, plasma aldosterone concentration; SBP, systolic blood pressure.

Discussion

To our knowledge, this is the first study to compare the cardiometabolic profiles between ACS–PA patients and patients with isolated ACS and patients with PA-only. Moreover, it is the largest Spanish study of patients with PA focused on the impact of glucocorticoid cosecretion on cardiometabolic and on surgical outcomes in patients with PA.

Connshing syndrome involves the combination of uni- or bilateral autonomous aldosterone excess with mild hypercortisolism, but the criteria for defining cortisol excess vary across studies as does it is the overall reported prevalence. In our study, based on the definition of a post-DST cortisol >1.8 µg/dL, we found that almost 30% of patients had mild hypercortisolism associated with PA. Although the prevalence of concurrent hypercortisolism in PA was initially reported to be less than 5% (25), more recent studies report prevalences similar to ours, ranging from 10% to 20% (7, 25, 26, 27). When a less strict criterion was used to define hypercortisolism, up to 78% of PA patients were classified as ACS–PA (11). However, the percentage dropped to 21.7% when only patients with a post-DST cortisol >1.8 µg/dL were included in this category, a prevalence that is similar to ours. The definition of ACS based on the threshold of 1.8 µg/dL on DST is probably the most appropriate, taking into account the recommendation of the ESE/ENSAT guidelines (16) and the studies demonstrating an increase in cardiometabolic and mortality risk above this threshold (28). Nevertheless, the use of a less strict criterion to define ACS, such as the one used in the German Conn registry, would probably lead to a better characterization of cardiometabolic risk in patients with PA, since it has been reported that even in patients with apparently non-functioning adrenal incidentalomas, there is an increased risk of cardiometabolic comorbidities compared to the general population, probably related to the secretion of some adrenal steroids (29). In this regard, Wiebke Arlt *et al.* (4) performed mass spectrometry-based analysis of a 24-h urine steroid metabolome in 174 newly diagnosed patients with PA, compared to 162 healthy controls, 56 patients with endocrine inactive adrenal adenoma, 104 patients with mild subclinical, and 47 with clinically overt adrenal cortisol excess. They found that patients with PA had significantly higher excretion of total cortisol and glucocorticoid metabolites (all $P < 0.001$), only exceeded by glucocorticoid output in patients with clinically overt adrenal Cushing's syndrome. Furthermore, 24-h total glucocorticoid production correlated significantly with

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adverse metabolic risk parameters of patients with PA. The determination of ACTH and DHEAS levels may also be useful to characterize the degree of glucocorticoid excess (30).

Although we found no differences in the cardiometabolic profile of patients with ACS–PA and PA only, when comparing the ACS–PA group and the ACS-only group, the prevalence of hypertension and cardiovascular events was significantly higher in the ACS–PA group. To our knowledge, no previous study has compared the cardiometabolic profile of patients with ACS–PA and patients with isolated ACS. Other previously published series have evaluated if there are differences between patients with ACS–PA and patients with PA-only (5, 7, 8, 9, 13, 25) with conflicting results. Some studies reported a higher prevalence of cardiometabolic comorbidities in the former (5, 7, 8, 9). Thus, Gerards *et al.* (8) found that patients with PA and a pathological DST result were more often diagnosed with type 2 diabetes than PA patients with a normal DST (20% versus 0.8%, $P < 0.0001$), and Tsai *et al.* (5) also described a higher prevalence of type 2 diabetes in patients with cosecretion of cortisol and aldosterone than in those with isolated aldosterone hypersecretion. In addition, they found more vascular fibrosis in patients ACS–PA (fibrosis area: 25.6 ± 8.4%) compared to patients without ACS (fibrosis area: 19.8 ± 7.7%, $P = 0.020$). Similarly, another study showed a higher incidence of cardiovascular events among ACS–PA patients than among PA-only patients (7), while in a very recent paper (9) the incidence of renal complications was more higher in patients with Connshing syndrome than in PA-only patients. In contrast, other studies found no differences in the cardiometabolic profile between PA patients with and without associated ACS (25), like our results. Several factors may have influenced the different results between studies, such as different definitions of ACS and comorbidities, variability of study populations, and retrospective vs prospective study design.

In our series, patients with ACS–PA were older and had larger adrenal tumors than patients with isolated PA. These findings are in agreement with data previously reported by other authors; in fact, tumor size has been described as a classic risk factor for ACS in adrenal incidentalomas (31, 32, 33). We also found in a previous work on patients with adrenal incidentalomas that tumor size was a predictor of ACS with an odds ratio (OR) of 1.1 per 1 mm increase in size, and that tumor size correlated positively with the results of the DST (31). The same finding was also reported in patients with ACS–PA by Desrochers et al., who demonstrated that patients with post-DST cortisol levels over 1.5 µg/dL had larger tumors than patients with levels below this cutoff point ($P = 0.02$) (34). The positive correlation between age and ACS risk was also demonstrated, although weak, in a large series of 654 patients with nonfunctioning adrenal incidentalomas ($r = 0.16$, $P = 0.006$) (35). However, to our knowledge, no previous study has described the positive association between older age and ACS in PA patients. It is possible that adrenal incidentalomas, including aldosterone-secreting adenomas, or hyperplasia with mild unrecognized hypercortisolism, may have had more time to progress in glucocorticoid secretion in older patients and, therefore, show pathologic DST results more frequently.

ACS in our patients with PA (ACS–PA) did not affect the surgical outcomes. However, a recent study focused on the impact of cortisol cosecretion on left ventricular hypertrophy in patients with PA described that the decrease in the left ventricular mass index was positively correlated with total glucocorticoid excretion and systolic 24-h blood pressure (15). In addition, the study by Peng *et al.* (35) described a lower rate of complete clinical response in patients with wild-type KCNJ5 and 1 mg DST >1.5 µg/dL. Although we could not demonstrate differences in the evolution of the cardiometabolic profile between PA–ACS patients who underwent adrenalectomy and those medically treated, taking into account that adrenalectomy resolves both mineralocorticoid and glucocorticoid excess, while targeted medical treatment only control the mineralocorticoid excess, a more favorable effect with the surgical treatment would have been expected. In fact, in the comparative analysis, we found a non-significant trend in favor of surgery, possibly limited by the low number of cases.

The main strengths of our study are the large cohort of PA patients who were evaluated with 1 mg DST test and the comparison to a control group with isolated ACS. Nevertheless, the retrospective design is a limitation that reduces the possibility of drawing conclusions in terms of causality. Another weakness of the study is the fact that only a minority of patients underwent AVS, which limits the power to determine if the prevalence of ACS is different between unilateral and bilateral PA. Another limitation, inherent to all studies using DST for the definition of ACS, is the potential false positive results in this test due to other circumstances such as drugs, obesity, type 2 diabetes, and other comorbidities (36). In addition, we are aware that the staining of

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CYP11B1, DHEA-sulfotransferase, and CYP11B2 would be useful for a better characterization of the surgical outcomes in our cohort, but these determinations were not available in most of the cases (37). Moreover, the influence of cortisol cosecretion on the results of AVS is another point to consider due to the potential biases induced by cosecretion of cortisol on the selectivity index that may lead to a false interpretation of the results (14).

Conclusion

Co-secretion of cortisol and aldosterone is common in patients with PA, affecting one-third of the patients. Its presence is more common in patients with larger tumors and advanced age. However, the cardiometabolic profile of patients with ACS–PA is similar to that of patients with isolated PA, although patients with ACS–PA had a higher prevalence of hypertension and cardiovascular events than those with isolated ACS. The surgical outcomes of patients with ACS–PA and PA-only are similar, both in terms of cardiometabolic profile and hypertension cure and improvement.

Declaration of interest
The authors declare no conflict of interest

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Institutional review board statement
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Hospital Universitario Ramón y Cajal. Madrid. Spain (approval date: 10th November 2020, code: ACTA 401).

Informed consent statement
Patient consent was waived due to the retrospective nature of the study.

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