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Original Research

Influence of smoking on cardiometabolic profile and surgical outcomes in patients with primary aldosteronism: a cohort study

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Abstract

Aim: To evaluate the influence of smoking on cardiometabolic profile and surgical outcomes in patients with primary aldosteronism (PA).

Methods: Multicentre retrospective study of patients with PA evaluated in 36 Spanish tertiary hospitals with available information on smoking habits [smokers and non-smokers (never smokers and ex-smokers)].

Results: A total of 881 patients were included, of whom 180 (20.4%) were classified as smokers and 701 as non-smokers. At diagnosis, smokers and non-smokers did not differ in blood pressure or serum potassium levels between. However, smokers had a higher prevalence of left ventricular hypertrophy (LVH) than non-smokers [odds ratio (OR) 2.0, 95% confidence interval (CI) 1.23-3.25], and smokers were more likely to have severe LVH than non-smokers (12.5% vs 6.6%, $P = .164$). A larger mean tumour size of the adrenal nodule/s was observed in the smoking group (18.6 ± 9.66 vs 15.8 ± 8.66 mm, $P = .002$). In addition, the odds of mild autonomous cortisol secretion (MACS) was greater in smokers than in non-smokers (OR 2.1, 95% CI 1.14-4.06), but these differences disappeared when adjusted for the size of the adrenal nodule/s (adjusted OR 1.6, 95% CI 0.76-3.37). The rate of biochemical and hypertension cure was similar in both groups; however, hypertension cure tended to be more frequent in the non-smoker group (41.2% vs 29.9%, $P = .076$).

Conclusions: Patients with PA who smoke have a higher prevalence of LVH and MACS and larger adrenal nodule/s than non-smokers. Smoking has no significant effect on the probability of hypertension response after adrenalectomy in patients with PA; however, a tendency to a lower probability of hypertension cure is observed in smokers compared to non-smokers.

Keywords: primary aldosteronism, smoking, cigarettes, adrenalectomy, hypertension

Significance

This is the first study focused on the evaluation of the influence of smoking on cardiometabolic profile and surgical outcomes in patients with primary aldosteronism (PA). We evaluated these outcomes in a large cohort of 881 patients with PA. As the main findings, we found that smokers had a higher prevalence of left ventricular hypertrophy than non-smokers. In addition, adrenal nodules were larger and the prevalence of mild autonomous cortisol secretion higher in smokers than in non-smokers. In relation with surgical outcomes, we observed that hypertension cure tended to be 1.4 times more frequent in the non-smoker group (but statistical significance was not demonstrated). Our research demonstrated the negative impact of smoking in both the cardiometabolic profile and surgical outcomes of patients with PA.

Introduction

Primary aldosteronism (PA) is recognized as the most common cause of endocrine hypertension, accounting for approximately 5%-15% of hypertensive patients.[1] Long-term exposure to inappropriately high aldosterone levels in patients with PA increases cardiovascular risk beyond blood pressure (BP) effects.[2,3] Aldosterone hypersecretion is known to have a direct negative effect on vascular function, inflammation, and fibrosis, leading to endothelial dysfunction.[4] Some studies have evaluated the impact of aldosterone excess on cardiometabolic outcomes when compared with patients with essential hypertension matched by age, sex, and smoking habit,[5] but no previous study has evaluated how smoking affects the cardiometabolic profile of PA patients.

Smoking is one of the major risk factors for malignancy and cardiovascular disease, but smoking habits in patients with adrenal tumours have not been well studied. In this regard, in an epidemiological study including 6946 patients with adrenal cortical tumours, a significant association between smoking and adrenocortical carcinoma was found.[6] Some authors previously have investigated the relationship between smoking and adrenal incidentalomas and mild autonomous cortisol secretion (MACS), supporting that smoking patients have larger unilateral adrenal incidentalomas and higher prevalence of bilateral adrenal incidentalomas and MACS.[7,8] However, it has not been investigated whether this association is due to causality or to case selection. A recent study suggested that current or former smoking status and an increased Charlson Comorbidity Index increased the likelihood of MACS.[9] Furthermore, some authors found that smoking increased hypertension risk in non-functioning adrenal incidentalomas.[10] However, the impact of smoking on PA severity, cardiometabolic profile, and/or on the surgical outcomes in patients with PA has not been previously reported.

Therefore, our aim was to evaluate the prevalence of smoking in patients with PA and its impact on the cardiometabolic profile and on the severity of the PA (degree of hypertension and prevalence of hypokalaemia) and also on surgical outcomes in a large cohort of Spanish patients with PA.

Methods

Study population

As we have previously described,[11] SPAIN-ALDO Register is a nationwide multicentre and retrospective study of patients with PA evaluated in 36 Spanish tertiary hospitals. Patients diagnosed with PA between January 2018 and January 2023 were enrolled. At the time of the analysis for the current study (December 30, 2023), information from 899 patients with PA was available. The study was approved by the Ethics Committee of the Ramón y Cajal Hospital in Madrid. Patient consent was waived due to the retrospective nature of the study.

Inclusion criteria for the current analysis were (1) being at least 18 years of age and having a PA diagnosis according to the Endocrine Society guidelines[12] and (2) available information about smoking habit and cardiometabolic burden. A total of 881 patients were included in the analyses (Figure 1).

Clinical and hormonal evaluation and definitions

As we have previously described,[13] the SPAIN-ALDO Registry is an electronic database (REDCap® database) in which patients with PA are included after pseudoanonymization using an identification number (record_Id). It contains information

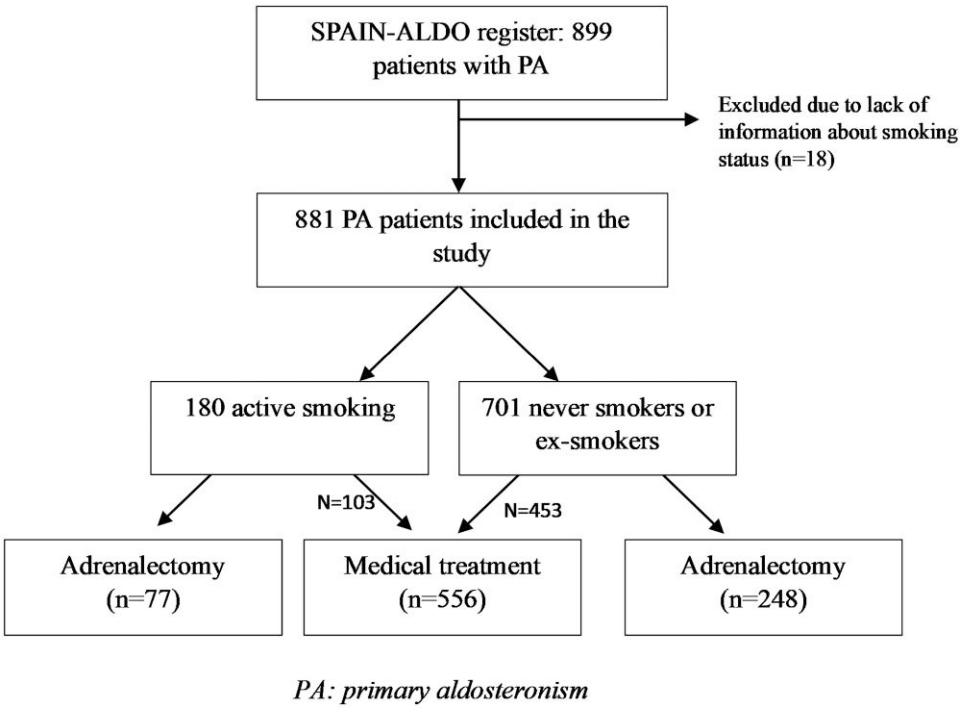

Figure 1. Study population. PA, primary aldosteronism.

on demographic characteristics, comorbidities, and biochemical, radiological, and adrenal venous sampling (AVS) parameters, as well as about medical and surgical treatment. The diagnostic procedures and subtype diagnosis were performed according to the recommendations of the current PA clinical guidelines of PA.[3] Computed tomography (CT) and magnetic resonance imaging (MRI) were performed in all patients at diagnosis, but radiological data about laterality and tumour size were available only in 854 patients. In addition, AVS was performed in 354 patients, and the procedures used and the criteria to evaluate its success have been described in our recent study.[14]

Cardiometabolic comorbidities were defined as follows: type 2 diabetes and dyslipidaemia based on current standards; obesity [body mass index (BMI) > 30 kg/m^2]; cardiovascular disease (ischaemic heart disease, hypertensive heart disease, heart failure, ventricular arrhythmias, atrial fibrillation, and/or valvular heart disease); cerebrovascular disease (transient ischaemic attack or acute stroke); and chronic kidney disease [estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for a period of more than 3 months]. We also collected data about cancer diagnosis and the localization of the cancer (colon, haematological, breast, prostate, lung, thyroid, pancreas, neuroendocrine, or other types). Physical evaluation information included office systolic BP (SBP), office diastolic BP (DBP), and BMI (kg/m^2) at the time of the PA diagnosis and at the last follow-up visit.

Comprehensive transthoracic echocardiographic examination was performed by experienced examiners in the different local centres. Echocardiographic parameters were measured according to the recommendation of the American Society of Echocardiography. Left ventricular hypertrophy (LVH) was defined as left ventricular mass index (LVMI) ≥ 50 g/m^2 in males and ≥47 g/m^2 in females.[15] Information about left ventricular mass was available in 452 patients.

Regarding smoking habit, patients were classified into 2 groups: smokers, if they smoked at the time of the PA diagnosis, and non-smokers if they did not smoke at the time of the PA diagnosis (Figure 1). Non-smokers were further divided into 2 groups: never smokers and ex-smokers. Information on the number of daily cigarettes was only available in 59 patients and therefore not included in the study.

As we have previously described,[16] biochemical data on fasting plasma glucose, glycated haemoglobin (HbA1c), total cholesterol, HDL-c, LDL-c, triglycerides, serum creatinine, eGFR (MDR-4), microalbuminuria, proteinuria, sodium, and serum potassium, at the initial and the last visit in the Hypertension/Endocrinology Unit, were collected. In addition, measurement of plasma aldosterone concentration (PAC) and plasma renin activity (PRA) or direct renin concentration (DRC) was performed in all patients at diagnosis. Plasma aldosterone concentration was measured using radioimmunoassay. Plasma renin activity and DRC were measured using either an enzyme immunoassay or radioimmunoassay, respectively. MACS was defined by a cortisol after a 1 mg dexamethasone suppression test (DST) > 1.8 μg/dL in the absence of overt signs of hypercortisolism.[17] A total of 239 patients in our study had an available result in the DST and in baseline serum ACTH concentration (164 patients of the non-smokers group and 75 of the smoker group).

Surgical outcomes

A total of 325 patients underwent adrenalectomy. Surgical and medical outcomes were assessed by office BP, number of antihypertensive drugs, potassium level, and aldosterone/renin ratio (ARR) and categorized according to the PASO criteria for clinical outcome (complete, partial, or no cure of hypertension) and biochemical outcomes (normalization or persistent hypokalaemia and/or abnormal ARR).[18]

Statistical analysis

All statistical analyses were performed with STATA.15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). Shapiro–Wilk´s test was used to assess normality of continuous variables.

All data are expressed as the mean ± standard deviation for normally distributed variables and the median (25th–75th percentile) for non-normally distributed variables. Student's *t*-test was used to compare continuous variables and the X^2 test for categorical variables between 2 groups. For the estimation of odds ratios (OR) and confidence intervals (CI), we employed a logistic regression analysis. Multivariable logistic regression analysis was used to estimate the association variables when adjusted for potential confounding factors. Because previous studies have demonstrated an association between tumour size and prevalence of MACS, we adjusted the association between smoking and MACS by tumour size.[19] Similarly, due to the association between MACS and LVH,[20] we estimated the OR between smoking and LVH after adjusting by the prevalence of MACS. Ordinal logistic regression analysis was employed to calculate the association between smoking habit and clinical surgical outcomes (hypertension cure, hypertension improvement, and no clinical response). The follow-up time after surgery was considered since the date of the PA diagnosis to the last available follow-up visit after surgery.

The model that evaluates the probability of hypertension cure was developed using a multivariable logistic regression model. We have included the variables that we have previously selected as associated with the probability of hypertension cure in addition to smoking habit.[21] As we have previously defined, the selection of these variables for the model was based on the results of the univariate logistic regression model to predict hypertension cure or improvement after adrenalectomy in PA patients ($P < .2$) and on previous literature reports. Only variables with <30% of missing values were considered to enter in the model. The estimation of all possible equations was used to select the model with the best diagnostic accuracy (lower Akaike index). In addition, we have estimated the model using the stepwise regression approach (backward stepwise). Non-parametric receiver operating characteristic curves were constructed to estimate the validity indexes for the model that evaluates the probability of hypertension cure. The comparison of the models that evaluates the probability of hypertension cure (the model with the variable smoking habit and the model without this variable) was estimated with the X^2 test. An internal validation of the model was performed using a cross-validation, considering that the model had a good adjustment when the loss of prediction (R^2-r^2) was lower than 10%. The power of the study to detect differences in the prevalence of LVH between smokers (66%) and non-smokers (49%), considering a α value of .05, was of 99%. A 2-tailed $P < .05$ was considered statistically significant.

Results

Patient characteristics

A total of 881 patients were included, of whom 180 (20.4%) were classified as smokers and 701 as non-smokers (Figure 1). Of these 701 patients, 177 were ex-smokers (25.3%) and 524 had no history of smoking. The median age of the cohort at the PA diagnosis was 57.9 years (range 40.1-63.0), and 58.3% ($n = 514$) were males. Hypokalaemia was present at PA diagnosis in 59% ($n = 520$) of the cases, and the median number of BP-lowering drugs was 3 (range 1-6). The duration of hypertension at PA diagnosis was 9.3 years (range 0-41 years). The CT/MRI findings were variable: 544 patients with unilateral adrenal nodules/hyperplasia, 253 with apparently normal adrenal glands, and 84 with bilateral adrenal nodules/hyperplasia. Adrenal venous sampling was performed in 354 patients and was successful in 224 (63.3%). Of these 224 cases, 59.8% ($n = 134$) were classified as unilateral and 90 as bilateral PA.

Association of smoking and the severity of PA and the cardiometabolic profile

There were no differences in the prevalence of hypokalaemia, BP, or serum potassium levels at diagnosis between smokers and non-smokers; but hypertension duration was slightly lower in the group of smokers (Table 1). Smokers had a higher prevalence of LVH than non-smokers (OR 2.00, 95% CI 1.23-3.25). These differences remained significant after adjustment by MACS prevalence (adjusted OR 3.48, 95% CI 1.35-8.96). In addition, smoker patients tended to have severe LVH more commonly than non-smokers (12.5% vs 6.6%, $P = .164$). No other significant differences were observed in the cardiometabolic profile of these patients. The same results were observed when ex-smokers were excluded from the group of non-smokers and compared them with smokers (Table S1). In addition, a larger tumour size of the adrenal nodule/s was detected in the group of smokers. However, no differences in mean tumour size were observed between never smokers and ex-smokers (16.3 ± 8.63 vs 17.1 ± 10.16 mm, $P = .405$). We found that ex-smokers were younger than smokers (57.3 ± 4.31 vs 56.2 ± 4.30, $P = .023$), so we may speculate that the duration of smoking was longer in the former.

Furthermore, cortisol values after the DST were significantly higher in smokers. In fact, the prevalence of MACS was higher in these patients than in non-smokers (OR 2.15, 95% CI 1.14-4.06). These differences disappeared after adjustment for the tumour size of the adrenal nodule/s (adjusted OR 1.59, 95% CI 0.76-3.37). In this regard, we observed that the likelihood of having MACS increased with the size of the adrenal nodule/s (OR 2.20 per each increase in 10 mm, 95% CI 1.52-3.18) (Table 1).

Association of smoking and surgical outcomes

Adrenal surgery was performed in 325 patients (248 non-smokers and 77 smokers) (Figure 1), resulting in biochemical cure of PA in 99% of the patients. After a median follow-up of 28 (interquartile range: 11.6-60.4) months, 84.6% ($n = 275$) of patients achieved a hypertension response: 123 were cured and 152 improved hypertension control. No statistically significant differences were observed in the main surgical outcomes between smokers and non-smokers (OR 0.76, 95% CI 0.47-1.22); however, hypertension resolution tended to be more frequent in the non-smoker group (41.2% vs 29.9%, $P = .076$) (Table 2). A multivariable analysis was performed to evaluate the impact of smoking on hypertension cure considering the effect of relevant variables associated with the probability of hypertension cure that we have previously described[21] (female sex, use of 2 or fewer antihypertensive medications, hypertension grade 1, type 2 diabetes, and obesity), and no significant effect of smoking was found in the probability of hypertension response (complete and partial response) after adjusting by these variables (OR 1.05, 95% CI 0.48-2.30). Nonetheless, when we try to predict hypertension cure, a tendency to a higher rate of hypertension cure was observed in non-smokers (OR 1.76, 95% CI 0.89-3.48) (Table 3). The diagnostic accuracy of the model in our current population with the variable smoking was quite similar to the model that does not include this variable [area under the curve

Table 1. Differences in the primary aldosteronism presentation between smokers and non-smokers.

	Smokers ($n = 180$)	Non-smokers ($n = 701$)	*P*
Demographic information			
Age (years)	56.2 ± 4.29	56.6 ± 5.36	0.363
Male sex	63.3% ($n = 114$)	57.1% ($n = 400$)	0.128
Clinical data/comorbidities			
Hypertension duration (years)	9.4 ± 7.87	11.2 ± 9.94	0.031
Screening of PA due to an adrenal incidentaloma	27.8% ($n = 50$)	21.7% ($n = 152$)	0.083
Type 2 diabetes	23.3% ($n = 42$)	21.1% ($n = 148$)	0.518
Dyslipidaemia	48.3% ($n = 87$)	44.3% ($n = 309$)	0.336
Cardiovascular events ($n = 876$)	25.3% ($n = 45/178$)	25.9% ($n = 181/698$)	0.859
LVH ($n = 452$)	65.5% ($n = 57/87$)	48.8% ($n = 178/365$)	0.005
Cerebrovascular events ($n = 873$)	6.7% ($n = 12/180$)	7.7% ($n = 53/693$)	0.655
Chronic kidney disease	10% ($n = 18$)	12.7% ($n = 89$)	0.323
Obesity	40.3% ($n = 71$)	39.6% ($n = 271$)	0.862
Hypokalaemia at any time	58.9% ($n = 106$)	59.1% ($n = 414$)	0.967
Albuminuria ($n = 676$)	15.4% ($n = 21/136$)	12.8% ($n = 69/540$)	0.414
MACS ($n = 239$)	45.1% ($n = 23/51$)	27.7% ($n = 52/188$)	0.017
Medical treatment at diagnosis			
% of patients treated with			
<2 antihypertensive drugs	45.1% ($n = 79$)	43.3% ($n = 299$)	0.552
2-3 antihypertensive drugs	24.6% ($n = 43$)	28.7% ($n = 198$)	
≥4 antihypertensive drugs	30.3% ($n = 53$)	28.1% ($n = 194$)	
Classes of antihypertensive drugs			
ACEIs	22.2% ($n = 40$)	21.8% ($n = 153$)	0.909
ARBs	42.8% ($n = 77$)	46.4% ($n = 325$)	0.389
Alpha-blockers	39.4% ($n = 71$)	28.4% ($n = 199$)	0.004
Beta blockers	29.4% ($n = 53$)	33.0% ($n = 231$)	0.369
Calcium blockers	65.6% ($n = 118$)	63.8% ($n = 447$)	0.655
Diuretics	37.8% ($n = 68$)	40.8% ($n = 289$)	0.461
Physical examination			
BMI (kg/m^2)	29.6 ± 5.52	29.4 ± 6.16	0.757
SBP, mmHg	149.7 ± 20.65	149.6 ± 22.04	0.954
DBP, mmHg	89.8 ± 13.20	89.4 ± 13.22	0.725
Biochemical and hormonal data			
Serum potassium (mEq/L)	3.7 ± 0.58	3.7 ± 0.61	0.793
Fasting plasma glucose (mg/dL)	103.4 ± 22.43	103.8 ± 22.65	0.862
HbA1c (%)	5.9 ± 0.72	6.2 ± 0.38	0.660
Total cholesterol (mg/dL)	184.3 ± 41.27	180.9 ± 40.51	0.340
Triglycerides (mg/dL)	133.7 ± 74.57	114.1 ± 63.99	0.003
Total cholesterol/HDL ratio	3.9 ± 1.14	3.7 ± 1.20	0.132
Estimated glomerular filtration rate, mL/min per 1.73 m^2	86.0 ± 21.21	85.4 ± 20.88	0.748
PAC (ng/mL)	37.0 ± 33.92	40.3 ± 47.96	0.304
PRA (ng/mL/h) ($n = 547$)	0.5 ± 1.04	0.4 ± 0.54	0.120
DRC (μU/mL) ($n = 419$)	4.1 ± 5.18	5.5 ± 24.49	0.308
Cortisol after 1 mg DST ($n = 239$)	3.0 ± 3.37	1.8 ± 2.13	0.003
Serum ACTH (pg/mL) ($n = 239$)	16.9 ± 11.61	25.0 ± 34.43	0.003
Radiological and AVS data			
Bilateral adrenal nodules in CT/MRI ($n = 881$)	12.8% ($n = 23/180$)	8.7% ($n = 61/701$)	0.097
Maximum tumour size adrenal nodule/s ($n = 601$)	18.6 ± 9.66	15.8 ± 8.66	0.002
Adrenal nodule/s > 2 cm in CT/MRI	44.1% ($n = 60/136$)	25.8% ($n = 120$)	<0.001
Successful S ($n = 354$)	67.1% ($n = 51/76$)	62.2% ($n = 173/278$)	0.435
Unilaterality according to AVS ($n = 224$)	58.8% ($n = 30/51$)	60.1% ($n = 104/173$)	0.869

For variables with missing data, we have included the number of cases in parentheses next to the variable. Student's *t*-test was used to compare continuous variables and the X^2 test for categorical variables between 2 groups. Continuous variables are expressed as the mean ± standard deviation and categorical variables as % and absolute values.
Abbreviations: AVS, adrenal venous sampling; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; DBP, diastolic blood pressure; DST, dexamethasone suppression test; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

(AUC) 0.793 (95% CI 0.740-0.846) vs AUC 0.790 (95% CI 0.737-0.843); $P = .606$]. With the cross-validation, we proved that the model that includes the variable smoking had a good diagnostic accuracy in external samples (pseudo-R^2 mean = 0.223). The AUC of the model with the internal validation was 0.777 (95% CI 0.721-0.834).

However, based on the backward stepwise regression approach, the best model with the highest accuracy to predict hypertension cure combined the variables female sex, hypertension grade 1, obesity, size of the adrenal nodule/s, and hypertension duration, reaching an AUC of 0.800 (95% CI 0.745-0.851). When the variable smoking was included, the AUC increased to 0.804 (95% CI 0.750-0.854).

Discussion

The prevalence of current smokers in our population of patients with PA was 20.4%. No previous studies have been performed focusing specifically on smoking habit and PA. However, some studies have described the prevalence of this

Table 2. Differences in surgical outcomes between smokers and non-smokers ($n = 325$).

	Smokers ($n = 77$)	Non-smokers ($n = 248$)	*P*
Pre-surgical information			
Age (years)	54.9 ± 4.69	55.3 ± 5.22	.524
Male sex	58.4% ($n = 45$)	50.4% ($n = 125$)	.217
Hypertension duration	7.7 ± 6.30	9.8 ± 8.55	.051
Hypokalaemia (years)	75.3% ($n = 58$)	71.4% ($n = 177$)	.498
Type 2 diabetes	22.1% ($n = 17$)	16.1% ($n = 40$)	.231
Obesity	40.5% ($n = 30$)	40.9% ($n = 97$)	.953
MACS ($n = 81$)	45.5% ($n = 10/22$)	35.6% ($n = 21/59$)	.417
BMI (kg/m^2)	29.6 ± 6.22	28.8 ± 6.58	.378
SBP, mmHg	153.5 ± 21.06	150.3 ± 21.54	.259
DBP, mmHg	91.7 ± 12.89	90.02 ± 11.44	.271
Surgical outcomes			
Biochemical cure	98.7% ($n = 74$)	98.7% ($n = 229$)	.979
Hypertension response[a]	85.7% ($n = 66$)	84.3% ($n = 209$)	.760
Hypertension cure	29.9% ($n = 23$)	41.2% ($n = 100$)	.076
Hypertension improvement	65.2% ($n = 43$)	52.2% ($n = 109$)	.064
ΔSBP	−17.7 ± 21.09	−17.1 ± 24.50	.783
ΔDBP	−8.9 ± 14.39	−8.5 ± 14.85	.780
ΔAntihypertensive drugs	−0.5 ± 1.40	−0.6 ± 1.45	.481
ΔSerum potassium	0.7 ± 0.74	0.7 ± 0.78	.992
New cardiovascular event ($n = 499$)	6.1% ($n = 6/98$)	8.7% ($n = 35/401$)	.400
LVH development ($n = 119$)	5.6% ($n = 1/18$)	11.9% ($n = 12/101$)	.428
CKD development ($n = 584$)	8.5% ($n = 10/118$)	10.5% ($n = 49/466$)	.511
Diabetes development ($n = 544$)	5.7% ($n = 6/105$)	5.7% ($n = 25/439$)	.994
Obesity development ($n = 365$)	10% ($n = 7/70$)	7.8% ($n = 23/295$)	.546
Dyslipidaemia development ($n = 377$)	13.2% ($n = 9/68$)	14.6% ($n = 45/309$)	.777

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; MACS, mild autonomous cortisol secretion; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
[a]The estimated odds ratio with the ordinal regression model considering hypertension response as an ordinal variable (1, no response; 2, hypertension improvement; and 3, hypertension cure) was 0.76 (95% CI 0.47-1.22). For variables with missing data, we have included the number of cases in parentheses next to the variable. Student's *t*-test was used to compare continuous variables and the X^2 test for categorical variables between 2 groups. Continuous variables are expressed as the mean ± standard deviation and categorical variables as % and absolute values.

Table 3. Variables associated with the probability of hypertension cure after adrenalectomy, including the impact of smoking.

Variable	Odds ratio and 95% confidence interval	*P* value
Non-smoking habit	1.76, 95% CI 0.89-3.48	.107
Female sex	2.80, 95% CI 1.56-5.01	.001
Use of 2 or fewer antihypertensive medications	2.55, 95% CI 1.44-4.53	.001
Hypertension grade 1	2.63, 95% CI 1.43-4.81	.002
Non-type 2 diabetes	2.26, 95% CI 0.96-5.34	.062
Non-obesity	2.38, 95% CI 1.32-4.29	.004
Constant	0.03, 95% CI 0.01-0.10	<.001

Number of observations: 284; LR $\chi^2(6)$: 76.48; Prob > χ^2: 0.0000; Pseudo R^2: 0.205.

variable in their studies populations of PA cases, reporting figures ranging between 6% and 36%.[22] For example in the Ginzberg SP study,[22] the prevalence was as high as 36%; while in the Manosroi series,[23] only 13% of the cases were smokers and in the BiLiGe *et al*. study,[24] 6% of the patients were active smokers.[5] Other authors described prevalences similar to our study, of 26.2%.[25] In relation to the link between smoking and PA, based on the results of a recent study, the absence of a smoking history was associated with a higher probability of having PA among hypertensive patients (OR in the multivariable analysis of 1.38, 95% CI 1.14-1.65).[22] Nevertheless, other authors found that current smokers were more likely to screen positive for PA compared to non-smokers (OR 2.79, $P < .001$),[23] and others did not find any relationship between smoking habit and the probability of having PA.[25] The differences across these studies may be justified due to differences in the study populations, selection biases, and variations in the employed definitions of smoking habit.

According to our data, no differences were detected in the prevalence of hypokalaemia nor in the severity of PA between smokers and non-smokers. No previous study has evaluated this specific topic in patients with PA. However, it is well known that cigarette smoking invokes a sympathetically mediated pressor response that causes a rise in BP that lasts for about 15 min.[26] Nonetheless, the chronic effects of cigarette smoking on BP remain unclear even in the general hypertensive population. In this regard, some epidemiological studies have shown that current smoking was associated with higher SBP,[27] while other studies reported similar or even lower BP level in smokers than non-smokers.[28] Based on the fact that serum cotinine, a metabolite of nicotine, is associated with increased activation of the renin-angiotensin-aldosterone system,[29] the expected results would be that smokers have higher BP levels and also lower serum potassium levels. Nevertheless, in our series, both serum potassium and BP levels were comparable in smokers and non-smokers, as it was PAC.

Cardiac damage including left ventricular dilatation, myocardial fibrosis, and LVH has been frequently reported in patients with PA and with a higher prevalence compared to patients with essential hypertension.[30] However, the impact of smoking in LVH in patients with PA has not been previously studied. In our cohort, smokers had a higher risk of LVH than non-smokers and tended to have severe LVH more commonly than non-smokers. In this regard, it is not surprising that patients with PA who are current smokers have a higher

risk of cardiovascular events caused by an increased oxidative stress resulting in endothelial injury.[31] Few data exist about the impact of aldosterone hypersecretion on cardiometabolic profile. However, in accordance with our results, one previous prospective study that included 519 cases with PA found that smoking habit was associated with a higher probability of presenting LVH.[32] Nonetheless, the most important risk factor of LVH in these patients was the presence of albuminuria. In our study, we did not find differences in the prevalence of positive albuminuria neither in other important cardiovascular risk factors between smokers and non-smokers. Thus, the higher likelihood of LVI in PA smokers compared to PA non-smokers seems to be linked to smoker habit itself. In this regard, it is recognized that tobacco smoking has an impact on several human organs, especially on the cardiovascular system. It is known that smoking can cause cardiac remodelling, especially resulting in left ventricular (LV) dysfunction and hypertrophy.[33] In this line, in a large prospective study of 4129 patients (2884 never smokers, 503 current smokers, and 742 former smokers), current smoking was associated with higher mean LVMI and lower mean LV circumferential strain in comparison with never smokers. These observations are supported by several previous studies which demonstrated a positive relationship between current smoking and LVH.[34,35]

In our study, a larger tumour size of the adrenal nodule/s was detected in the group of smokers with PA compared to non-smokers. These results are in accordance with those reported by Olsen *et al.*[7] in a series of 1049 patients with adrenal incidentalomas, but without PA. In this study, 35% of the patients were smokers and they found that smokers were younger and had lower BMI, more often bilateral adrenal incidentalomas, larger unilateral adrenal incidentalomas, lower ACTH, and higher cortisol after the DST than non-smokers. The real reason of why adrenal nodules are larger in smoker patients than in non-smokers is unknown; however, it may be related to the effect of reactive oxygen species generated from tobacco use, genetic variations in carcinogen metabolism, cell-cycle regulation, and DNA repair that may influence tobacco-related carcinogenesis.[36] Another important finding was that when never smokers and ex-smokers were compared, no differences were detected in tumour size. These results may be related to a shorter duration of smoking in the groups of ex-smokers than in active smokers, but the real explanation is unknown since we do not have information about the duration of smoking and the number of cigarettes smoked daily. Nonetheless, ex-smokers were younger than smokers, and it is known that the duration of smoking is usually correlated to the age of the patients.

We found that the prevalence of MACS was greater in smokers than in non-smokers, but these differences disappeared after adjusting by the size of the adrenal nodules. No previous studies have evaluated this aspect in patients with PA, but there are some data coming from series of adrenal incidentalomas without associated PA. For example in the Olsen *et al.* series,[7] the prevalence of MACS was 54% in the smokers group compared to 40% in non-smokers ($P < .001$). A higher prevalence of MACS was also reported in other previous studies of patients with adrenal incidentalomas.[37,38] Some authors speculated that the increased prevalence of MACS found in smokers could be explained by an activation of the HPA axis, but, as in our study, they described lower ACTH levels in smoker patients.[7] Other hypotheses are based on the fact that smoking is known to be an inducer of Cyp3A[39] and may increase the risk of a false-positive result in the DST. However, a previous study evaluating the accuracy of plasma dexamethasone determination for MACS diagnosis found similar serum dexamethasone levels in smokers and non-smokers.[38] Our data suggest that the higher prevalence of MACS in the smoker group is related to the larger size of the adrenal nodules since the association MACS smoking disappeared after adjusting by this variable. These results are supported by those described in one of our series of 823 patients with adrenal incidentalomas, where we described that tumour size was a good predictor of MACS (OR = 1.1 for each mm, $P < .001$), and the cut-off of 25 mm presented a good diagnostic accuracy to predict MACS (sensitivity of 69.4%, specificity of 74.1%).[19]

The rate of biochemical and hypertension cure was similar between both groups; however, hypertension cure tended to be more common in the group of non-smokers patients (41.2% vs 29.9%, $P = .076$). As far of our knowledge goes, this is the first study that has identified smoking habit as a potential negative predictive factor for hypertension cure in patients with PA. Other series focused on identified factors associated with the probability of hypertension cure did not find differences in the probability of hypertension cure after adrenalectomy between smokers and non-smokers. For example, in one observational study that included 126 patients with unilateral PA, the rate of hypertension cure did not differ between smokers and non-smokers groups (22.4% vs 29.4%, $P = .370$).[24] Furthermore, several studies focused on identified predictive factors for hypertension cure in PA patients did not evaluate the impact of this variable on surgical outcomes.[40,41] In fact, in our previous study that aimed to develop a model that estimates the probability of hypertension resolution after adrenalectomy in patients with PA, the variable smoking has not been considered neither.[21] Based on the results of our current study, we can propose to include the smoking habit as a potential predictor for hypertension persistence after adrenalectomy.

Although our results are strengthened by our large study population and the high validity of the studied variables, several limitations, including its retrospective design, preclude to establish a causal relationship between smoking habit and the cardiometabolic profile and surgical outcomes. In addition, as we have described in the Methods section, information about the duration of smoking and amount of daily smoking in smokers was not available in most cases. In addition, DST results were not available in the majority of the included cases. Nonetheless, even though the small sample of patients with available DST results, we found an association between MACS and smoking habit in patients with PA.

Conclusion

Patients with PA who smoke have a higher prevalence of LVH and MACS and larger adrenal nodule/s than non-smokers. Smoking has no significant effect on the probability of hypertension response after adrenalectomy in patients with PA; however, a tendency to a lower probability of hypertension cure is observed in smokers compared to non-smokers.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

Marta Araujo-Castro (Conceptualization [lead], Data curation [lead], Formal analysis [lead], Funding acquisition [lead], Investigation [lead], Methodology [lead], Project administration [lead], Resources [lead], Software [equal], Writing—original draft [lead], Writing—review & editing [lead]), Miguel Paja Fano (Methodology [equal], Writing—review & editing [equal]), Marga González-Boillos (Methodology [equal], Writing—review & editing [equal]), Eider Pascual-Corrales (Methodology [equal], Writing—review & editing [equal]), Paola Parra Ramírez (Methodology [equal], Writing—review & editing [equal]), Patricia Martín Rojas-Marcos (Methodology [equal], Writing—review & editing [equal]), Ana García-Cano (Methodology [equal], Writing—review & editing [equal]), Jorge Gabriel Ruiz-Sanchez (Methodology [equal], Writing—review & editing [equal]), Almudena Vicente (Methodology [equal], Writing—review & editing [equal]), Emilia Gómez-Hoyos (Methodology [equal], Writing—review & editing [equal]), Ana Casterás (Methodology [equal], Writing—review & editing [equal]), Albert Puig-Perez (Methodology [equal], Writing—review & editing [equal]), Iñigo García Sanz (Methodology [equal], Writing—review & editing [equal]), Mònica Recasens (Methodology [equal], Writing—review & editing [equal]), Rebeca Barahona San Millan (Methodology [equal], Writing—review & editing [equal]), María José Picón César (Methodology [equal], Writing—review & editing [equal]), Patricia Díaz Guardiola (Methodology [equal], Writing—review & editing [equal]), Carolina Perdomo (Methodology [equal], Writing—review & editing [equal]), Laura Manjón-Miguélez (Methodology [equal], Writing—review & editing [equal]), Ángel Rebollo Román (Methodology [equal], Writing—review & editing [equal]), Cristina Robles Lázaro (Methodology [equal], Writing—review & editing [equal]), José María Recio (Methodology [equal], Writing—review & editing [equal]), Manuel Morales-Ruiz (Writing—review & editing [equal]), María Calatayud (Methodology [equal], Writing—review & editing [equal]), Noemi Jiménez López (Methodology [equal], Writing—review & editing [equal]), Diego Meneses (Methodology [equal]), Miguel Sampedro Nuñez (Methodology [equal]), Elena Mena Ribas (Methodology [equal]), Alicia Sanmartín Sánchez (Methodology [equal]), Cesar Gonzalvo Diaz (Methodology [equal]), Cristina Lamas (Methodology [equal], Writing—review & editing [equal]), María del Castillo Tous (Methodology [equal]), Joaquín Serrano (Methodology [equal]), Theodora Michalopoulou (Methodology [equal]), Susana Tenes Rodrigo (Methodology [equal]), Ricardo Roa Chamorro (Methodology [equal]), Fernando Jaén Aguila (Methodology [equal]), Eva María Moya Mateo (Methodology [equal]), Sonsoles Gutiérrez-Medina (Methodology [equal]), and Felicia Alexandra Hanzu (Methodology [equal], Writing—review & editing [equal])

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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: November 10, 2020, code: ACTA 401).

Informed consent statement

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

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