RESEARCH

Differences in the presentation and evolution of primary aldosteronism in elderly (≥65 years) and young patients (<65 years)

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Abstract

Objective: To compare the presentation and evolution of primary aldosteronism (PA) in the elderly (≥65 years) and young patients (<65 years).
Methods: A retrospective multicenter study was performed in 20 Spanish hospitals of PA patients in follow-up between 2018 and 2021.
Results: Three hundred fifty-two patients with PA <65 years and 88 patients ≥65 years were included. Older PA patients had a two-fold higher prevalence of type 2 diabetes, dyslipidemia, and cerebrovascular disease, but these differences disappeared after adjusting for hypertension duration. At diagnosis, diastolic blood pressure was lower than in young patients (83.3 ± 11.54 vs 91.6 ± 14.46 mmHg, *P* < 0.0001). No differences

Key Words

▶ primary aldosteronism
▶ adrenal venous sampling
▶ adrenalectomy
▶ elderly

in the rate of overall correct cannulation (56.5% vs 42.3%, *P* = 0.206) or the diagnosis of unilaterality (76.9% vs 62.5%, *P* = 0.325) in the adrenal venous sampling (AVS) was observed between the elderly and young groups. However, there was a lower proportion of PA patients who underwent adrenalectomy in the elderly group than in the younger group (22.7% (*n* = 20) vs 37.5% (*n* = 132), *P* = 0.009). Nevertheless, no differences in the rate of postsurgical biochemical (100% (*n* = 14) vs 92.8% (*n* = 90), *P* = 0.299) and hypertension cure (38.6% (*n* = 51) vs 25.0% (*n* = 5), *P* = 0.239) were observed between both groups.

Conclusion: Older patients with PA have a worse cardiometabolic profile than young patients with PA that it is related to a longer duration of hypertension. However, the results of the AVS, and adrenalectomy are similar in both groups. Therefore, the management of elderly patients with PA should be based not only on age, but rather on the overall medical, physical, social, and mental characteristics of the patients.

Introduction

Primary aldosteronism (PA) is the most common and curable cause of endocrine-related hypertension, with a prevalence of 5–10% among patients with hypertension in primary care and 20% among patients with resistant hypertension (1). Patients with PA have a higher cardiometabolic risk profile, with four times increased risk for stroke and six times for nonfatal myocardial infarction, than patients with essential hypertension (EHT) matched by blood pressure (BP), sex, and age (2, 3). Therefore, early diagnosis of PA and targeted treatment are necessary to prevent or mitigate cardiovascular complications (1).

On the other hand, people worldwide are living longer. Globally, a person who turned 65 years old could live 17 years from 2015 to 2020; however, this number could rise to 19 years in 2045–2050(4). Likewise, the prevalence of hypertension is increasing globally owing to population aging (5). This would mean that the candidate population for hypertension screening could be progressively older. This latter point has important implications for hypertension study. Postmortem studies suggest two notable adrenal histopathologic changes that are observed with older age: (i) the normal and contiguous expression of CYP11B2 appears to decline; (ii) aldosterone-producing cell clusters (APCC) appear to be more prevalent with older age (6, 7). These histopathological observations indicate that aging may be associated with an impaired ability to physiologically secrete aldosterone and an increased autonomous and pathophysiological aldosterone secretion (8). In fact, it has been proposed that the APCC can also be a cause of bilateral idiopathic hyperaldosteronism (9). Moreover, more recently, the HISTALDO consensus proposes that the CYP11B2 immunohistochemistry should be incorporated into the routine clinical diagnostic workup to localize the likely source of aldosterone production (10).

In addition, in older patients, the aldosterone-renin ratio (ARR) increases, mainly attributed to the reduction of renin in the context of the deterioration of kidney function, and thus the number of false-positive screening results can be high (11). In this context, PA is frequently a challenging condition in clinical practice. Currently, there are no specific recommendations for screening, diagnosis, and treatment for elderly patients with PA. Data on PA prevalence or outcomes in the elderly are scarce and there are few studies specific to the age group (12, 13).

The aim of our study was to compare the characteristics of PA that are present at diagnosis and during follow-up, including the results in adrenal venous sampling (AVS) and adrenalectomy, in elderly patients (≥65 years) and younger patients than 65 years old, to determine if it would be recommendable to follow specific recommendations for the screening, diagnosis, and treatment of elderly patients with PA.

Methods

Participants

The Spanish Primary Aldosteronism Registry (SPAIN-ALDO Registry) was created in February 2021 on the initiative of the work group of adrenal diseases of the Spanish Endocrinology and Nutrition Society. At the time of the analysis of this study (4 December 2021), 450 participants with a diagnosis of PA in follow-up between 2018 and 2021 in twenty Spanish tertiary hospitals were included in the registry. The participation of the different centers in the

study is voluntary, all Spanish centers that attend patients with PA are invited to participate. The study investigators included endocrinologists, clinical biochemists, and general surgeons. We stratified the population according to age, considering age 65 as the threshold for old age in accordance with accepted conventional measures of aging (14).

Two control groups were selected from the ADRENAL INCIDENTALOMA register at Ramón y Cajal University Hospital (RCUH) (15), which contains information from 730 patients with adrenal incidentalomas (AIs). Patients with primary hypertension, matched by age (±5 years old) in whom PA (normal plasma aldosterone (PAC)/renin ratio) and glucocorticoid excess (cortisol post-dexamethasone suppression test <1.8 µg/dL) was excluded, were included as control groups. Two control groups were established: one group <65 years old (*n* =60) and another group ≥65 years old (*n* = 112).

Figure 1 shows the flow of patient selection for the study. Patients were entered into an online database (REDCap® database) (16, 17) after pseudonymization using an identification number (record_Id). This study was approved by the ethical committee of the RCUH (approval date: 10 November 2020, code: ACTA 401).

Clinical evaluation and definitions

Clinical and laboratory data were extracted from the medical records of each referral center. As we previously published (18), the register included more than 230 variables per patient, including data about demographic factors (age, sex, and smoking habits), comorbidities such as hypertension (grade based on ESC 2018 classification (19)), hypertension duration, target organ damage (chronic kidney disease, left ventricular hypertrophy, and cardiovascular and cerebrovascular events), family history of hypertension, hypokalemia, type 2 diabetes mellitus, obesity, dyslipidemia and sleep apnea

syndrome. Information about pharmacological history with antihypertensive (type, number, and doses), oral antidiabetic and lipid-lowering medications, potassium supplements and antiplatelet agents was also registered. Data about physical examination including systolic blood pressure (SBP), diastolic blood pressure (DBP), and BMI (kg/m^2). All variables were measured in the outpatient clinic and data were collected from the moment of the diagnosis of PA, after surgery, and in the last available visit during the follow-up as registered in clinical records.

The diagnosis of PA was established according to the current clinical International guidelines of PA (1, 20). A total of 267 patients underwent a confirmatory test (162 saline infusion test, 89 captopril test, and 16 oral sodium loading test), whereas 173 patients meeting the criteria of plasma aldosterone concentration (PAC) >20 ng/dL in the context of a spontaneous hypokalemia, suppressed renin, pathological PAC/renin ratio and hypertension did not submit to dynamic tests.

Radiological evaluation, adrenal venous sampling, and surgical outcomes

CT and/or MRI were performed at diagnosis in all patients included in the study. Furthermore, (6β-131I) iodomethyl-19-norcholesterol scintigraphy was evaluated in 75 patients. AVS was not a prerequisite for a hospital to participate in the registry. When the selectivity index, computed as the ratio of concentrations of cortisol from an adrenal vein and the infra-renal inferior vena cava, was at least 2 without ACTH stimulation and at least 3 with ACTH stimulation, AVS was deemed successful. Lateralization index (LI) was calculated by dividing the aldosterone-to-cortisol ratio on the dominant side by that on the nondominant side. LI was indicative of unilaterality if it was higher than 2 or 3 without or with ACTH stimulation, respectively (21).
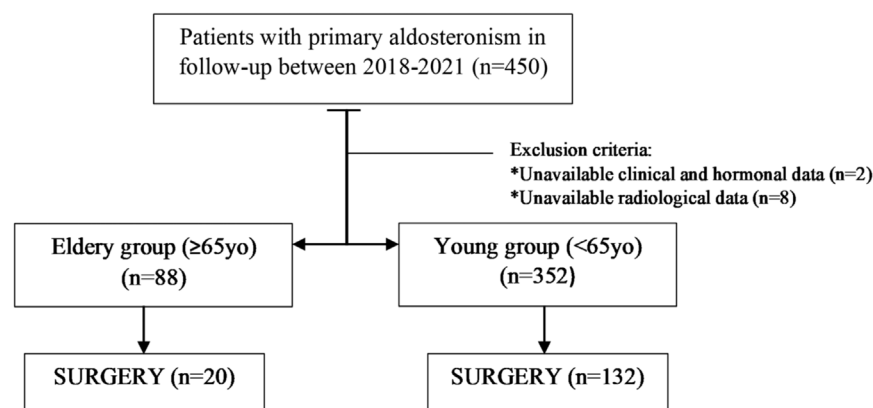

Figure 1
Study population.

In patients who underwent adrenalectomy, the definitions of biochemical and clinical cure for PA were based on the PASO classification system (22), as we have previously described (18). Only patients with complete biochemical response (normokalemia and normalization of the ARR) were classified as biochemically cured.

Statistical analysis

STATA 15 (StataCorp LLC, College Station, TX, USA) was used for statistical analysis. Data for continuous variables were expressed as mean ± s.d. or median and (interquartile range), and as percentages (and absolute values) for categorical variables. We checked continuous variables for normality using the Shapiro–Wilk test, and for homogeneity of the variances using Levene's test. The Student's *t*-test was used to compare quantitative variables and the $x^2\beta$ test for qualitative variables between two groups. Odds ratios (OR) were calculated using a logistic regression analysis, considering the younger group as a reference. For the adjustment by possible confounding factors, a multivariate logistic regression analysis was employed. In all cases, a two-tailed *P* value <0.05 or a 95% CI not including the number 1, were considered statistically significant. Pearson's correlation coefficient (r) was used for the estimation of the correlation between continuous variables.

Results

Age distribution of patients with primary aldosteronism

Data from 440 patients with PA were examined. A total of 88 (20%) were included in the group of ≥65 years old and 352 in the group of <65 years old. The mean age of the cohort was 54.6 ± 12.1 years old. The distribution of patients according to age is shown in Fig. 2.

Differences in clinical and hormonal characteristics

As expected, patients with PA of the elderly group had a two-fold higher prevalence of type 2 diabetes (OR = 1.9 (1.1–3.3), dyslipidemia (OR = 2.2 (1.4–3.5), and cerebrovascular disease (OR = 2.4 (1.1–5.2) than the younger patient group (Table 1). These differences in the cardiometabolic profile disappeared after adjusting for hypertension duration. A longer time elapsed between the diagnosis of hypertension and primary hyperaldosteronism was observed in the group of PA ≥65 than in the younger group (10.2 ± 10.26 vs 4.1 ± 7.54 years, *P* < 0.0001). We found that the older group had lower levels of DBP than the younger group. A negative correlation between age and DBP was observed (r = −0.29, *P* < 0.0001), but not with SBP (r = −0.00, *P* = 0.952). Nevertheless, no correlation was found between age and PAC levels (r = −0.04, *P* = 0.466), renin activity (r = −0.03, *P* = 0.636) nor concentration (r = 0.01; *P* = 0.971). The mean creatinine clearance in the elderly was significantly lower than in the non-elderly PA group. Based on CT/MRI, 66.4% of the patients had unilateral disease. Overall, unilateral PA was significantly more common in women than men (73.3% vs 61.0%, *P* = 0.007); however, when we considered only patients ≥65 years old in the analysis, these differences disappeared (65.7% vs 66.0%, *P* = 0.975).

Compared with the control group of the same age, patients with PA ≥65 years old had higher DBP and SBP levels and a higher prevalence of cerebrovascular events (OR = 7.9 (1.7–36.5)). However, patients with primary hypertension ≥65 years old had diabetes more frequently than patients with PA of the same age, and the control group <65 years old had a higher prevalence of dyslipidemia than PA patients of the same age (Table 2). Similar to the observed in patients with PA, patients with primary hypertension in
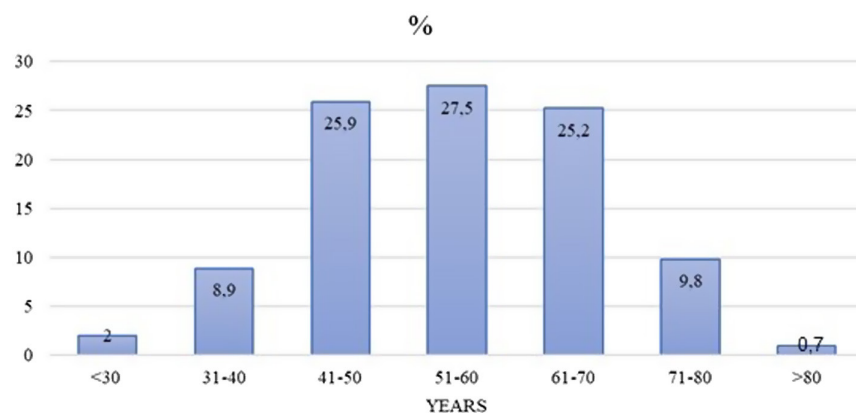

Figure 2
Age distribution of patients with primary aldosteronism.

Table 1 Clinical characteristics and laboratory parameters of the two age groups of patients with primary aldosteronism at diagnosis.

	Global cohort	≥65 years old (*n* = 88)	<65 years old (*n* = 352)	*P* value
Age (years)	54.6 ± 12.1	71.3 ± 4.81	50.5 ± 9.49	<0.0001
Female, *n* (%)	191 (43.4)	35 (39.8)	156 (44.3)	0.442
Treatment				
Antihypertensive medications (*n*)	2.6 ± 1.4	2.8 ± 1.15	2.6 ± 1.43	0.300
Antihypertensive drug classes, *n* (%)				
MRAs	96 (21.8)	16 (18.2)	80 (22.7)	0.356
IECAS/ARA2s	281 (63.9)	56 (63.6)	225 (63.9)	0.960
Alpha blockers	129 (29.3)	27 (30.7)	102 (29.0)	0.753
Beta blockers	137 (31.1)	33 (37.5)	104 (29.6)	0.149
Calcium blockers	259 (58.9)	60 (68.2)	199 (56.5)	0.047
Diuretics	165 (37.5)	35 (39.8)	130 (36.9)	0.622
Other drugs	22 (5.0)	5 (5.7)	17 (4.8)	0.743
Hypertension				
Hypertension grade ≥2 (*n* = 432), (%)	262 (60.7)	47 (53.4)	215 (62.5)	0.119
Hypertension duration (*years*) (*n* = 390)	9. 8 ± 9.0	16.0 ± 10.33	8.2 ± 7.85	**<0.0001**
PA duration (years)	4.4 ± 0.97	5.7 ± 0.39	4.1 ± 0.77	**<0.0001**
Comorbid disease, *n* (%)				
Type 2 diabetes	82 (18.6)	24 (27.3)	58 (16.5)	**0.020**
Dyslipidemia	179 (40.9)	49 (56.3)	130 (37.0)	**0.001**
Cardiovascular events	106 (24.1)	28 (31.8)	78 (22.2)	0.058
Cerebrovascular events	31 (7.1)	11 (12.5)	20 (5.6)	**0.025**
Hypokalemia at any time	251 (57.1)	52 (61.9)	187 (55.7)	0.301
SBP (mmHg)	150.0 ± 22.6	150. 2 ± 23.11	150.0 ± 22.51	0.936
DBP (mmHg)	89.9 ± 14.3	83.3 ±11.54	91.6 ± 14.46	**<0.0001**
BMI (kg/m^2) (*n* = 389)	29.7 ± 5.8	29.2 ± 4.16	29.9 ± 6.19	0.293
Blood chemistry				
Creatinine (mg/dL)	1.2 ± 4.62	1.0 ± 0.41	1.3 ± 5.18	0.263
Creatinine clearance (MDRD-4) (mL/min per 1.73 m^2)	85.1 ± 22.33	76.8 ± 21.91	87.3 ± 21.95	**<0.001**
Serum potassium (mEq/L)	3.7 ± 0.6	3.7 ± 0.58	3.7 ± 0.62	0.510
Serum sodium (mEq/L)	141.4 ± 9.9	142.2 ± 2.64	141.3 ± 10.98	0.144
PAC (ng/dL)	36.6 ± 25.1	35.0 ± 25.97	37.0 ± 24.9	0.524
PRA (ng/mL/h) (*n* = 204)	0.4 ± 0.9	0.3 ± 0.41	0.5 ± 1.0	0.062
PRC (μU/mL) (*n* = 104)	3.7 ± 8.6	2.5 ± 2.79	3.7 ± 7.82	0.150
CT and MRI evaluation				
Tumour size (*n* = 315, mm)	17.5 ± 8.25	17.2 ± 8.41	17.6 ± 8.22	0.703
Unilaterality (*n*, %)	292 (66.4)	58 (65.9)	234 (66.5)	0.920

Diagnostic value for PA were established as described in the 'Materials and methods' section.
Bold indicates statistical significance.
DBP, diastolic blood pressure; IECAS/ARA2, ACE inhibitor or angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonists; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration; SBP, systolic blood pressure.

Table 2 Differences in the cardiometabolic profile between patients with primary aldosteronism and primary hypertension.

Variable	Group ≥65 years old	Group <65 years old
	PA (*n* = 88) vs primary hypertension (*n* = 112)	PA (*n* = 352) vs primary hypertension (*n* = 93)
Age	71.3 ± 4.81 vs 71.9 ± 3.96, *P* = 0.329	50.5 ± 9.49 vs 52.9 ± 5.29, *P* = 0.056
Female sex	39.8% vs 52.7%, *P* = 0.069	44.3% vs 53.3%, *P* = 0.195
Type 2 diabetes	27.3% vs 42.0%, ***P* = 0.031**	16.5% vs 23.3%, *P* = 0.196
Dyslipidemia	43.7% vs 31.3%, *P* = 0.071	37.0% vs 51.7%, ***P* = 0.032**
Cardiovascular events	68.2% vs 79.5%, *P* = 0.069	22.2% vs 13.3%, *P* = 0.120
Cerebrovascular events	12.5% vs 1.8%, ***P* = 0.002**	5.7% vs 3.3%, *P* = 0.455
SBP (mmHg)	150.2 ± 23.11 vs 143.1 ± 16.26, ***P* = 0.017**	150.0 ± 22.51 vs 136.0 ± 17.79, ***P* < 0.001**
DBP (mmHg)	83.3 ± 11.54 vs 79.0 ± 9.91, ***P* = 0.008**	91.6 ± 11.46 vs 84.3 ± 10.56, ***P* = 0.005**
BMI (kg/m^2)	29.2 ± 4.16 vs 30.5 ± 3.99, *P* = 0.045	29.9 ± 6.19 vs 31.4 ± 6.12, *P* = 0.119

BMI, body mass index; DBP, diastolic blood pressure; PA, primary aldosteronism; SBP, systolic blood pressure.
Bold indicates statistical significance.

the elderly group had a higher prevalence of type 2 diabetes (OR = 2.4 (1.2–4.8) and dyslipidemia (OR = 2.1 (1.1–3.9) than the younger patient group.

Differences in the success rate of the adrenal venous sampling and surgical outcomes

Of the 440 patients with PA, 153 (34.8%) underwent AVS. It was performed with adrenocorticotropic hormone stimulation in 111 patients and without stimulation in 42 cases. Of the 153 patients underwent AVS, there was a tendency to higher proportion of patients <65 years old (85.0%) than ≥65 years old (15.0%). Nevertheless, the proportion of patients who underwent AVS in both groups was similar (36.9% of the younger group and 26.1% of the elderly group, $P = 0.057$). Overall, both adrenal veins were correctly canulated in 45.1% ($n = 69$) of the procedures (77.8% of success rate in the left adrenal vein and 48.4% in the right adrenal vein). The rate of overall correct canulation was similar between patients <65 years old (42.3%) and ≥65 years old (56.5%) ($P = 0.206$). Based on a properly performed AVS, 35 patients <65 years old (62.5%) had unilateral disease and 10 patients ≥65 years old (76.9%) ($P = 0.325$). Only three patients experienced AVS complications, all of them mild (1 patient ≥65 years old experienced chest pain with spontaneously resolution and 2 patients <65 years old an adrenal hemorrhage without significant hemodynamic repercussion).

Differences in surgical outcomes

A total of 152 patients underwent adrenalectomy. According to age, 86.8% of the patients who underwent adrenalectomy were <65 years old ($n = 132$) and 13.2% ($n = 20$) ≥65 years old. Surgery was based on the results of AVS in 34 patients (6 in the group ≥65 years old and 28 in the group <65 years old), based on CT/MRI in 99 patients, and based on CT/MRI and (6β-131I) iodomethyl-19-norcholesterol scintigraphy in 19 patients. There was a higher proportion of PA patients who underwent adrenalectomy in the younger group than in the elderly group (37.5% vs 22.7%, $P = 0.009$). Overall, biochemical response was achieved in 93.7% (104/111) (there were 41 patients in whom the results of renin activity nor renin concentration were available, so biochemical response could not be classified) and clinical response in 88.4% (HTA resolution in 56 patients and improvement in 74). No differences in the probability of hypertension cure were observed between the group of <65 years old and ≥65 years old (38.6% vs 25.0%, $P = 0.239$), nor in the rate of biochemical cure (92.8% vs 100%, $P = 0.299$). After a mean follow-up of 40.4 ± 46.9 months, no differences were observed in the need for antihypertensive drugs for BP control nor in the evolution of clinical and hormonal parameters during the follow-up (Table 3). Compared to patients medically treated, we observed a decrease in the number of antihypertensive pills for BP control (−1.2 ± 1.2 vs −0.1±1.2, $P < 0.001$) and there was an increased tendency to discontinue potassium supplements (78.1% vs 62.7%, $P = 0.103$) in the group of surgery. The reduction of BP pills was similar between elderly and young patients who underwent adrenalectomy (−1.0 ± 1.2 vs −1.3 ± 1.2, $P = 0.421$).

Discussion

As far as our knowledge goes, this is one of the largest studies focused on comparing the clinical and hormonal

Table 3 Clinical and hormonal evolution after adrenalectomy according to the age group.

	≥65 years old ($n = 20$)	<65 years old ($n = 132$)	*P* value
ΔNumber of antihypertensive drugs ($n = 118$)	−1.0 ± 1.19	−1.3 ± 1.21	0.421
ΔSBP (mmHg) ($n = 132$)	−23.8 ± 37.51	−20.8 ± 22.22	0.746
ΔDBP (mmHg) ($n = 132$)	−8.4 ± 16.29	−13.2 ± 14.35	0.198
ΔGFR (MDRD-4) ($n = 71$)	−15.7 ± 18.32	−14.2 ± 24.36	0.819
ΔSerum potassium (mEq/L) ($n = 143$)	1.2 ± 0.83	1.0 ± 0.74	0.339
ΔSerum Na (mEq/L) ($n = 141$)	−1.5 ± 3.09	1.0 ± 0.74	0.339
ΔPAC (ng/dL) ($n = 118$)	−12.0 ± 17.29	−20.6 ± 28.47	0.115
ΔPRA (ng/mL/h) ($n = 59$)[a]	1.4 ± 2.02	1.1 ± 1.64	0.713
ΔPRC (ng/mL/h) ($n = 41$)[a]	64.4 ± 89.54	26. 7 ± 81.79	0.414

Diagnostic value for PA were established as described in the 'Materials and method' section.

[a]There were 41 patients in whom the results of renin activity nor renin concentration were available, but these patients had resolution of hypokalemia after surgery.

Δ, mean differences between the value at list visit and first visit; DBP, diastolic blood pressure; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure.

characteristics and AVS and surgical outcomes of elderly patients (≥65 years) and patients younger than 65 years old with PA. The main findings of our study were the following: (i) 20% of the patients with PA were older than 65 years old; (ii) as expected, they have a longer hypertension history, with a negative impact on the cardiometabolic profile of these patients; iii) patients with PA ≥65 years old had a higher prevalence of cerebrovascular events than the control group of the same with primary hypertension; (iv) AVS is a safe procedure in elderly patients, with a rate of success canulations similar to the observed in younger patients; (v) despite a longer duration of hypertension in elderly patients, no differences were observed in rates of hypertension and biochemical cure compared with younger patients.

The study of PA in the elderly has been poor and the prevalence in this population has rarely been reported (23); however, the higher prevalence of adrenal adenomas and hypertension has been confirmed in previous studies (24, 25). Approximately 65% of men and 75% of women develop high BP by 70 years (26), and the peak prevalence of adrenal incidentalomas is in the fifth and seventh decades (27). This is consistent with our results where 66% of patients had a CT or MRI showing an adrenal adenoma.

As could be expected, patients with PA ≥65 years old had a worse cardiometabolic profile than patients with PA younger than 65 years. These differences disappeared after adjusting for hypertension duration. Hypertension duration might be reflecting a longer duration of PA in the elderly group. Supporting this hypothesis, we found a difference between the diagnosis of hypertension and PA of more than 10 years in the elderly group and of 4 years in the young group. This could be related to a delay in the diagnosis of PA, which seems to be higher in the elderly than in the young group, or the coexistence of primary hypertension. In this sense, it is known that with a longer duration of PA, a greater negative effect in the cardiometabolic system is expected (28). However, when we compared patients with PA and primary hypertension in the same group, the differences in the cardiometabolic profile disappeared, suggesting the worse cardiometabolic profile in elderly patients could be more related to the effects of age itself. Nevertheless, a negative effect of aldosterone excess was proved in the elderly group, where we found a prevalence of cerebrovascular events eight times higher in PA patients than in the control group of the same age. These results are in accordance with the reported previously by several authors (2, 3).

Regarding the evaluation of the ARR in an elderly patient, the following considerations should be taken into account: (i) there is a reduction in renin production, both basal and stimulated by sodium depletion, evident from the sixth decade of life (29). This reduction in renin levels is probably due to age-related decline in renal function (approximately 1 mL/min/year from the fourth decade); (ii) and there is a modest concomitant decrease in aldosterone levels, although to a lesser extent than renin concentrations. This could be attributed to the aging-related reduction in potassium excretion. In our series, we did not find any correlation between biochemical parameters such as aldosterone, renin, and age. However, it is important to realize that there is a continuum of renin-independent aldosteronism, with a broad clinical spectrum. In this regard, it might be expected that the severity of PA would be greater in older patients due to longer exposure to hypertension, but we found no difference in the prevalence of hypokalemia or hypertension grade ≥2. In fact, we even observed that older patients with PA had significantly lower DBP than younger patients. In this line, previous studies have shown an age-related late fall in DBP in normotensive and untreated hypertensive subjects, especially after 60 years (26, 30). Although this phenomenon has not been adequately explained, the most plausible theory suggests that it is the manifestation of increased large artery stiffness. In addition, with aging, there is an increase in amplitude and velocity of incident pulse waves, so left ventricular ejection becomes affected during systole rather than diastole (31). These changes will produce a higher SBP and lower DBP with a wider pulse pressure. Therefore, it seems that the arterial hypertension phenotype in PA does not vary with age with respect to patients with essential hypertension. A longer observation is necessary to investigate whether the phenotypic presentation of PA in older patients is milder than in younger patients; if it shows a more insidious disease onset or if, on the contrary, it takes us a while to suspect and diagnose it.

We found that only 26.1% of the older patients with PA underwent AVS; however, the proportion of AVS performance was also low in the younger group. Little has been reported about the diagnosis performance of AVS in the elderly. A retrospective analysis of a Japanese dataset reported a similar proportion of unilateral PA in patients older and younger than 65 years (32). Although in our study there was a low rate of AVS performance, our results agree with those communicated by Takeda *et al.* (32). On the contrary, Akasaka *et al.* (33) found a trend of decreased incidence of unilateral PA with aging in women and increase incidence in men. However, there were modest age differences with a large overlap between men and

women. In any case, AVS appears to be a safe strategy for PA subclassification also in the elderly.

On the other hand, population aging is a multidimensional phenomenon. Assuming the people are older at a fixed chronological age (e.g. 65 years) means that the characteristics of individuals are invariant at that age. People's characteristics are very different; however, there is a tendency in the medical field to believe that the benefits of making a PA diagnosis are low in the elderly cohort because they can be poor candidates for anesthesia or surgery. Despite the underlying disease and the significant comorbidity and longer hypertension duration in the elderly group, we did not find statistically significant differences in the rates of biochemical and clinical success between the elderly and non-elderly groups. Our findings are consistent with the previously reported that no significant differences in clinical or biochemical cure rate in PA were observed when stratified by age (34). Most patients experienced at least partial clinical success, even in the group older than 65 years, and complete biochemical success after adrenalectomy was found in at least 50% of patients, regardless of age at the time of surgery (34). A long history of hypertension has been described as an independent predictor of hyperkalemia after surgery in elderly patients (32), however, in our analysis we found no significant differences. Therefore, we believe that age should not be a limiting factor when screening, diagnosing, and treating PA. Nevertheless, we are aware that the limited sample size of patients who experienced hypertension could have limited the ability to find statistically significant differences, since only 5 out of 20 patients in the elderly group (25%) and 51 out of 132 in the young group (38.6%) experienced hypertension cure, difference that seems at least clinically relevant. Screening for PA and associated comorbidities in older adults should be individualized and periodically revised. Clinical judgment and discussion with patients would be the key to decide AVS or to undergo adrenalectomy. Importantly, prolonged follow-up is needed to examine whether biochemical improvement after adrenalectomy can decrease cardiovascular events and mortality in older patients.

We are aware that there are some limitations in our study. First, its retrospective nature does not allow to fully control the risk of confounding factors. Secondly, only 153 patients had performed AVS studies, and the rate of overall success rate of AVS was as low as 45%. In this sense, only in 34 patients who underwent adrenalectomy the decision of surgery was based on the AVS that is considered the gold standard for the subtyping of PA (35). Moreover, due to the multicenter character of our study, the indications of AVS

in an individual patient differ depending on the decisions of the physicians in each center. Thus, this factor could explain the lower rate of hypertension cure observed in our cohort study, reducing the probability to find differences between the group of elderly patients (≥65 years) and patients younger than 65 years old.

Conclusion

Older patients with PA have a long hypertension history that also may reflect a higher duration of the aldosterone excess. Both, associated with the effects of age itself, justify the presence of a worse cardiometabolic profile than young patients. However, AVS is a safe technique in the elderly, with comparable results in terms of cannulation rate that are observed in younger PA patients. Moreover, adrenalectomy offers a similar chance of biochemical and hypertension cure in older and young patients with PA. Therefore, the management of elderly patients with PA should be based not only on age, but rather on the overall medical, physical, social, and mental characteristics of the patients.

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