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ORIGINAL ARTICLE

# Assessment of the Aldosteronona resolution score as a predictive resolution score of hypertension after adrenalectomy for aldosteronoma in French patients

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**Abstract**
*Purpose* Aldosteronoma Resolution Score (ARS) is a predictive score for cure of hypertension after adrenalectomy for hyperaldosteronism and has been validated in American patients. The aim of the study was to validate this score in a French population.
*Method* Data concerning patients operated from 2002 to 2015 in 7 French University Hospitals were retrospectively collected. Diagnosis of Aldosterone-producing adenoma (APA) was confirmed with clinical and biochemical hyperaldosteronism and adrenal nodule on CT scan. Adrenal venous sampling was performed when CT failed to identify laterality. ARS is based on four variables: female sex, BMI ≤25 kg/m$^2$, duration of hypertension ≤6 years, number of antihypertensive medications ≤2. One point is attributed for the first three and 2 points for the last. Patients were considered as cured if they had no hypertension and no antihypertensive medications at least 6 months after surgery. Patients with bilateral adrenal hyperplasia were excluded.
*Results* This multicenter study included 310 patients with APA. ARS and follow-up were obtained in 257 patients. 46.6% of patients were cured and potassium serum level was normalized in 97.7%. In multivariate analysis, odds ratio for female sex, BMI ≤25 kg/m$^2$, duration of hypertension ≤6 years, and number of antihypertensive medications ≤2 were 1.60 ($p$ = 0.09), 1.77 ($p$ = 0.04), 1.28 ($p$ = 0.4), 3.41 ($p$ < 0.001), respectively. Cure rate were, respectively, 22.2, 41.4 and 74% for patients with a score ARS 0–1, 2–3, 4–5. The area under the curve (AUC) of ARS was 0.715.
*Conclusion* ARS is not a predictive score efficient enough in a French population maybe due to different metabolic data and genetic conditions.

**Keywords** Aldosterone producing adenoma · Adrenalectomy · Hypertension · Aldosteronoma resolution score

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## Introduction

Primary aldosteronism (PA) is caused by a renin-independent overproduction of aldosterone, and characterized by drug-

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resistant hypertension and hypokalemia. The prevalence is estimated at about 10% in adult population [1]. PA is caused commonly by either an aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia, respectively, in 60–65% and 30–35% of cases. Other rare causes of PA include unilateral adrenal hyperplasia (1–2%), aldosterone-secreting adrenocortical carcinoma (1%), familial hyperaldosteronism (1%), and ectopic aldosterone-producing adenoma or carcinoma (1%) [2]. Surgery is the gold standard treatment for aldosterone-producing adenoma and cure hypertension in 42% of patients [3].

Zarnegar et al. created a predictive model based on four preoperative factors that could accurately predict complete resolution of hypertension after adrenalectomy for APA. This externally validated model, termed the Aldosteronoma Resolution Score (ARS), includes the following four preoperative variables: taking ≤2 anti hypertensive medications, BMI ≤25 kg/m2, duration of hypertension ≤6 years, and female sex. If ≤2 antihypertensive medications were taken preoperatively, 2 points are attributed to that variable. One point is attributed to each of the other variables, if present. The range of the resulting ARS is 0 to 5 points. The higher the ARS, the greater is the likelihood of resolution of hypertension after adrenalectomy. The proportions of patients with complete resolution according to ARS were 13.7% in patients with an ARS 0 or 1, 44.1% in patients with an ARS 2 or 3, and 80.0% in patients with an ARS 4 or 5 [4].

Utsumi et al. have shown that three variables were independently associated with complete resolution of hypertension: number of preoperative antihypertensive medications ≤2, duration of hypertension <6 years, and female sex. They confirmed the high predictive accuracy of the ARS, in Japanese people, using not only cross tabulation but also the AUC (area under curve) [5].

Currently there is not score to predict healing of hypertension after adrenalectomy for APA in a French population.

The aim of our study was to identify the clinical factors that influence the postoperative outcomes of hypertension and to validate the accuracy of ARS in predicting complete resolution of hypertension after adrenalectomy in French patients with APA.

## Methods

We retrospectively collected data from seven university hospitals in France. Criteria used to establish the diagnosis of primary aldosteronism included a history of persistent hypertension, with or without hypokalemia, and biochemical evidence of primary hyperaldosteronism. Biochemical evidence of primary aldosteronism was defined as a plasma aldosterone concentration/plasma renin activity ratio ≥ 23 with a plasma aldosterone concentration ≥ 15 ng/dL, and suppressed plasma renin ≤1 ng /dL or less. Patients with APA were distinguished from those with IHA on the basis of whether a unilateral adrenal tumor was identified on abdominal CT-scan. When CT-scan failed to identify a unilateral tumor, or in case of patients >50 years, or according local use of medical team, adrenal venous sampling was performed to determine laterality.

The blood pressure (BP) of each patient was classified in accordance with the World Health Organization 1999 guidelines as normal BP (<140/90 mmHg) or hypertension [6]. After adrenalectomy, patients were considered as cured if they had no hypertension and were not taking any antihypertensive medications at least 6 months postoperatively.

The following baseline variables before surgery were obtained by a review of medical records: date of birth, date of operation, sex, body mass index (BMI), size of tumor, other cardiovascular diseases, number of antihypertensive medications and duration of hypertension. Laboratory data collected included blood levels of potassium and aldosterone, plasma renin, and aldosterone-to-plasma renin ratios. Clinical outcome data consisted of post-operative blood pressure, number of antihypertensive, medications at the 6-month postoperative consultation, and long term kaliemia.

Univariate and multivariate analyses were conducted to find relevant prognostic variables using a Cox proportional hazards model. We evaluated the predictive accuracy of ARS in our dataset using area under the curve (AUC) derived from the ROC curve. Continuous data are expressed as mean (± SD) and median (± extreme). Statistical calculations were performed with SPSS® statistics software (version 23.0, Armonk, NY: IBM Corp). Statistical significance was taken at $p < 0.05$.

**Table 1** Characteristics of patients before surgery

| | Mean (± SD) | Median [extreme] |
|---|---|---|
| Age at the surgery (years) | 50.02 (± 10.69) | 51 [17–83] |
| Duration of hypertension (years) | 6.32 (± 6.55) | 4 [0–35] |
| Number of antihypertensive medications | 2.25 (± 1.18) | 2 [0–7] |
| Body mass index (kg/m$^2$) | 26.67 (± 5.09) | 26 [17.4–48] |
| Adenoma size (mm) | 16.82 (± 7.16) | 15 [5–50] |
| Kaliemia (mmol/L) | 3.39 (± 0.64) | 3.3 [1,5–5.4] |
| Aldosterone-renin ratio | 307 (± 1178.77) | 101.75 [1.2–14,666] |

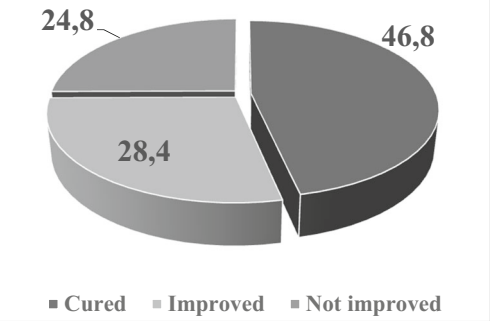


**Fig. 1** Performance of the Aldoteronoma Resolution Score (ARS) for patients with primary aldosteronism. The percentages of patients with complete resolution and incomplete resolution were correlated with predictive score

## Results

This retrospective multicenter study included 310 patients who underwent adrenalectomy for APA in seven university hospitals (Angers, Limoges, Lyon, Nancy, Nantes, Paris, and Tours) in France between 2002 and 2015.

One hundred and seventy women (54.8%) and 140 men (45.2%) (sex ratio = 1.21) were operated. ARS and follow-up were obtained for 257 patients (82.9%). ARS could not be calculated for 23 patients. Follow-up was unknown for 32 patients (for two patients ARS and follow up was missing).

Characteristics of population are summarized in Table 1. Some 8.2% patients had mellitus diabetes and 10.5% patients were smokers.

Of the patients, 73.6% had preoperative adapted antihypertensive medications (anti-aldosterone medication) (amiloride, spironolactone, eplerenone). Among these patients, 44.2% had a normal preoperative BP; however, 26.8% patients without anti-aldosterone treatment had a normal preoperative BP, $p = 0.01$. Patients with normal preoperative BP had a mean of 1.96 antihypertensive medications, versus 2.44 for patients with high preoperative BP.

Forty-four patients (14.2%) had adrenal venous sampling, 45.2% of these patients were cured.

Laparoscopy was successfully performed in 96.8% of patients. Six patients had a laparoscopy converted into laparotomy, and one patient had a planned laparotomy given its history of splenectomy. Three patients underwent robotic procedure. Morbidity and mortality were 2.9 and 0.3%, respectively (three patients had acute urine retention, one renal infarction, one hematoma of the adrenal bed, one hemoperitoneum requiring transfusion, one abdominal wall hematoma, one patient had chronic pain, one pancreatitis after a laparoscopic left adrenalectomy, one incisional hernia).

At least 6 months after adrenalectomy, 46.8% of the patients (130/278) had a complete resolution of hypertension, 28.4% (79/278) were improved with a normal BP with less consummation of antihypertensive medications than previously, 24.8% (69/278) were not improved after adrenalectomy (Figure 1).

Final pathologic findings confirmed solitary adenoma in 95.8 while 4.2% of patients had an adenoma within the background of hyperplasia. There is no significant difference for complete resolution of hypertension between patients who had adenoma alone and those who had adenoma with hyperplasia ($p = 0.92$). Potassium serum level was normalized in 98.3%.

In univariate analysis, female sex, BMI, diabetes and number of antihypertensive medications were significant variables for complete resolution of hypertension (Table 2). In multivariate analysis, odds ratio for female sex, BMI ≤25 kg/m$^2$, duration of hypertension ≤6 years, and number of antihypertensive medications ≤2 were 1.60 [0.94; 2.73] ($p = 0.09$), 1.77 [1.04; 3.05] ($p = 0.04$), 1.28 [0.72 ; 2.29] ($p = 0.4$), 3.41 [1.91; 6.11] ($p < 0.001$), respectively.

Only age of patients at adrenalectomy was another significant variable ($p < 0.05$). Preoperative BP, size of adenoma, aldosterone-renine ratio, adrenal venous sampling were not significant variables. Number of antihypertensive medications was the main predictive factor for cure. The mean number of antihypertensive medication before and after adrenalectomy were 2.24 (± 1.16) and 0.81 (± 1.02) respectively ($p < 0.0001$) for all patients and 2.67 (±1.21) before and 1.52 (±0.94) after adrenalectomy ($p < 0.0001$) for non-cured patients. There was no significant difference for cure rate between patients who underwent adrenal venous sampling and those who did not ($p = 0.87$). Cure rates were, respectively,

**Table 2** Means and percentages of the different variables depending on the cure of hypertension in univariate analysis

| Variables | Cured (130 patients) | Not cured (148 patients) | *P* |
|---|---|---|---|
| Age at the surgery (years) | 46.9 ± 10.7 | 52.9 ± 10.7 | 0.107 |
| Female sex | 87 (66.9%) | 62 (41.9%) | 0.0001 |
| Body mass index (kg/m$^2$) | 25.4 ± 4.8 | 28.0 ± 5.1 | 0.008 |
| Diabetes | 2 (8.7%) | 146 (91.3%) | 0.0001 |
| Active smoking | 12 (10.3%) | 13.2% | 0.57 |
| Duration of hypertension (years) | 4.6 ± 6.1 | 8 ± 8.1 | 0.366 |
| Number of antihypertensive medications | 1.76 ± 1.02 | 2.67 ± 1.17 | < 0.0001 |
| Adenoma size (mm) | 16.8 ± 7.4 | 16.5 ± 7.2 | ns |

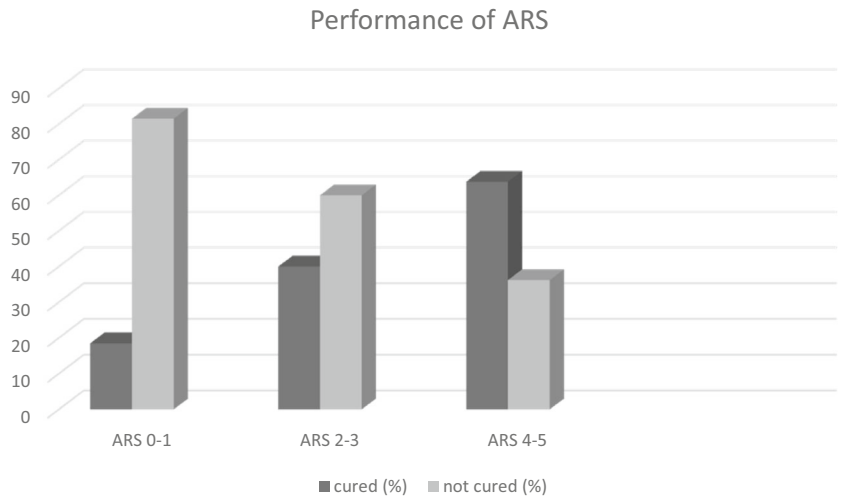


**Fig. 2** Results at least 6 months after adrenalectomy for APA

18.5% (12/65 patients), 40% (36/90), and 63.8% (74/116) for patients with an ARS 0–1, 2–3, 4–5 (Figure 2). When the performance of the ARS was tested using cross tabulation, an ARS of 0–1 had a negative predictive value of 82% (53/65 patients), while an ARS of 4–5 had a positive predictive value of 64% (74/116 patients). A ROC curve was generated, and the AUC was calculated to assess the predictive accuracy. The area under the curve (AUC) of ARS was 0.71 (Figure 3). We failed to improve the accuracy of ARS by adding variables as preoperative BP, ARR, age, adrenal venous sampling, because AUC was 0.76 (Figure 4).

## Discussion

The main objectives of adrenalectomy in patients with APA are a complete resolution of hypertension or, at least, improvement of BP with fewer medications, and the correction of hypokaliemia. In our study, adrenalectomy led to normalize kaliema in 98.2% of patients and 46.8% patients were cured. These results are not different to several studies [3]. Almost

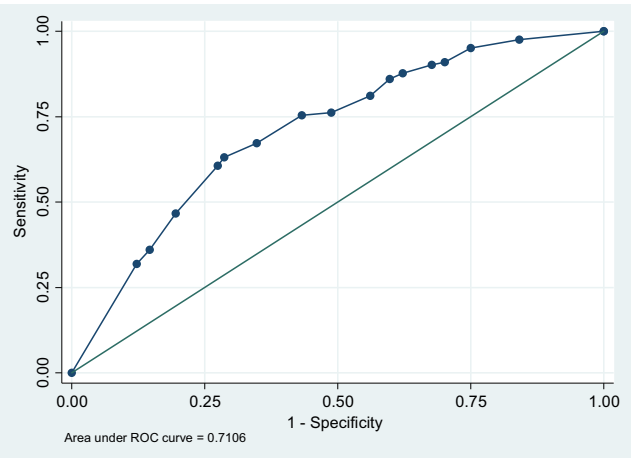


**Fig. 3** ROC curve of the ARS in French population

75% of patients benefited from adrenalectomy. A significant less consummation of medications for control of hypertension even if patients are not cure, is a good reason for purpose surgery for patients with APA. It has been already proved that adrenalectomy for APA is cost effective [7].

We found that an adapted antihypertensive medication is significantly better for preoperative BP control. Only 75% of our patients had this kind of treatment; information for health professionals could help to avoid vascular events.

ARS only uses data from medical history and clinical examination, so it can help clinicians and surgeons with simple and objective data to predict results of the surgical procedure on BP. We did not find the same variables used in ARS by Zarnegar et al. as independent predictors associated with complete resolution of hypertension [4]. Indeed, all variables had a lower odds ratio in our French population. Only two of these were significant in multivariate analysis (BMI $\leq$25 kg/m$^2$ and number of medications $\leq$2).

The ARS model had a negative predictive value and positive predictive value of, respectively, 72.4 and 75.0% in the validation dataset, 86.3 and 80.0% in the combined derivation and validation dataset when the patient's score was 0 or 1. Negative predictive value and positive predictive value were also important in Utsumi et al. study (respectively, 88.0 and 75.0%) [4]. In our model, the negative predictive value and positive predictive value were lower (respectively 82 and 64%).

We could not confirm the predictive accuracy of the ARS with the AUC, maybe due to a longer follow up. Indeed, the postoperative BP of some patients has been collected few years after surgery and essential hypertension may have appeared. This assumption was demonstrated by another American external validation group 1 year later after adrenalectomy, showing a AUC of ARS of 0.838 [2].

Our results indicate that ARS cannot be used with the original accuracy to identify, in a French APA population, patients who would have complete resolution of hypertension.

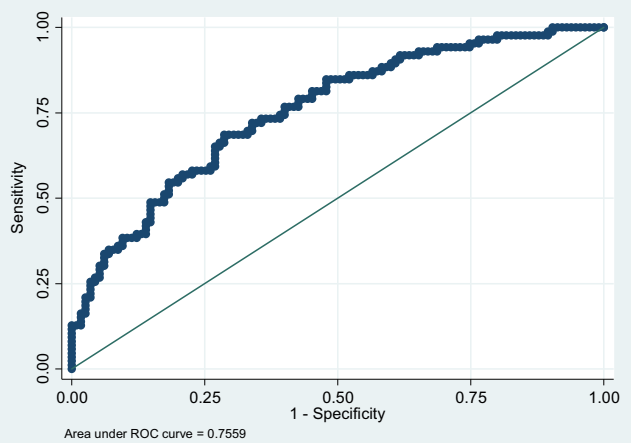


**Fig. 4** ROC curve in french population by adding variables as preoperative blood pressure, ARR, age, and adrenal venous sampling

Hypothesis for the failure correction of hypertension are the presence of concomitant essential hypertension or cardiovascular damage (as cardiac fibrosis, left ventricular hypertrophy) caused by aldosterone excess [8].

Even though it is, according to our knowledge, the most important series of surgery for APA, there are many biases in our study.

Data of long-term BP were, sometimes, collected much more than 6 months after adrenalectomy; this is the main interference to compare the cohort of Zarnegar and ours. Indeed an essential hypertension could appear few years later after surgery.

There may be also a recruitment bias with patients operated on in university hospitals who probably have more comorbidities than those operated on in other institutions. Anymore, methods of aldosterone measurement may differ between biochemical laboratories. Data regarding tobacco use, familial history of hypertension may lack. Moreover, we did not have the mutations in this group. Somatic mutations of different genes coding for ion channel and ATPases have been identified in APA. Clinical and biochemical phenotypes are linked to specific genetic alteration [9–14]. KCNJ5 mutations are more present in young females and ATPase mutations are more present in men [1, 9]. Patients with KCNJ5 mutations need significant less antihypertensive medications compared with those without mutation after surgery [15].

## Conclusion

ARS is not a predictive score efficient enough in a French population maybe due to different metabolic data and genetic conditions between American and French population. We cannot found an easy and accurate score to predict cure of hypertension.

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**Compliance with ethical standards**

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