SUPPLEMENTAL DATA

Development of a prediction score to avoid confirmatory testing in patients with suspected primary aldosteronism.

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Summary

Table S1. Patient Characteristics of Study Cohort: Univariate Regression Analysis

Variable (ref. PA confirmed)	OR (CI 95%)	*P*-value
Age at diagnosis (years)	0.99 (0.98-1.01)	0.202
Female sex, n (%)	0.34 (0.24-0.46)	**<0.001**
Duration of HTN (months)	1.01 (1.00-1.01)	0.089
Systolic BP (mmHg)	1.01 (1.01-1.02)	**0.003**
Diastolic BP (mmHg)	1.01 (1.00-1.03)	0.052
Antihypertensive medication (DDD)	1.40 (1.27-1.54)	**<0.001**
BMI (Kg/sqm)	1.02 (0.99-1.06)	0.204
PRA at screening (ng/mL/h)	0.28 (0.14-0.57)	**<0.001**
Aldosterone at screening (ng/dL)	1.06 (1.04-1.08)	**<0.001**
Lowest Potassium (mEq/L)	0.13 (0.09-0.19)	**<0.001**
eGFR (mL/min)	1.00 (0.99-1.01)	0.666
Diabetes, n (%)	1.60 (0.82-3.12)	0.166
Organ damage, n (%)	3.13 (2.28-4.29)	**<0.001**
CV events, n (%)	2.16 (1.27-3.67)	**0.004**

Odds ratio (OR) and the 95% confidence interval (CI) were evaluated by univariate logistic regression analysis for each variable. An OR greater than 1 indicates an increased likelihood of confirmed PA, and an OR less than 1 a decreased likelihood. HTN, Hypertension; BP, Blood Pressure; DDD, Defined Daily Dose (average maintenance dose per day for a drug used for its main indication in adults); PRA, Plasma Renin Activity; eGFR, estimated Glomerular Filtration Rate; CV, Cardiovascular. Organ damage is defined as presence of left ventricular hypertrophy at echocardiography and/or microalbuminuria.

Table S2. Patient Characteristics of Study Cohort: Multivariate Regression Analysis

Variable (ref. PA confirmed)	OR (CI 95%)	*P*-value
Female sex, n (%)	0.42 (0.28-0.62)	**<0.001**
Systolic BP (mmHg)	1.00 (0.99-1.01)	0.566
Antihypertensive medication (DDD)	1.21 (1.07-1.36)	**0.002**
PRA at screening (ng/mL/h)	0.07 (0.03-0.19)	**<0.001**
Aldosterone at screening (ng/dL)	1.08 (1.06-1.11)	**<0.001**
Lowest Potassium (mEq/L)	0.15 (0.09-0.23)	**<0.001**
Organ damage, n (%)	2.64 (1.74-4.01)	**<0.001**
CV events, n (%)	1.40 (0.72-2.72)	0.315

Odds ratio (OR) and the 95% confidence interval (CI) were evaluated by multivariate logistic regression analysis for variables associated to a confirmed PA diagnosis in the univariate model. An OR greater than 1 indicates an increased likelihood of confirmed PA, and an OR less than 1 a decreased likelihood. BP, Blood Pressure; DDD, Defined Daily Dose (average maintenance dose per day for a drug used for its main indication in adults); PRA, Plasma Renin Activity; CV, Cardiovascular. Organ damage is defined as presence of left ventricular hypertrophy at echocardiography and/or microalbuminuria.

Table S3. Characteristics of Training versus Internal Validation cohort

Variable	Combined Cohort (n=696)	Training Cohort (n=522)	Validation Cohort (n=174)	*P*-value
Confirmed PA, n (%)	421 (60.5)	322 (61.7)	99 (56.9)	0.263
Subtyping, UPA (%)	133 (19.1)	98 (18.8)	35 (20.1)	0.313
Age at diagnosis (years)	50 ± 9.9	50 ± 10.2	50 ± 9.3	0.770
Female sex, n (%)	318 (45.7)	239 (45.8)	79 (45.4)	0.930
Duration of HTN (months)	64 [21; 131]	59 [21; 128]	75 [23; 134]	0.300
Systolic BP (mmHg)	155 ± 20.3	155 ± 20.4	155 ± 20.2	0.889
Diastolic BP (mmHg)	95 ± 11.0	95 ± 11.1	94 ± 10.8	0.531
Antihypertensive medication (DDD)	2.15 [1.00; 4.00]	2.00 [1.00; 3.69]	2.33 [1.00; 4.00]	0.765
BMI (Kg/sqm)	25.7 ± 4.28	25.9 ± 4.23	25.4 ± 4.45	0.224
PRA at screening (ng/mL/h)	0.30 [0.15; 0.40]	0.22 [0.15; 0.40]	0.30 [0.20; 0.45]	0.086
Aldosterone at screening (ng/dL)	25.6 [18.7; 35.5]	25.8 [18.8; 35.5]	24.3 [18.5; 35.1]	0.791
Lowest Potassium (mEq/L)	3.8 ± 0.62	3.8 ± 0.62	3.8 ± 0.61	0.414
eGFR (mL/min)	91 ± 17.0	91 ± 17.2	91 ± 16.6	0.914
Diabetes, n (%)	44 (6.3)	33 (6.3)	11 (6.3)	1.000
Organ damage, n (%)	404 (58.0)	298 (57.1)	106 (60.9)	0.375
CV events, n (%)	81 (11.6)	62 (11.9)	19 (10.9)	0.733

Characteristics of patients included in the developmental cohort: patients from the combined cohort (n=696) were randomly assigned to training (n=522), or validation cohort (n=174). HTN, Hypertension; BP, Blood Pressure; DDD, Defined Daily Dose (average maintenance dose per day for a drug used for its main indication in adults); PRA, Plasma Renin Activity; eGFR, estimated Glomerular Filtration Rate; CV, Cardiovascular. Organ damage is defined as presence of left ventricular hypertrophy at echocardiography and/or microalbuminuria. Normally and non-normally distributed variables were reported as mean ± standard deviation or median [interquartile range], respectively. Categorical variables were reported as absolute number (n) and proportion (%).

Table S4. Characteristics of Developmental versus Validation cohort

Variable	Developmental Cohort (n=696)	External Validation Cohort (n=328)	*P*-value
Confirmed PA, n (%)	421 (60.5)	173 (52.7)	**0.019**
Subtyping, UPA (%)	133 (19.1)	89 (27.1)	0.299
Age at diagnosis (years)	50 ± 9.9	50 ± 13.5	0.467
Female sex, n (%)	318 (45.7)	192 (58.5)	**<0.001**
Duration of HTN (months)	64 [21; 131]	48 [11; 138]	**0.006**
Systolic BP (mmHg)	155 ± 20.3	150 ± 19.6	**<0.001**
Diastolic BP (mmHg)	95 ± 11.0	93 ± 12.4	0.136
Antihypertensive medication (DDD)	2.15 [1.00; 4.00]	1.00 [0.00; 2.50]	**<0.001**
BMI (Kg/sqm)	25.7 ± 4.28	27.0 ± 5.09	**<0.001**
PRA at screening (ng/mL/h)	0.30 [0.15; 0.40]	N.A.	N.A.
DRC at screening (mU/L)	N.A.	2.7 [2.0; 5.6]	N.A.
Aldosterone at screening (ng/dL)	25.6 [18.7; 35.5]	12.8 [8.2; 20.0]	**<0.001**
Lowest Potassium (mEq/L)	3.8 ± 0.62	3.5 ± 0.51	**<0.001**
eGFR (mL/min)	91 ± 17.0	87 ± 19.9	**0.001**
Diabetes, n (%)	44 (6.3)	36 (11.0)	**0.010**
Organ damage, n (%)	404 (58.0)	129 (39.3)	**<0.001**
CV events, n (%)	81 (11.6)	39 (11.9)	0.907
Confirmatory testing Saline infusion test, n (%) Captopril Challenge test, n (%)	 560 (80.5) 136 (19.5)	 319 (97.3) 9 (2.7)	**<0.001**
PRA pre-confirmatory test (ng/mL/h)	0.20 [0.10; 0.40]	N.A.	N.A.
DRC pre-confirmatory test (mU/L)	N.A.	3.4 [2.0; 8.3]	N.A.
Aldosterone pre-confirmatory test (ng/dL)	22.7 [16.5; 31.4]	12.0 [7.5; 18.0]	**<0.001**
PRA post-confirmatory test (ng/mL/h)	0.15 [0.10; 0.30]	N.A.	N.A.
DRC post-confirmatory test (mU/L)	N.A.	2.0 [2.0; 4.3]	N.A.
Aldosterone post-confirmatory test (ng/dL)	7.5 [3.5; 15.1]	5.6 [3.5; 11.4]	0.068

Characteristics of patients included in the analysis: patients from the developmental cohort from Torino (n=696) were compared to patients from the external validation cohort from Munich (n=328). HTN, Hypertension; BP, Blood Pressure; DDD, Defined Daily Dose (average maintenance dose per day for a drug used for its main indication in adults); PRA, Plasma Renin Activity; eGFR, estimated Glomerular Filtration Rate; CV, Cardiovascular. Organ damage is defined as presence of left ventricular hypertrophy at echocardiography and/or microalbuminuria. Normally and non-normally distributed variables were reported as mean ± standard deviation or median [interquartile range], respectively. Categorical variables were reported as absolute number (n) and proportion (%).

Table S5. Diagnostic performance of machine learning based models

	PACT Score Accuracy	Predicted Diagnosis		Performance	
LDA Model	**Training cohort** (N = 522)	PA confirmed	PA not confirmed	Accuracy (%)	79.7
	PA confirmed	272	50	Sensitivity (%)	84.5
	PA not confirmed	56	144	Specificity (%)	72.0
	Validation cohort (N = 174)	PA confirmed	PA not confirmed	Accuracy (%)	77.6
	PA confirmed	82	17	Sensitivity (%)	82.8
	PA not confirmed	22	53	Specificity (%)	70.7
	Combined cohort (N = 696)	PA confirmed	PA not confirmed	Accuracy (%)	79.2
	PA confirmed	354	67	Sensitivity (%)	84.1
	PA not confirmed	78	197	Specificity (%)	71.6
RF Model	**Training cohort** (N = 522)	PA confirmed	PA not confirmed	Accuracy (%)	82.8
	PA confirmed	286	36	Sensitivity (%)	88.8
	PA not confirmed	54	146	Specificity (%)	73.0
	Validation cohort (N = 174)	PA confirmed	PA not confirmed	Accuracy (%)	79.9
	PA confirmed	84	15	Sensitivity (%)	84.8
	PA not confirmed	20	55	Specificity (%)	73.3
	Combined cohort (N = 696)	PA confirmed	PA not confirmed	Accuracy (%)	82.0
	PA confirmed	370	51	Sensitivity (%)	87.9
	PA not confirmed	74	201	Specificity (%)	73.1
Linear SVM	**Training cohort** (N = 522)	PA confirmed	PA not confirmed	Accuracy (%)	80.7
	PA confirmed	272	50	Sensitivity (%)	84.5
	PA not confirmed	51	149	Specificity (%)	74.5
	Validation cohort (N = 174)	PA confirmed	PA not confirmed	Accuracy (%)	78.2
	PA confirmed	82	17	Sensitivity (%)	82.8
	PA not confirmed	21	54	Specificity (%)	72.0
	Combined cohort (N = 696)	PA confirmed	PA not confirmed	Accuracy (%)	80.0
	PA confirmed	354	67	Sensitivity (%)	84.1
	PA not confirmed	72	203	Specificity (%)	73.8
Gaussian SVM	**Training cohort** (N = 522)	PA confirmed	PA not confirmed	Accuracy (%)	83.9
	PA confirmed	284	38	Sensitivity (%)	88.2
	PA not confirmed	46	154	Specificity (%)	77.0
	Validation cohort (N = 174)	PA confirmed	PA not confirmed	Accuracy (%)	74.7
	PA confirmed	81	18	Sensitivity (%)	81.8
	PA not confirmed	26	49	Specificity (%)	65.3
	Combined cohort (N = 696)	PA confirmed	PA not confirmed	Accuracy (%)	81.6
	PA confirmed	365	56	Sensitivity (%)	86.7
	PA not confirmed	72	203	Specificity (%)	73.8

The table shows real and predicted diagnosis (PA confirmed vs. not confirmed), accuracy, sensitivity, specificity for the training cohort (n=522), the validation cohort (n=174), and the combined cohort from Torino (n=696). Diagnostic performance is shown for LDA (linear discriminant analysis), RF (random forest), linear and gaussian SVM (support vector machine) models.

Table S6. Diagnostic performance of the models at training and validation

Performance		N	Cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
LDA Model	Training	522	N.A.	84.5	72.0	82.9	74.2	79.7
	Internal Validation	174		82.8	70.7	78.8	75.7	77.6
	External Validation	328		65.9	92.3	90.5	70.8	78.4
RF Model	Training	522	N.A.	88.8	73.0	84.1	80.2	82.8
	Internal Validation	174		84.8	73.3	80.8	78.6	79.9
	External Validation	328		77.5	67.7	72.8	72.9	72.9
Linear SVM	Training	522	N.A.	84.5	74.5	84.2	74.9	80.7
	Internal Validation	174		82.8	72.0	79.6	76.1	78.2
	External Validation	328		63.6	94.8	93.2	70.0	78.4
Gaussian SVM	Training	522	N.A.	88.2	77.0	86.1	80.2	83.9
	Internal Validation	174		81.8	65.3	75.7	73.1	74.7
	External Validation	328		68.2	90.3	88.7	71.8	78.7
PACT Score (Best Accuracy)		522	≥ 8	92.2	71.0	83.7	85.0	84.1
	Internal Validation	174		91.9	73.3	82.0	87.3	83.9
	External Validation	328		78.6	83.9	84.5	77.8	81.1
PACT Score (Max Sensitivity)		522	≥ 5	100.0	23.5	67.8	100.0	70.7
	Internal Validation	174		100.0	21.3	62.7	100.0	66.1
	External Validation	328		100.0	28.4	60.9	100.0	66.2
PACT Score (Max Specificity)		522	≥ 13	24.8	100.0	100.0	45.2	53.6
	Internal Validation	174		21.2	100.0	100.0	49.0	55.2
	External Validation	328		14.5	100.0	100.0	51.2	54.9

Sensitivity (Sens), specificity (Spec), positive/negative predictive value (PPV/ NPV), and accuracy (Acc) for proposed models (each indicator is derived considering a confirmed diagnosis of PA as referral category). LDA, Linear Discriminant Analysis; RF, Random Forest; SVM, Support Vector Machine; PACT, Primary Aldosteronism Confirmatory Testing Score. Internal and external validations are provided on Torino and Munich cohorts, respectively.

Table S7. Score development and validation

PACT Score Accuracy		Predicted Diagnosis		Performance	
Real Diagnosis (Cut-off ≥ 5)	**Training cohort** (N = 522)	PA confirmed	PA not confirmed	Accuracy (%)	70.7
	PA confirmed	322	0	Sensitivity (%)	100.0
	PA not confirmed	153	47	Specificity (%)	23.5
	Validation cohort (N = 174)	PA confirmed	PA not confirmed	Accuracy (%)	66.1
	PA confirmed	99	0	Sensitivity (%)	100.0
	PA not confirmed	59	16	Specificity (%)	21.3
	Combined cohort (N = 696)	PA confirmed	PA not confirmed	Accuracy (%)	69.5
	PA confirmed	421	0	Sensitivity (%)	100.0
	PA not confirmed	212	63	Specificity (%)	22.9
Real Diagnosis (Cut-off ≥ 8)	**Training cohort** (N = 522)	PA confirmed	PA not confirmed	Accuracy (%)	84.1
	PA confirmed	297	25	Sensitivity (%)	92.2
	PA not confirmed	58	142	Specificity (%)	71.0
	Validation cohort (N = 174)	PA confirmed	PA not confirmed	Accuracy (%)	83.9
	PA confirmed	91	8	Sensitivity (%)	91.9
	PA not confirmed	20	55	Specificity (%)	73.3
	Combined cohort (N = 696)	PA confirmed	PA not confirmed	Accuracy (%)	84.1
	PA confirmed	388	33	Sensitivity (%)	92.2
	PA not confirmed	78	197	Specificity (%)	71.6
Real Diagnosis (Cut-off ≥ 13)	**Training cohort** (N = 522)	PA confirmed	PA not confirmed	Accuracy (%)	53.6
	PA confirmed	80	242	Sensitivity (%)	24.8
	PA not confirmed	0	200	Specificity (%)	100.0
	Validation cohort (N = 174)	PA confirmed	PA not confirmed	Accuracy (%)	55.2
	PA confirmed	21	78	Sensitivity (%)	21.2
	PA not confirmed	0	75	Specificity (%)	100.0
	Combined cohort (N = 696)	PA confirmed	PA not confirmed	Accuracy (%)	54.0
	PA confirmed	101	320	Sensitivity (%)	24.0
	PA not confirmed	0	275	Specificity (%)	100.0

The table shows real and predicted diagnosis (PA confirmed vs. not confirmed), accuracy, sensitivity, specificity for the training cohort (n=522), the validation cohort (n=174), and the combined cohort from Torino (n=696). Diagnostic performance is shown for the PACT (Primary Aldosteronism Confirmatory Testing) score. A cut-off of equal or greater than 5 identifies patients with a confirmed diagnosis of PA with the maximum sensitivity; a cut-off of equal or greater than 8 identifies patients with a confirmed diagnosis of PA with the higher accuracy; a cut-off of equal or greater than 13 identifies patients with a confirmed diagnosis of PA with the maximum specificity.

Table S8. Correlation of the PACT score with hormonal measurements at confirmatory testing

Variable	Pearson's R	*P*-value
Aldosterone pre-confirmatory test (ng/dL)	0.479	**<0.001**
ARR (PRA) pre-confirmatory test ([ng/dL]/[ng/mL/h])	0.247	**<0.001**
ARR (DRC) pre-confirmatory test ([ng/dL]/[mU/L])	0.415	**<0.001**
Aldosterone post-confirmatory test (ng/dL)	0.443	**<0.001**
ARR (PRA) post-confirmatory test ([ng/dL]/[ng/mL/h])	0.251	**<0.001**
ARR (DRC) post-confirmatory test ([ng/dL]/[mU/L])	0.240	**<0.001**

Correlations between the PACT score and hormonal measurements at confirmatory testing (aldosterone and ARR pre- and post-test). The ARR (aldosterone-to-renin ratio) is calculated by dividing aldosterone for PRA or DRC. Pearson's R and P-value are reported for each correlation.

Table S9. Distribution of patients with PA according to the score

Score Points	Total (n)	PA not confirmed		PA confirmed	
		(n)	(%)	(n)	(%)
0.0-2.0	14	14	100.0	0	0.0
2.1-4.0	49	49	100.0	0	0.0
4.1-6.0	138	106	76.8	32	23.2
6.1-8.0	145	63	43.4	82	56.6
8.1-10.0	137	25	18.2	112	81.8
10.1-12.0	112	18	16.1	94	83.9
12.1-14.0	87	0	0.0	87	100.0
14.1-16.0	14	0	0.0	14	100.0
Total	696	275	N.A.	421	N.A.

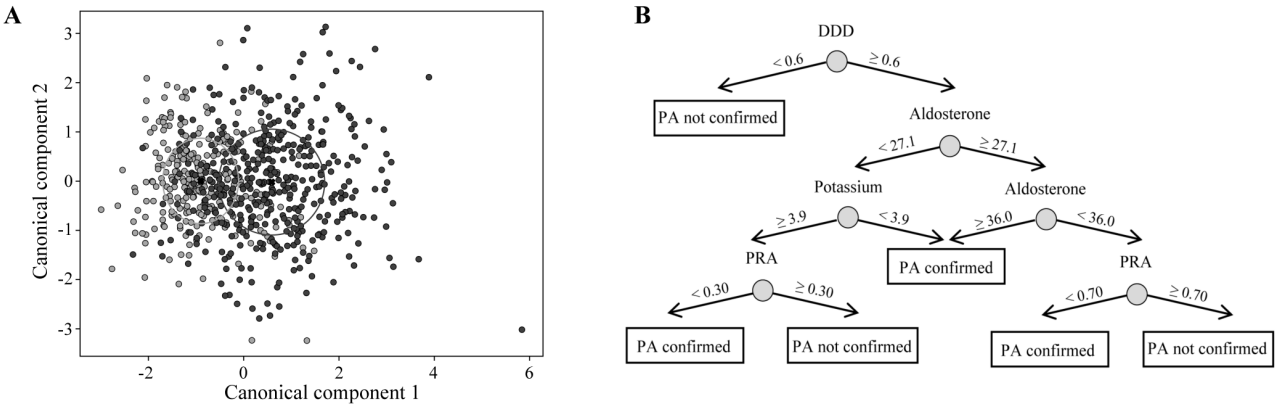
Number (n) and proportion (%) of patients stratified for diagnosis (PA confirmed *vs.* not confirmed) is shown according to the score in the developmental cohort of Torino (n=696). N.A., Not Applicable.

Table S10. Diagnostic performance in patients with unilateral PA

Performance	Accuracy (%)	Missed UPA Patients (n)
LDA Model	95.0	11
RF Model	97.7	5
Linear SVM	95.0	11
Gaussian SVM	96.8	7
PACT Score	98.2	4
Flow chart – 1st model	100.0	0
Flow chart – 2nd model	100.0	0

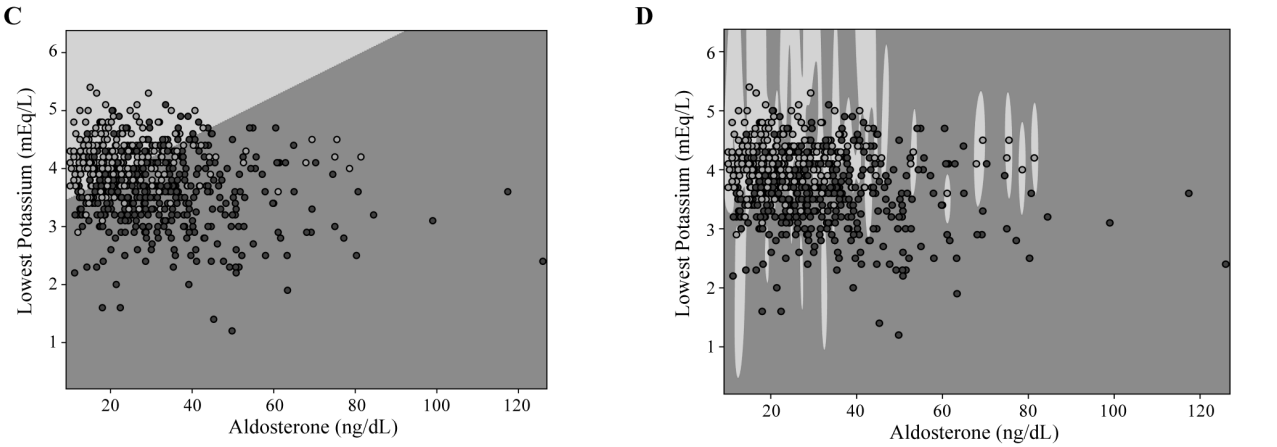
The table shows the accuracy of all the proposed models in patients with a diagnosis of unilateral PA (UPA; n=222) and the number of patients with UPA which would be missed by each different approach. See Figure 2 and Figure S3A for flow chart 1st and 2nd model, respectively. LDA, Linear Discriminant Analysis; RF, Random Forest; SVM, Support Vector Machine; PACT, Primary Aldosteronism Confirmatory Testing Score.

Figure S1. Diagnostic modelling



LDA Model		Predicted	
		PA confirmed	PA not confirmed
Real	PA confirmed	**354**	67
	PA not confirmed	78	**197**
		Accuracy (%)	79.2
		Sensitivity (%)	84.1
		Specificity (%)	71.6

RF Model		Predicted	
		PA confirmed	PA not confirmed
Real	PA confirmed	**370**	51
	PA not confirmed	74	**201**
		Accuracy (%)	82.0
		Sensitivity (%)	87.9
		Specificity (%)	73.1



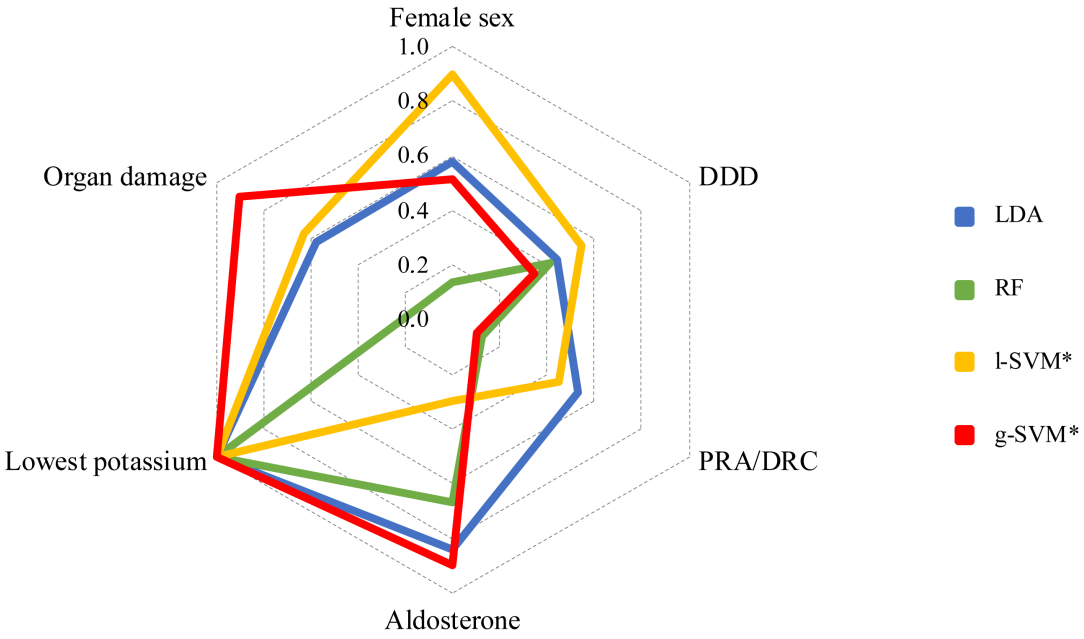
Linear SVM		Predicted	
		PA confirmed	PA not confirmed
Real	PA confirmed	**354**	67
	PA not confirmed	72	**203**
		Accuracy (%)	80.0
		Sensitivity (%)	84.1
		Specificity (%)	73.8

Gaussian SVM		Predicted	
		PA confirmed	PA not confirmed
Real	PA confirmed	**365**	56
	PA not confirmed	72	**203**
		Accuracy (%)	81.6
		Sensitivity (%)	86.7
		Specificity (%)	73.8

Machine learning based models to discriminate patients with a confirmed diagnosis of PA (n=421) from patients with not confirmed PA (n=275). The models included the 6 variables with the highest prediction power. Confusion matrix shows real and predicted diagnosis, accuracy, sensitivity, and specificity for each model in the developmental cohort (n=696). Data on training and validation of the models are reported in Table S5. (**A**) Canonical plot representing diagnostic performance of LDA; each patient is indicated by a point and diagnosis are reported by colour (confirmed PA, black; not confirmed PA, grey). The axes (canonical component 1 and 2) are calculated by weighted linear combination of the 6 variables included in the model to maximize the separation between groups. The crosses indicate the means of (canonical 1; canonical 2) for patients with UPA or BPA, the ellipse included patients with a linear combination coefficient that falls within the mean ± SD. (**B**)

The first classification tree of the forest is shown for the prediction of PA confirmed *vs.* not confirmed. (**C**, **D**) Graphs showing the performance of SVM models (Support Vector Machine, Linear and Gaussian). Axes report the two best support vector classifiers: aldosterone at screening on x-axis and lowest recorded potassium levels on y-axis. Each patient is indicated by a point and diagnosis are reported by colour (confirmed PA, dark grey; not confirmed PA, grey). Model prediction areas are indicated by colours, as appropriated.

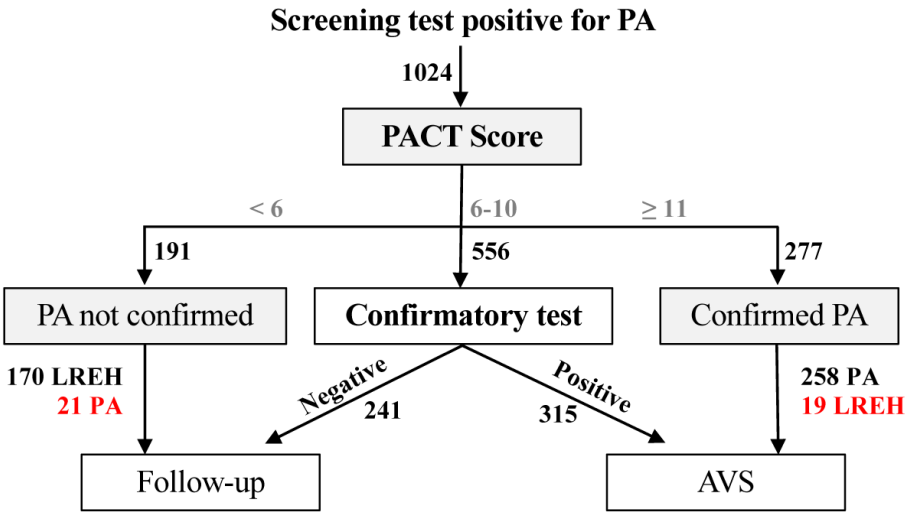
Figure S2. Predictor importance for machine learning based models



The graph shows predictor importances for the machine learning based models (coefficients are normalized between 0 and 1). *For l-SVM and g-SVM, an estimate of predictor importances was computed by recursive feature elimination method. DDD, Defined Daily Dose; PRA, Plasma Renin Activity, DRC, Direct Renin Concentration; LDA, Linear Discriminant Analysis; RF, Random Forest; l-SVM and g-SVM, linear and gaussian Support Vector Machine.

Figure S3. Flow chart for the management of patients with PA

A



B

Diagnosis		Predicted			
		PA confirmed	PA not confirmed	Sensitivity (%)	96.5
				Specificity (%)	95.6
Real	PA confirmed	573	21	PPV (%)	96.8
	PA not confirmed	19	411	NPV (%)	95.1
Accuracy 96.1% - Necessary confirmatory test – 45.7%					

Flow chart for the management of patients with a positive screening test (Developmental Cohort + External Validation Cohort; n=1,024). (**A**) Management of patients with PA using the PACT score; the number of patients is indicated in bold; cut-offs are indicated in grey. Misclassified patients are reported in red. (**B**) Confusion matrix representing real and predicted subtype diagnosis, sensitivity, specificity, positive and negative predictive value (PPV; NPV). AVS, Adrenal Venous Sampling; PA, Primary Aldosteronism; LREH, Low Renin Essential Hypertensive patients (PA positive screening test with a negative confirmatory test); PACT, Primary Aldosteronism Confirmatory Testing Score.