The Primary Aldosteronism Surgical Outcome Score for the Prediction of Clinical Outcomes after Adrenalectomy for Unilateral Primary Aldosteronism

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MINI-ABSTRACT

Clinical remission after unilateral adrenalectomy to treat unilateral primary aldosteronism is achieved in less than half of patients. A linear discriminant model with 6 presurgical predictors of clinical remission was used to build a 25-point prediction score of postsurgical clinical outcomes. The prediction score was integrated into a user-friendly online tool which can be used in a clinical setting to differentiate patients who are likely to be clinically cured after surgery from those who will need continuous surveillance after surgery due to remnant hypertension.

STRUCTURED ABSTRACT

Objective: To develop a prediction model for clinical outcomes after unilateral adrenalectomy for unilateral primary aldosteronism.

Summary Background Data: Unilateral primary aldosteronism is the most common surgically curable form of endocrine hypertension. Surgical resection of the dominant overactive adrenal in unilateral primary aldosteronism results in complete clinical success with resolution of hypertension without antihypertensive medication in less than half of patients with a wide between-center variability.

Methods: A linear discriminant analysis (LDA) model was built using data of 380 patients treated by adrenalectomy for unilateral primary aldosteronism to classify post-surgical clinical outcomes. The total cohort was then randomly divided into training (280 patients) and test (100 patients) datasets to create and validate a score system to predict clinical outcomes. An online tool (PASO [Primary Aldosteronism Surgical Outcome] predictor) was developed to facilitate the use of the predictive score.

Results: Six presurgical factors associated with complete clinical success (known duration of hypertension, sex, antihypertensive medication dosage, body mass index, target organ damage and size of largest nodule at imaging) were selected based on classification performance in the LDA model. A 25-point predictive score was built with an optimal cut-off of greater than 16 points (accuracy of prediction = 79.2%; specificity = 84.4%; sensitivity = 71.3%) with an area under the curve of 0.839.

Conclusions: The predictive score and the PASO predictor can be used in a clinical setting to differentiate patients who are likely to be clinically cured after surgery from those who will need continuous surveillance after surgery due to persistent hypertension.

INTRODUCTION

Primary aldosteronism (PA) is a frequent cause of endocrine hypertension with prevalence estimates ranging from 5-15% in the general population with hypertension[1-3] and as high as 20% in patients with resistant hypertension[4]. The overproduction of aldosterone is mainly caused by a unilateral aldosterone-producing adenoma or bilateral adrenal hyperplasia which are specifically treated by laparoscopic adrenalectomy or with a mineralocorticoid receptor antagonist, respectively[5-6]. The deleterious effects of excessive aldosterone production on cardiovascular, cerebrovascular and renal function highlight the importance of an early diagnosis and initiation of specific treatment strategies for unilateral and bilateral forms of PA[7-10].

The differentiation of unilateral from bilateral forms is achieved by computed tomography (CT) or adrenal venous sampling (AVS). AVS is the recommended approach by the Endocrine Society Guideline[11] because of the lack of specificity and sensitivity of CT[12-13]. The objective of adrenalectomy is to resolve excessive aldosterone production, normalize plasma potassium concentrations (if the patient was hypokalemic pre-surgically), and to normalize or at least improve the elevated blood pressure which is characteristic of the disorder. Although more than 4 in every 5 patients with unilateral PA experience a clinical benefit from surgery[14], the proportion of patients with clinical remission with normalization of blood pressure without the aid of antihypertensive medication represents 16-72%[14-19].

Several studies have identified presurgical predictors of clinical cure (complete clinical success[14]) such as younger age, female sex, shorter duration of hypertension before surgery, number of antihypertensive drugs, low serum potassium and high urinary aldosterone levels[14,18,20,21].
A prediction score for the resolution of hypertension after surgery has been developed[17] which also performed well in a patient cohort from Japan[22] but not in a French population[23]. The aldosteronoma

resolution score is based on a points system to predict 3 levels (low, medium, high) of likelihood of clinical cure. A positive predictive value of 75.0% (9 of 12 patients) was achieved with the validation dataset at the high likelihood level albeit with a low sensitivity of 31.0% (9 of 29 patients with clinical cure were accurately predicted). The negative predictive value of the lowest likelihood score was 72.4% (21 of 29 patients) with a specificity of 55.3% (21 of 38 patients)[17].

We developed a prediction score (PASO [Primary Aldosteronism Surgical Outcome] score) for complete clinical success after adrenalectomy for unilateral PA using patient data from a large multicenter cohort with outcomes assessed in accordance with a standardized set of criteria[14,24]. The PASO score requires input of 6 presurgical variables and can be calculated either manually or with an online tool (PASO predictor) to facilitate the use of the prediction score in the clinical setting. To provide additional information on the probability of a complete, partial or absent clinical outcome, the PASO predictor also computes the proportion of patients from the multicenter cohort in each outcome group. The PASO score can be used by clinicians for the management of patient expectations of post-surgical clinical outcomes and to identify which patients will need close follow up due to persistent hypertension.

METHODS

Study Cohort

Patient data from the PASO study[14] were used to train and validate a predictive model for clinical outcomes after adrenalectomy for unilateral PA. Variables associated with complete clinical success were selected from unadjusted and adjusted logistic regression models (Table 1) and all patients without missing values for these variables were included for further analyses (n= 380). The clinical characteristics of the study cohort are reported in Table 2. These patients were a subset of 8 of the 12 centers that participated to the PASO study (Berlin [n=29], Brisbane [n=44], Munich [n=98],

Nijmegen [n=8], Yokohama City [n=61], Sendai [n=63], Torino [n=75] and Warsaw [n=2]). The study cohort was randomly divided into a training dataset (n= 280) to develop the predictive model and a test dataset (n= 100) to validate the model (see Supplemental Digital Content Table 1, for a comparison of clinical parameters of patients in the training and test datasets). Written informed consent was obtained in accordance with the ethical standards of all institutions except in Yokohama City because written consent for the analysis of patient data is not required in Japan.

PA was diagnosed in accordance with the US Endocrine Society or the Japan Endocrine Guideline[11,25]. Unilateral PA was differentiated from bilateral PA by adrenal venous sampling in all patients before adrenalectomy. Clinical and biochemical outcomes were classified as complete, partial and absent success, and were evaluated in accordance with the PASO consensus[14]. Clinical outcomes were defined by blood pressure measurements and antihypertensive medication dosages. Patients with complete clinical success comprise those with normalized blood pressure levels without the use of antihypertensive medication after surgery. Biochemical outcomes were defined according to serum potassium concentrations and the aldosterone-to-renin ratio (ARR). Patients with normalization of hypokalemia (if present pre-surgery) and normalization of the ARR were classified as complete biochemical success. Further details on the criteria defining clinical and biochemical outcomes are described elsewhere[14].

Linear Discriminant Analysis

Linear discriminant analysis (LDA) was performed using MATLAB R2017b software on the combined cohort (n = 380 patients) employing linear combinations of variables to maximize the separation between groups by increasing precision estimates by variance reduction[26,27]. LDA models have been widely exploited in the context of prediction modelling for clinical research as described previously[28-32]. In the model used herein, the algorithm computes a set of coefficients for linear combination with each variable to predict clinical outcome. An estimation of clinical outcome is

derived from the following equation: $Complete\ clinical\ success = LDA_{coeff1}*Variable_1 + LDA_{coeff2}*Variable_2 + \ldots + LDA_{coeffn}*Variable_n > 0.2082$. LDA coefficients are reported in Supplemental Digital Content Table 2, whereas normalized coefficients are represented in Figure 1C. The combination of variables which gave the best accuracy of classification of complete clinical success *versus* partial and absent success combined was selected by the algorithm and the performance of the LDA model was assessed by 10-fold cross validation. The 10-fold cross validation analysis randomly divides the cohort into 10 subgroups. The model is trained with the first 9 subgroups, the remaining group is used for validation. The validation group is then changed and accordingly the training groups. The process is repeated a total of 10 times with the validation group rotating at each round and the remaining subgroups used for model training.

Prediction score

The 6 variables selected by the LDA model were used to develop a 25-point prediction score (PASO score); variables were categorized using the MATLAB R2017b software algorithm and cut-offs were automatically derived to achieve the best accuracy; points were assigned on the basis of discriminant analysis normalized coefficients and ORs from the adjusted regression analyses.

The PASO score was generated using a training dataset (n= 280) and validated on the test dataset (n= 100). A receiver operating characteristic (ROC) curve was used to assess the area under the curve (AUC) and the best cut-off to discriminate complete *versus* (partial + absent) clinical success after adrenalectomy was automatically defined by the software (MATLAB R2017b) algorithm and confirmed by evaluation of the Youden Index (J = sensitivity + specificity - 1). An online tool was developed that automatically calculates the defined daily dose (DDD), the score and the predicted clinical outcome (PASO predictor available at https://github.com/ABurrello/PASO-Predictor/raw/master/00%20-%20PASO%20Predictor.xlsm

Statistical Analyses

IBM SPSS Statistics 24 (IBM Corp. Armonk, New York, USA) was used for statistical analyses. The normally distributed variable (BMI) is expressed as the mean ± SD and analyzed by a one-way ANOVA test; non-normally distributed variables (duration of hypertension, DDD, nodule diameter) are expressed as medians and interquartile range and analyzed using the Mann-Whitney's test. Categorical variables (sex, target organ damage) are expressed as absolute numbers and proportions (%) and analyzed by a chi square test. Unadjusted and adjusted logistic regression analyses were used to determine odds ratios (ORs) for the 6 variables selected by the LDA on the combined cohort (n= 380 patients). An OR greater than 1 indicates an increased likelihood of complete clinical success, an OR less than 1, a decreased likelihood. Correlations were evaluated by a Pearson test. A *P*-value of less than 0.05 was considered significant.

RESULTS

LDA prediction model

The cohort included 380 surgically-treated patients for unilateral PA with complete datasets (see Table 2 for patient characteristics). Complete clinical success was achieved in 150 of the 380 patients (39.5%), partial or absent clinical success in 173 (45.5%) and 57 patients (15%), respectively. Complete biochemical success was achieved in 357 of 380 (93.9%) patients, with a further 16 (5.2%) and 7 (1.8%) patients displaying partial or absent biochemical success after surgery, respectively. Using unadjusted univariate and adjusted multivariate analyses, we selected the variables with the strongest association with complete clinical success (Table 1). In the unadjusted analysis, all selected variables were significantly associated with complete clinical success ($P < 0.001$) except largest nodule size. In the adjusted model, duration of hypertension (OR 0.99 per month; CI 95% 0.98-0.99; $P < 0.001$), sex (reference female; OR 2.91; 95% CI 1.74-4.86; $P = < 0.001$), DDD (OR 0.81 per unit increase; 95% CI 0.72-0.92; $P = 0.001$), target organ damage (reference presence; OR 2.84; 95% CI

1.69-4.78; $P < 0.001$) and largest nodule at imaging (OR 1.03 per mm; 95% CI 1.01-1.06; $P = 0.048$) were all confirmed as independent predictors.

The combination of variables with the best accuracy of prediction of complete clinical success *versus* (partial + absent) success was used in the LDA model. The variables were known duration of hypertension (months), sex (female/male), BMI (Kg/m^2), antihypertensive medication (defined by DDD), presence of target organ damage (left ventricular hypertrophy and/or microalbuminuria) and largest nodule size at imaging (diameter, mm). Known duration of hypertension had a greater predictive performance than age (a correlated confounding variable) and was selected for inclusion. The linear combination of variables included in the LDA is shown in the canonical plot (Figure 1A). Each point represents a patient and the distribution of clinical outcomes indicates that the model can distinguish complete from partial + absent clinical success combined whereas patients with partial clinical success cannot be differentiated from those with absent success.

The LDA model correctly predicted the outcomes of 293 of 380 patients (77.1% accuracy) with a sensitivity of 69.3% and a specificity of 82.2% (Figure 1B). In detail, 104 of 150 and 189 of 230 patients were correctly assigned to the complete and the partial + absent clinical success groups, respectively. To exclude overfitting and to assess how the prediction could generalize in an independent cohort, the LDA model was validated by 10-fold cross validation analysis that confirmed a high predictive performance with an accuracy of 75.3% (with cross validation), compared with 77.1% (with the LDA model), thus excluding any risk of bias. In the LDA model, the strongest predictor of complete clinical success was known duration of hypertension (LDA normalized coefficient equal to 1.0), followed by antihypertensive medication and largest nodule size at imaging (0.8 and 0.5, respectively; Figure 1C and Supplemental Digital Content Table 2 that shows the normalized LDA coefficients for each of the 6 variables).

PASO score

Patients included in the LDA model (n = 380) were randomly assigned to a training dataset (n = 280) and a test dataset (n = 100). There were no differences in clinical outcomes or in any of the 6 variables used in the LDA model between the 2 cohorts (see Supplemental Digital Content Table 1 for a comparison of the training and test datasets).

The 6 variables selected by the LDA model were used to develop a 25-point score (the PASO score) on the training dataset. Figures 2A and 2C shows variables and points assigned to each category. The best cut-off was identified by the ROC curve (Figure 2B); the area under the curve was 0.839 (95% CI 0.798-0.881). In the training dataset, a cut-off greater than 16 correctly predicted complete clinical success in 78 of 110 patients, whereas a cut-off equal or lower than 16 predicted partial and absent clinical success combined in 150 of 170 patients (sensitivity 70.9% and specificity 88.2%). The overall accuracy of the model was 81.4% (Figure 2D). With validation of the score using the test dataset, 73 of 100 patients were correctly classified (accuracy 73%). The predictive performance on the combined cohort was still higher than the LDA model, with correct classification of 301 of 380 patients (accuracy, 79.2%; sensitivity, 71.3% and specificity, 84.4%) (Figure 2D). Positive and negative predictive values were respectively 74.8% and 81.6% (Table 3). The difference between the accuracy of the PASO score in the training dataset and in the test dataset (81.4% and 73.0%, respectively) revealed a modest bias due to the effect of overfitting (best performance of the model in the cohort in which it is trained), which was expected and did not affect the reliability of the model.

As expected, the PASO score was directly correlated with the proportion of patients with complete clinical success (R = 0.940; $P < 0.001$) (Figure 3). Supplemental Digital Content Table 3 shows patients in the combined cohort stratified for clinical outcomes and for PASO score. Patients with a score of 24.1-25 all had complete clinical success after surgery (n = 9); a single patient with a score of 0-2.0 had partial clinical success. For patients with a PASO score equal to or greater than 20,

complete clinical success was correctly predicted in 58 of 69 patients (positive predictive value 84.1%; Table 3). For patients with a PASO score less than 10, partial and absent clinical success combined was correctly predicted in 72 of 77 patients (negative predictive value 93.5%; Table 3).

The LDA model was adapted to predict all patients with a potential clinical benefit after surgery. For this we attempted to develop 2 additional models: (complete + partial) *versus* absent clinical success and complete *versus* partial *versus* absent clinical success. For the prediction of (complete + partial) *versus* absent clinical success, we achieved an accuracy of 85.3% and 71.8% for the LDA model and the PASO score (on the combined cohort), respectively but this was achieved with very low specificity (Supplemental Digital Content Table 4). For the prediction of complete *versus* partial *versus* absent clinical success, the model attained moderate accuracy (63.4% for the LDA model and 55.3% for the PASO score on the combined cohort; Supplemental Digital Content Table 5). The low performance of these two additional models is because of the difficulty in distinguishing patients with partial *versus* absent clinical success due to the relatively low number of patients in the absent clinical success group (44 in the training dataset and 13 in the test dataset) and to the similarity of the clinical characteristics of patients in the absent and partial subgroups for 5 of the 6 variables used in the predictive model (they differed only for antihypertensive medication dosage, a criteria used for the definition of clinical outcomes by the PASO consensus[14]; Supplemental Digital Content Table 6).

Finally, we assessed the generalizability of our model for each center included in the analysis. We found no significant differences for the accuracies of the LDA model and the PASO score ($P = 0.284$ and $P = 0.188$, respectively) applied to patients stratified by center (Supplemental Digital Content Table 7).

DISCUSSION

The optimal treatment for unilateral forms of PA is laparoscopic adrenalectomy which should remove the source of aldosterone overproduction and potentially cure the disorder. There is a wide variability in clinical outcomes with usually less than half of patients in a given center achieving complete clinical success after surgery with normalization of blood pressure without the aid of antihypertensive medication[14,17,18,33]. A substantial proportion of patients (35-66%) have a partial clinical response to adrenalectomy (partial clinical success) and the absence of clinical benefit (absent clinical success) is found in 0-32%[14]. Several factors influence clinical outcomes after adrenalectomy such as sex, age, concurrent primary hypertension and long-standing PA[14,18,20,21,34]. Presurgical factors associated with clinical outcomes can be exploited to develop prediction scores to provide objective measures of clinical outcomes and, if reliable, used to counsel patients on the probability of a surgical cure *versus* a lifetime of antihypertensive medication.

In this study we developed a prediction tool, the PASO predictor, for clinicians to differentiate patients with unilateral PA with a complete clinical response to unilateral adrenalectomy from those with a partial and absent response combined. Although not achieving clinical cure, patients with partial clinical success after unilateral adrenalectomy obtain substantial clinical benefits but will need continuous surveillance after surgery due to remnant hypertension. The PASO predictor may help clinicians evaluate the benefits of surgery and inform patients on their expected post-surgical outcomes as well as identifying which patients require close follow up.

A prediction score (Aldosteronoma Resolution Score) was developed previously based on a points system using 4 readily available variables (number of antihypertensive drugs, duration of hypertension, sex and BMI)[17]. We developed an improved prediction score (PASO score) using patient data from a multicenter international cohort. Applying the PASO score to the combined

dataset in the present study gave a positive predictive value of 84.1% (58 of 69 patients) using the highest level for likelihood of complete clinical success (≥ 20 points) and a negative predictive value of 93.5% (72 of 77 patients) for the lowest likelihood level (≥ 10 points). This compares favorably with the previously published aldosteronoma resolution score which, in the total dataset, had a positive predictive value of 80.0% (28 of 35 patients) for the highest likelihood of clinical cure (4-5 points) and a negative predictive value of 86.3% (63 of 73 patients) for the lowest likelihood level (0-1 points)[17]. Our validation of the score indicated an accuracy of prediction of 73.0% (72.5% sensitivity and 73.3% specificity) compared with an accuracy of 65.7% with the validation dataset of the aldosteronoma score (sensitivity, 31.0%; specificity, 92.1%).

Our score is more complex than the aldosteronoma resolution score. The LDA model identified 2 variables (largest nodule size at imaging and target organ damage evaluated by microalbuminuria and/or left ventricular hypertrophy) in addition to the same 4 variables used in the aldosteronoma resolution prediction score. These 2 variables were included because target organ damage displayed a better predictive performance than BMI; and nodule size performed better than both target organ damage and sex. Adrenal CT or MRI and target organ damage should be evaluated in all patients with PA because the possibility of an aldosterone-producing carcinoma requires exclusion by imaging[11] and the routine assessment of microalbuminuria and left ventricular hypertrophy is recommended in all patients with hypertension[35]. Evaluation of target organ damage to the kidneys and heart is particularly relevant in patients with PA because of their increased risk (which can be reversed with appropriate treatment) relative to patients with primary hypertension[7,8,10,36-38].

A prediction score that separates partial from an absent clinical outcome would also be useful because patients with a partial clinical outcome derive clinical benefits from surgery, potentially attaining a substantial improvement in hypertension status or antihypertensive drug requirements (possibly achieving normalization of blood pressure although with the aid of antihypertensive medication). The

LDA model described herein could not separate the partial from absent clinical success groups. However, to partially address this need, the PASO predictor indicates the probability of achieving each clinical outcome by calculating the proportion of patients with complete, partial and absent clinical success for the PASO score based on the clinical outcomes of the total cohort.

The strengths of our study include the multicenter inclusion of a large number of patients from a wide geographical spread and the high performance of the PASO score using a validation test which indicated the general applicability of the score. We also developed a user-friendly online tool to calculate the PASO score which automatically converts antihypertensive medication dosages to DDDs (a standardized measure of medication) and predicts the likelihood of complete clinical success after adrenalectomy as well as those patients in the partial and absent clinical success groups combined that require close post-surgical follow up. A potential limitation of the prediction score is the increased number of input variables relative to previous models with the requirement of adrenal imaging data and assessment of target organ damage which are nonetheless widely considered essential evaluations in patients with PA. Another limitation is the inability of the prediction score to differentiate patients with a clinical benefit after surgery (complete + partial from absent or complete *versus* partial *versus* absent clinical success), but the PASO predictor calculates the probability of each clinical outcome at any given PASO score which, although not a prediction score, can be used to advice patients on their likely clinical outcomes.

In conclusion, we developed a score system based on presurgical factors, integrated into an online tool, to reliably predict complete clinical success after adrenalectomy and to guide the clinical management of patients with PA.

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Table 1 – Predictive variables for complete clinical success after adrenalectomy

Variable (n = 380)	**Unadjusted Analysis**		**Adjusted Analysis**	
	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value
Duration of hypertension (months)	0.99 (0.98 – 0.99)	< 0.001	0.99 (0.98-0.99)	< 0.001
Sex (Female, %)	4.03 (2.60 – 6.25)	< 0.001	2.91 (1.74-4.86)	< 0.001
BMI (kg/m^2)	0.92 (0.88 – 0.96)	< 0.001	1.00 (0.95-1.05)	0.996
AntiHT medication (DDD)	0.71 (0.63 – 0.80)	< 0.001	0.81 (0.72-0.92)	0.001
Target organ damage (absence, %)	3.31 (2.14 – 5.13)	< 0.001	2.84 (1.69-4.78)	< 0.001
Largest nodule at imaging (mm)	1.02 (0.99 – 1.05)	0.061	1.03 (1.01-1.06)	0.048

Logistic regression analyses were performed to assess the odds ratios (OR) and 95% confidence intervals (CI) for the six variables selected by the LDA model. The unadjusted univariate and adjusted multivariate ORs are shown as indicated. An OR greater than 1 indicates an increased likelihood of complete clinical success (clinical cure) and an OR less than 1 a decreased likelihood. Patient data from the total cohort (n = 380) were included in the models. BMI (body mass index), DDD (defined daily dose), duration of hypertension and largest nodule at imaging were treated as continuous variables; sex and target organ damage were treated as categorical variables. AntiHT medication, antihypertensive medication.

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/).

Table 2. Patient characteristics of study cohort

Variables	Cohort (N = 380)
Age at surgery (years)	50.5 ± 11.2
Sex (Female; %)	184 (48.4)
BMI (kg/m^2)	26.9 ± 5.2
Systolic blood pressure (mmHg)	153 ± 23.1
Diastolic blood pressure (mmHg)	93 ± 14.2
Duration of hypertension (months)	99.5 [47.3-183.0]
AntiHT medication (DDD)	2.5 [1.5-4.3]
Plasma aldosterone (pmol/L)	881 [569-1430.5]
DRC (mU/L)	5.0 [3.2-12.5]
PRA (pmol/L)	2.6 [1.3-5.1]
Lowest serum potassium (mmol/L)	3.0 [2.7-3.5]
eGFR (mL/min)	85.0 [70.8-95.0]
Target organ damage (absence; %)	241 (63.4)
Largest nodule at imaging (mm)	13.5 [9.0-17.0]
Clinical Outcome	
Complete	150 (39.5)
Partial	173 (45.5)
Absent	57 (15.0)
Biochemical Outcome	
Complete	357 (94.0)
Partial	16 (4.2)
Absent	7 (1.8)

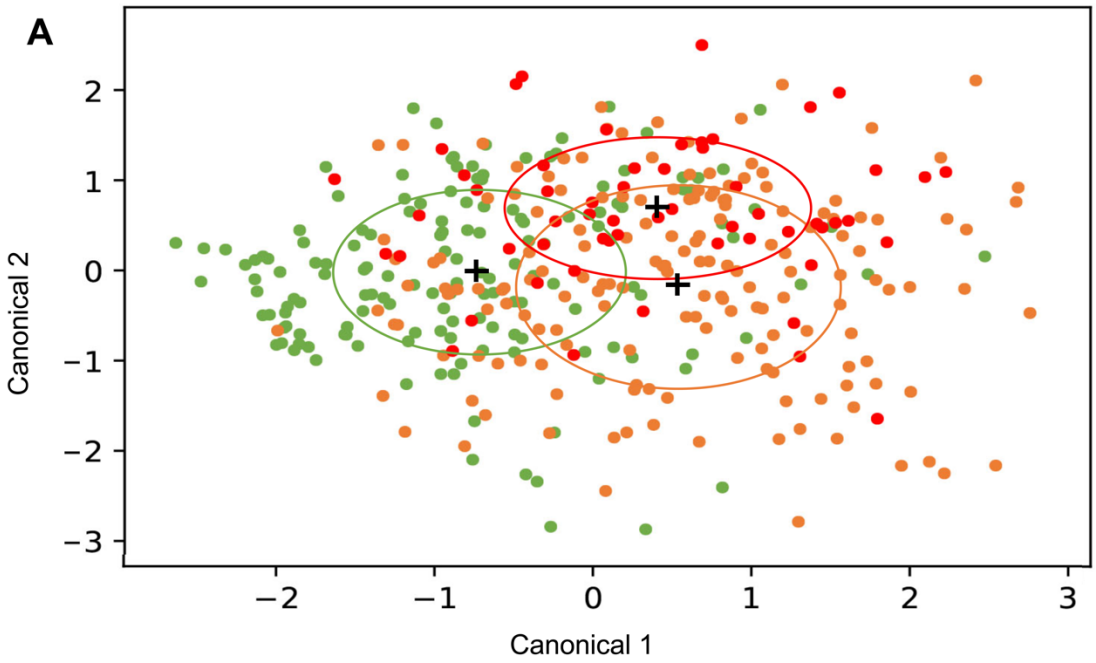
Clinical characteristics of patients included in the analysis. AntiHT medication, antihypertensive medication; BMI, body mass index; DDD, defined daily dose; DRC, direct renin concentration; eGFR, glomerular filtration rate; PRA, plasma renin activity. Age at surgery, BMI, systolic and diastolic blood pressure are expressed as the mean ± SD; duration of hypertension, DDD, plasma aldosterone, DRC, PRA, lowest serum potassium, eGFR and largest nodule at imaging are expressed as medians and interquartile range; sex, target organ damage, clinical and biochemical outcome are expressed as absolute numbers and proportions (%).

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/).

Table 3. Predictive performance of the LDA model and the PASO score

Model	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
LDA	69.3 (104/150)	82.2 (189/230)	71.7 (104/145)	80.4 (189/235)	77.1 (293/380)
≥ 20	38.7 (58/150)	95.2 (219/230)	**84.1 (58/69)**	70.4 (219/311)	72.9 (277/380)
> 16	71.3 (107/150)	84.4 (194/230)	74.8 (107/143)	81.6 (194/237)	79.2 (301/380)
≥ 10	96.7 (145/150)	31.3 (72/230)	47.9 (145/303)	**93.5 (72/77)**	57.1 (217/380)

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy are shown for the LDA model and the PASO score (with different cut-offs) in the combined cohort (n = 380). The optimal cut-off is >16 points which is derived from the ROC of the LDA model. A score ≥20 points gives the highest proportion of true positive results (84.1%) and a score ≥ 10 the highest proportion of true negative results (93.5%) for complete clinical success (shown in bold).



B

Clinical Outcome		Predicted	
		Complete	Partial + Absent
Real	Complete	104	46
	Partial + Absent	41	189
		Accuracy (%)	77.1
		Sensitivity (%)	69.3
		Specificity (%)	82.2
		10-fold cross validation (%)	75.3

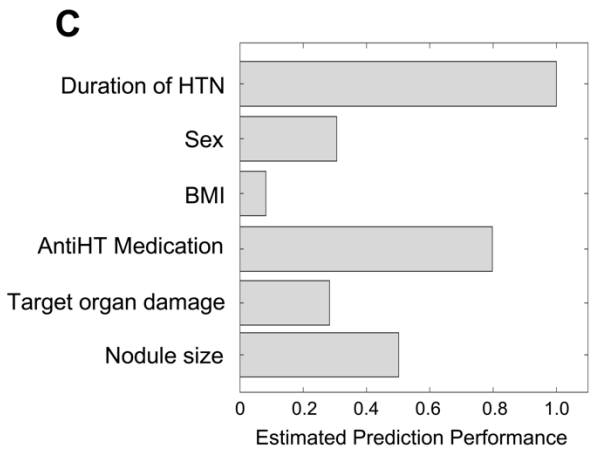
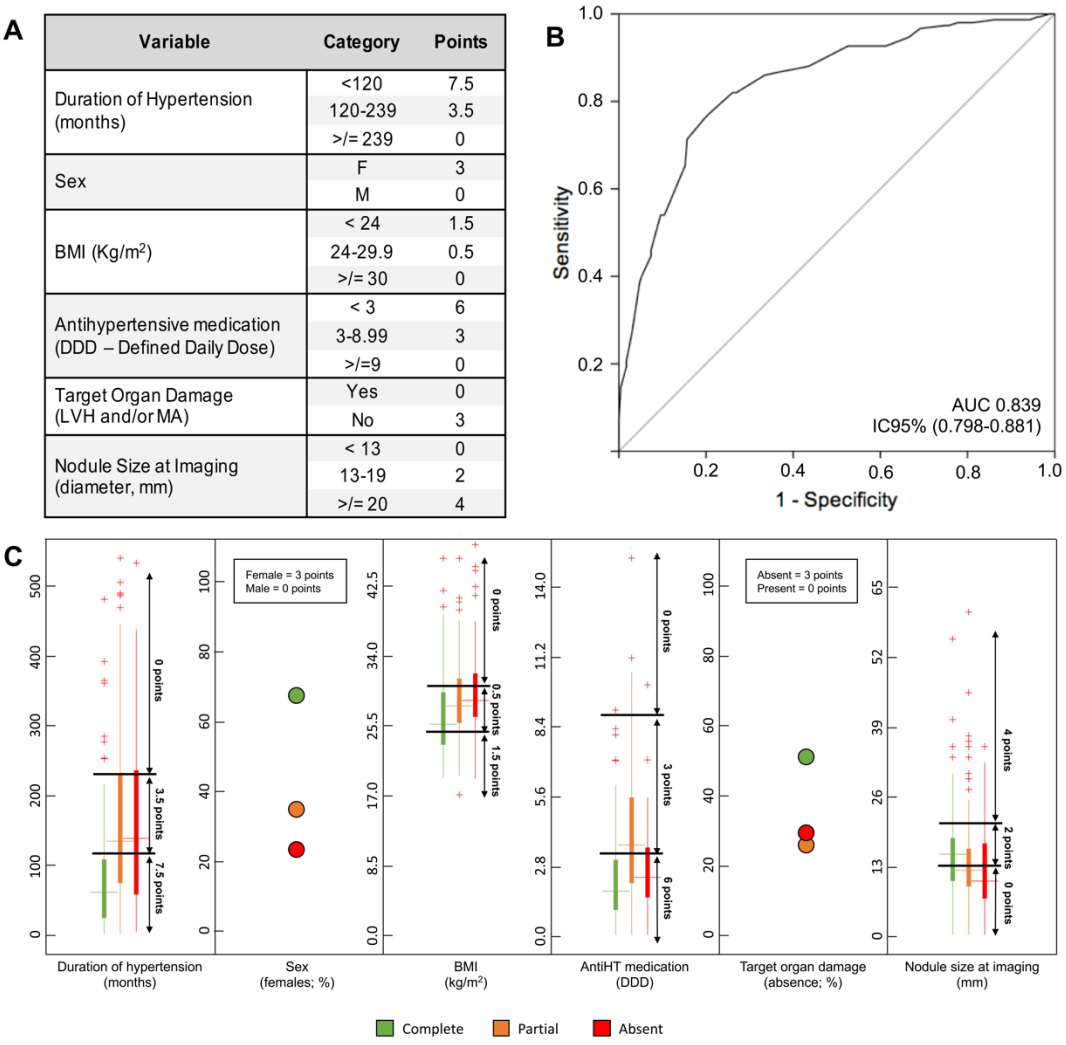


Figure 1 - Linear discriminant analysis model to predict clinical outcomes after unilateral adrenalectomy

The linear discriminant analysis (LDA) model included the 6 variables that gave the best classification of clinical outcomes for the combined cohort (n= 380 patients). **Panel A**, canonical plot showing the clinical outcome of each patient in the combined cohort. Each patient is indicated by a point and outcomes are represented by color (complete, green; partial, orange; absent, red). The canonical axes of the plot (canonical 1 and canonical 2) are calculated by the LDA from weighted linear combinations of the 6 variables included in the model to maximize separation between the 3 clinical outcome groups. The crosses indicate the means of (canonical 1; canonical 2) for each clinical outcome, the ellipses include patients with a linear combination coefficient that falls within the mean ± SD (canonical 1 ± SD; canonical 2 ± SD). **Panel B**, real and predicted clinical outcomes, the accuracy, sensitivity, specificity and 10-fold cross validation of the LDA model. **Panel C**, the normalized coefficients for each variable included in the LDA model. AntiHT medication, antihypertensive medication; BMI, body mass index, HTN, hypertension.

A

Variable	Category	Points
Duration of Hypertension (months)	<120	7.5
	120-239	3.5
	>/= 239	0
Sex	F	3
	M	0
BMI (Kg/m^2)	< 24	1.5
	24-29.9	0.5
	>/= 30	0
Antihypertensive medication (DDD – Defined Daily Dose)	< 3	6
	3-8.99	3
	>/=9	0
Target Organ Damage (LVH and/or MA)	Yes	0
	No	3
Nodule Size at Imaging (diameter, mm)	< 13	0
	13-19	2
	>/= 20	4



D

	PASO Score Accuracy	Predicted Clinical Outcome		Performance	
Real Clinical Outcome	**Training dataset** (n = 280)	Complete	Partial + Absent	Accuracy (%)	81.4
	Complete	78	32	Sensitivity (%)	70.9
	Partial + Absent	20	150	Specificity (%)	88.2
	Test dataset (n = 100)	Complete	Partial + Absent	Accuracy (%)	73.0
	Complete	29	11	Sensitivity (%)	72.5
	Partial + Absent	16	44	Specificity (%)	73.3
	Combined Cohort (n = 380)	Complete	Partial + Absent	Accuracy (%)	79.2
	Complete	107	43	Sensitivity (%)	71.3
	Partial + Absent	36	194	Specificity (%)	84.4

Figure 2 - PASO score to predict clinical outcomes after unilateral adrenalectomy

The LDA model and adjusted linear regression analysis were used to assign prediction points to each variable according to stratification level. The model was trained using a subset of patients (training set, n = 280 patients) to optimize the prediction score system. **Panel A,** shows the included variables and final points system used for the PASO score. **Panel B**, receiver operating characteristic (ROC) curve used to identify the best cut-off from the PASO prediction (greater than 16 score points) using the combined cohort (n = 380). AUC, Area Under the Curve. **Panel C,** illustration of cut-offs and assigned points for each variable after categorization; outcomes are represented by color (complete, green; partial, orange; absent, red); the bars indicate the median and interquartile range for each outcome. Categorization was performed using the MATLAB R2017b software algorithm and cut-

offs were automatically derived. Points were assigned to achieve the best accuracy based on normalized LDA coefficients (see Supplemental Digital Content Table 2 and Figure 1C), ORs from regression analyses (Table 1) and from the level of separation of complete clinical success from other outcome groups. **Panel D**, the real and predicted clinical outcomes, accuracy, sensitivity and specificity for the training dataset (n = 280), test dataset (n = 100) and the combined cohort (n = 380). AntiHT medication, antihypertensive medication; BMI, body mass index; DDD, define daily dose; LVH, left ventricular hypertrophy; MA, micro-albuminuria.

A downloadable PASO predictor is available at https://github.com/ABurrello/PASO-Predictor/raw/master/00%20-%20PASO%20Predictor.xlsm

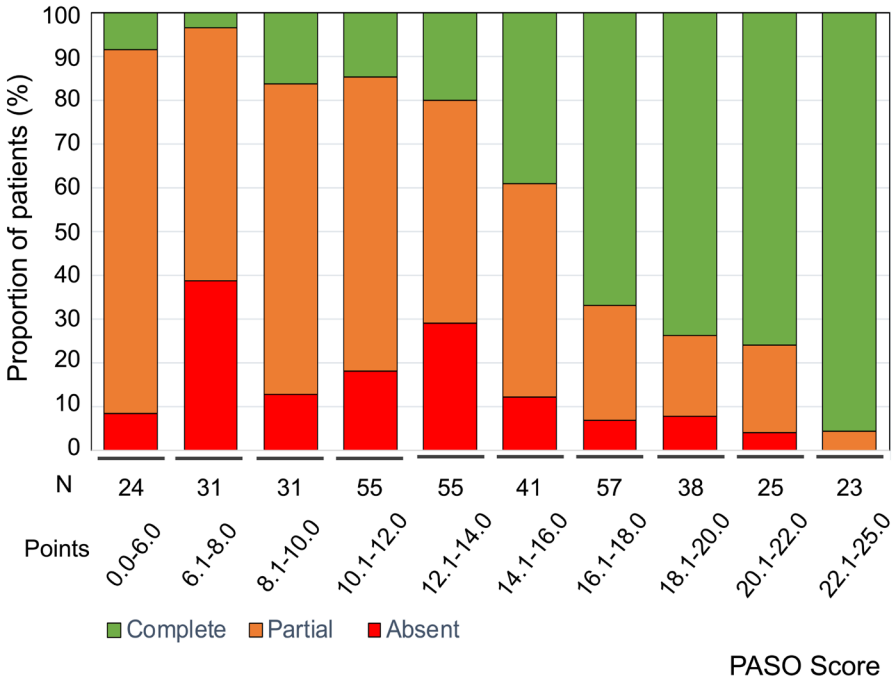


Figure 3 - Stratification of clinical outcomes after unilateral adrenalectomy by PASO prediction score

The histogram indicates the performance of the PASO predictor on the combined cohort (n= 380 patients) and shows the proportion of patients (y-axis, %) in each clinical success category (complete, green; partial, orange; absent, red) stratified by the PASO score (x-axis). The total number of patients (N) in each PASO score level is indicted. Supplemental Digital Content Table 3 shows the actual numbers and proportion of patients in each stratification level.

The Primary Aldosteronism Surgical Outcome Score for the Prediction of Clinical Outcomes after Adrenalectomy for Unilateral Primary Aldosteronism

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Supplemental Digital Content Table 1

Characteristics of patients with unilateral primary aldosteronism included in the training and test datasets

Variable		Combined cohort (n = 380)	Training Dataset (n = 280)	Test Dataset (n = 100)	*P*-value
Clinical Outcome	Complete	150 (39.5)	110 (39.3)	40 (40.0)	0.804
	Partial	173 (45.5)	126 (45.0)	47 (47.0)	
	Absent	57 (15.0)	44 (15.7)	13 (13.0)	
Biochemical Outcome	Complete	357 (94.0)	263 (93.9)	94 (94.0)	0.984
	Partial	16 (4.2)	12 (4.3)	4 (4.0)	
	Absent	7 (1.8)	5 (1.8)	2 (2.0)	
Duration of hypertension (months)		99.5 [47.3-183.0]	109.5 [47.0-187.8]	87.5 [48.0-162.0]	0.384
Sex (Female; %)		184 (48.4)	133 (47.5)	51 (51.0)	0.548
BMI (kg/m^2)		26.9 ± 5.2	26.8 ± 5.0	26.9 ± 5.6	0.880
AntiHT medication (DDD)		2.5 [1.5-4.3]	2.3 [1.5-4.5]	3.0 [1.4-4.2]	0.906
Target organ damage (absence; %)		241 (63.4)	179 (63.9)	62 (62.0)	0.731
Largest nodule at imaging (mm)		13.5 [9.0-17.0]	13.0 [9.0-17.0]	14.0 [9.0-17.0]	0.789

From the combined cohort (n = 380), patients were randomly assigned to the training dataset (n = 280) or the test dataset (n = 100). Patients did not differ for any of the variables included in the model. AntiHT medication, antihypertensive medication; BMI, Body Mass Index; DDD, defined daily dose. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/).

Supplemental Digital Content Table 2

LDA coefficients for the prediction of clinical outcomes

Variable	LDA Coefficient	Normalized Coefficient
Duration of hypertension (months)	-0.007	1.00
Sex (Female; %)	1.198	0.31
BMI (kg/m^2)	-0.010	0.08
AntiHT medication (DDD)	-0.207	0.80
Target organ damage (absence; %)	-1.110	0.28
Largest nodule at imaging (mm)	0.028	0.50

LDA coefficients and normalized coefficients. LDA coefficients can be used in combination with each single variable to predict patient outcome. Each variable is multiplied by its corresponding LDA coefficient and the adjusted coefficients are summed to derive value X according the following equation: Complete clinical success = LDA_{coeff1}*$Variable_1$ + LDA_{coeff2}*$Variable_2$ + … + LDA_{coeffn}*$Variable_n$ > 0.2082. If the value of X is more than the given cut-off (0.2082) then complete clinical success is predicted. AntiHT medication, antihypertensive medication; BMI, body mass index; DDD, defined daily dose.

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/).

Supplemental Digital Content Table 3

Distribution of patients with unilateral primary aldosteronism stratified by clinical success after adrenalectomy and PASO score

Score	Total (n)	Absent		Partial		Complete	
		(n)	(%)	(n)	(%)	(n)	(%)
0.0-2.0	1	0	0.0	1	100.0	0	0.0
2.1-4.0	9	0	0.0	8	88.9	1	11.1
4.1-6.0	14	2	14.3	11	78.6	1	7.1
6.1-8.0	31	12	38.7	18	58.1	1	3.2
8.1-10.0	31	4	12.9	22	71.0	5	16.1
10.1-12.0	55	10	18.2	37	67.3	8	14.5
12.1-14.0	55	16	29.1	28	50.9	11	20.0
14.1-16.0	41	5	12.2	20	48.8	16	39.0
16.1-18.0	57	4	7.0	15	26.3	38	66.7
18.1-20.0	38	3	7.9	7	18.4	28	73.7
20.1-22.0	25	1	4.0	5	20.0	19	76.0
22.1-24.0	14	0	0.0	1	7.1	13	92.9
24.1-25.0	9	0	0.0	0	0.0	9	100.0
Total	*380*	*57*	*N.A.*	*173*	*N.A.*	*150*	*N.A.*

The number (n) and proportion (%) of patients stratified for clinical success (complete, partial, absent) and PASO score is shown in the combined cohort (n = 380). N.A., not applicable.

Supplemental Digital Content Table 4

PASO score to predict clinical outcomes after unilateral adrenalectomy: complete + partial *versus* absent clinical success

(A)

Clinical Outcome [LDA Model]		Predicted			
		Complete + Partial	Absent	Accuracy (%)	85.3
Real	Complete + Partial	322	1	Sensitivity (%)	99.7
	Absent	55	2	Specificity (%)	3.5
				10K-Cross-validation (%)	84.7

(B)

PASO Score Accuracy		Predicted Clinical Outcome		Performance	
Real Clinical Outcome	**Training dataset** (n = 280)	Complete + Partial	Absent	Accuracy (%)	72.9
	Complete + Partial	187	49	Sensitivity (%)	79.2
	Absent	27	17	Specificity (%)	38.6
	Test dataset (n = 100)	Complete + Partial	Absent	Accuracy (%)	69.0
	Complete + Partial	68	19	Sensitivity (%)	78.2
	Absent	12	1	Specificity (%)	7.7
	Combined Cohort (n = 380)	Complete + Partial	Absent	Accuracy (%)	71.8
	Complete + Partial	255	68	Sensitivity (%)	78.9
	Absent	39	18	Specificity (%)	31.6

Panel A, shows the real and predicted clinical outcomes, the accuracy, sensitivity, specificity and 10-fold cross validation of the LDA model.

Panel B, shows the real and predicted clinical outcomes, accuracy, sensitivity and specificity for the training dataset (n = 280), test dataset (n = 180) and the combined cohort (n = 380) for the PASO score. A cut-off of greater than 10 points identifies patients with complete + partial clinical success.

Supplemental Digital Content Table 5

PASO score to predict clinical outcomes after unilateral adrenalectomy: complete *versus* partial *versus* absent clinical success.

(A)

Clinical Outcome [LDA Model]		Predicted			Accuracy 63.4% / Cross-Validation 61.6%	
		Complete	Partial	Absent	Sensitivity (%)	Specificity (%)
Real	Complete	113	35	2	75.3	55.7
	Partial	44	124	5	71.7	56.5
	Absent	17	36	4	7.0	73.4

(B)

PASO Score Accuracy		Predicted Clinical Outcome			Performance	
Real Clinical Outcome		Complete	Partial	Absent		
	Training dataset (n = 280)				Accuracy 57.5%	
					Sensitivity	Specificity
	Complete	78	27	5	70.9	48.8
	Partial	16	66	44	52.4	61.7
	Absent	4	23	17	38.6	61.0
	Test dataset (n = 100)				Accuracy 49.0%	
					Sensitivity	Specificity
	Complete	29	8	3	72.5	33.3
	Partial	12	19	16	40.4	56.6
	Absent	4	8	1	7.7	55.2
	Combined Cohort (n = 380)				Accuracy 55.3%	
					Sensitivity	Specificity
	Complete	107	35	8	71.3	44.8
	Partial	28	85	60	49.1	60.4
	Absent	8	31	18	31.6	59.4

Panel A, shows the real and predicted clinical outcomes, the accuracy, sensitivity, specificity and 10-fold cross validation of the LDA model.

Panel B, shows the real and predicted clinical outcomes, accuracy, sensitivity and specificity for the training dataset (n = 280), test dataset (n = 180) and the combined cohort (n = 380) for the PASO score. A cut-off of > 16 points identifies patients with complete clinical success; a cut-off of > 10 and ≤ 16 identifies patients with partial clinical success; a cut-off of ≤ 10 identifies patients with absent clinical success.

Supplemental Digital Content Table 6

Characteristics of patients stratified for clinical outcome

Clinical Outcome	**Complete** (N = 150)	***Partial** (N = 173)	***Absent** (N = 57)	**P*-value (Partial *vs* Absent)
Duration of hypertension (months)	61.0 [24.0-108.0]	134.0 [73.5-234.0]	138.0 [57.5-241.0]	0.705
Sex (Female, %)	103 (68.7)	67 (38.7)	14 (24.6)	0.056
BMI (kg/m^2)	25.6 ± 5.3	27.4 ± 4.6	28.7 ± 6.0	0.083
AntiHT medication (DDD)	1.8 [1.0-3.0]	3.6 [2.1-5.5]	2.3 [1.5-3.5]	0.001
Target organ damage (absence, %)	80 (53.3)	42 (24.3)	17 (29.8)	0.484
Largest nodule at CT (mm)	15.0 [10.0-18.0]	12.0 [9.0-16.0]	10 [6.5-17.0]	0.133

The *P*-value is referred to the comparison between patients with a partial *versus* absent clinical success. AntiHT medication, antihypertensive medication; BMI, Body Mass Index; DDD, defined daily dose. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/).

Supplemental Digital Content Table 7

LDA model and PASO predictor performances for the prediction of clinical outcomes of patients stratified by recruitment center

Center	N	Accuracy (%)	
		LDA model	PASO predictor
Berlin	29	65.5	62.1
Brisbane	44	68.2	75
Munich	98	79.6	82.7
Nijmegen	8	62.5	62.5
Yokohama City	61	83.6	83.6
Sendai	63	76.2	79.4
Torino	75	81.3	82.7
Warsaw	2	50.0	50.0

Our model generalizes to patients stratified by center (no significant differences among accuracies for the LDA model and PASO predictor, respectively, $P = 0.284$ and $P = 0.188$), thus excluding bias due to center heterogeneity.