Nomogram-based preoperative score for predicting clinical outcome in unilateral primary aldosteronism

(Article begins on next page)

Nomogram-Based Preoperative Score for Predicting Clinical Outcome in Unilateral Primary Aldosteronism

Running Title: NBPS and Clinical outcome in Unilateral PA

Yi Yang, MD*[1], Tracy Ann Williams, MD, PhD*[2,5], Ying Song, MD, PhD*[1], Shumin Yang, MD, PhD[1], Wenwen He, MD, PhD[1], Qingfeng Cheng, MD, PhD[1], Linqiang Ma, MD, PhD[1], Ting Luo, MD, PhD[1], Jun Yang, MD, PhD[3,4], Martin Reincke, MD, PhD[2], Jacopo Burrello, MD, PhD[5], Qifu Li, MD, PhD[#1], Paolo Mulatero, MD, PhD[#5], Jinbo Hu, MD, PhD[#1], the Chongqing Primary Aldosteronism Study (CONPASS) Group†

Affiliations:

[1] Department of Endocrinology, the First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

[2] Medizinische Klinik und Poliklinik IV, Klinikum der Universität, Ludwig-Maximilians-Universität München, Munich, Germany

[3] Centre for Endocrinology and Metabolism, Hudson Institute of Medical Research, Victoria, Australia.

[4] Department of Medicine, Monash University, Victoria, Australia

[5] Division of Internal Medicine and Hypertension Unit, Department of Medical Sciences, University of Torino, Italy

* These authors contributed equally to this work and share the first authors.
# These authors should be considered joint senior authors.

Reprint requests and correspondence:

Jinbo Hu, MD, PhD, Department of Endocrinology, the First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Street, Chongqing 400016, China, e-mail: hujinbo_568@163.com

Disclosures:

Authors have disclosed no conflicts of interest.

Abstract

Context: More than half of unilateral primary aldosteronism (UPA) suffer from persisting hypertension after unilateral adrenalectomy.

Objective: To develop and validate a nomogram-based preoperative score (NBPS) for prediction clinical outcome for UPA.

Design and setting: The NBPS were developed in an Asian cohort by incorporating predictors independently associated with hypertension remission in UPA patients in the multivariate analyses and validated in a Caucasian cohort.

Participants: UPA achieving complete biochemical success after unilateral adrenalectomy.

Main outcome measure: the predictive performance of NBPS compared with two previously developed outcome prediction scores: aldosteronoma resolution score (ARS) and primary

aldosteronism surgical outcome (PASO) score.

Results: Ninety-seven of 150(64.7%) patients achieved complete clinical success after unilateral adrenalectomy in the training cohort and 57 out of 165(34.5%) in the validation cohort. A nomogram was established by incorporating sex, duration of hypertension, aldosterone to renin ratio and target organ damage. The nomogram achieved good concordance indexes and calibration curve in both cohorts. The area under the receiver operating characteristic curve (AUC) of NBPS for predicting hypertension remission in the training cohort was 0.853(0.786-0.905), which was superior to ARS [0.745(0.667-0.812), p=0.019] and PASO score [0.747(0.670-0.815), p=0.012]. The AUC of NBPS in the validation cohort was 0.830 (0.764-0.884), which was higher than ARS [0.745 (95% CI 0.672-0.810), p=0.045], but not significantly different from PASO score [0.825 (95% CI 0.758-0.880), p=0.911].

Conclusion: The NBPS is useful in predicting clinical outcome for UPA patients, especially in the Asian population.

Precis: we developed a novel outcome prediction score based upon sex, duration of hypertension, aldosterone to renin ratio and target organ damage to allow estimating the clinical outcome for UPA patients.

Key Words: Nomogram, Clinical outcome, Unilateral PA, ARS, PASO score

Introduction

Primary aldosteronism (PA) is the most common cause of endocrine hypertension, with a prevalence of nearly 5-10% in the general hypertensive population and as high as 20% in resistant hypertensives (1-4). The inappropriate elevation of plasma aldosterone concentration predisposes PA patients to an increased risk of cardiovascular, cerebrovascular and renal complications when compared with age-, gender- and blood pressure-matched patients with essential hypertension (5,6). PA is typically classified into unilateral and bilateral subtypes, with unilateral PA (UPA) consisting of aldosterone-producing adenoma (APA) and unilateral adrenal hyperplasia. UPA can be cured biochemically, with complete resolution of the hyperaldosteronism after unilateral adrenalectomy. As for postoperative blood pressure, nearly half of patients with UPA suffer from persisting hypertension (7-9). According to the Primary Aldosteronism Surgical Outcome (PASO) study, only 37% (17%-63%) of patients with UPA achieved complete clinical success after unilateral adrenalectomy, defined as normalization of blood pressure without any anti-hypertensive drugs (10). Thus, for clinicians and patients to have realistic expectations of clinical outcomes, it is crucial for them to be aware of predictors of complete clinical success before they undergo surgery.

It has previously been reported that sex, duration of hypertension and body mass index (BMI) are preoperative predictors of clinical outcome after unilateral adrenalectomy for UPA (11-15). To utilize these parameters in clinical practice, an Aldosteronoma Resolution Score (ARS) was established (16), which incorporated sex, duration of hypertension, number of preoperative antihypertensive drugs and BMI in a points system to predict three levels (low,

medium, high) of likelihood of complete clinical success. The ARS performed well in an American cohort (17) and a Japanese cohort (18) but not in a French cohort (19). Utsumi T et al. also used a nomogram to estimate hypertension remission in UPA by incorporating age, female sex, duration of hypertension and number of anti-hypertensive drugs (20), although this normogram was only tested in a Japanese cohort. Recently, a Primary Aldosteronism Surgical Outcome (PASO) score was also developed (21) using clinical data from 8 different international centers, which additionally employed target organ damage (TOD) and adrenal nodule size on imaging as predictive factors. However, these predictive scores did not use certain pivotal clinical and biochemical predictors of hypertension remission in UPA. It was recently reported that the plasma aldosterone concentration (PAC) post saline infusion test (SIT) (22) and medical history of diabetes (23) can predict hypertension remission in UPA. Additionally, the aldosterone to renin ratio (ARR) is also associated with hypertension remission in UPA, although the association only existed in univariate analysis (24).

The present study is an international multi-center, multi-ethnic study, which comprehensively evaluated potential clinical and biochemical predictors of hypertension remission in UPA by stepwise selection. The selected predictors were incorporated into a novel user-friendly nomogram-based preoperative score (NBPS). We also compared the predictive performance of NBPS with the previously developed ARS and PASO score.

Methods

Study Cohort

Patient data were collected from 3 international hypertension referral centers between April 6, 2014, and February 22, 2020 [Chongqing China (n=163), Munich Germany (n=98), Torino Italy (n=75). The Chongqing cohort (Chinese) was used as the training cohort and the Munich/Torino cohort (European) are a subset of patients from the PASO study (10) and were used as the validation cohort. Ethics approval was given by local ethics committees in all centers and written informed consent was acquired from all participants enrolled. The

criterion for inclusion were: 1: confirmed diagnosis of UPA according to the Endocrine Society guideline (25), and as described below; 2: post-surgical follow-up for at least 6 months. The criterion for exclusion were: 1: patients with UPA who failed to achieve complete biochemical success after unilateral adrenalectomy; 2: with a post-surgical follow-up shorter than 6 months.

Diagnosis of PA and UPA

The diagnosis of PA was achieved in accordance with the Endocrine Society guidelines (25), consisting of case detection, confirmatory testing and subtype classification. All antihypertensive drugs interfering with case detection were stopped at least 2 weeks before screening (at least 4 weeks for diuretics). At least one diagnostic confirmation test of saline infusion testing or captopril challenge testing was used according to local protocols. In the training cohort, UPA was identified by: (1) adrenal venous sampling in 132 patients, or (2) typical adenoma on computed tomography (CT) scanning and age＜35 years old, as described previously (26-28), in 18 patients. In the validation cohort, UPA was confirmed by adrenal venous sampling in all patients. Criteria for case detection, confirmation tests and AVS interpretation were described in the Supplementary Materials (29).

Laboratory measurements

In the Chongqing and Munich cohort, direct renin concentrations (DRC, mU/liter) and plasma aldosterone concentrations (PAC, pg/ml) were measured using an automated

chemiluminescence immunoassay (LIAISON; DiaSorin, Italy). In the Torino cohort, plasma aldosterone concentration (PAC, pg/ml) was assessed by solid-phase radioimmunoassay ALDOCTK-2 (DiaSorin, Saluggia, Italy) and plasma renin activity (PRA, ng/ml/h) was assessed using the RENCTK RIA kit (DiaSorin). For the calculation of the aldosterone to renin ratio (ARR), PRA was converted to DRC using the conversion factor of 8.2 (1ng/mL/hr PRA = 8.2 mU/L DRC) based upon the Endocrine Society guideline (25).

Definition of Target organ damage, medical history of diabetes and hypokalemia.

Target organ damage was defined according to the guidelines of the European Society of Hypertension (30), namely presence of left ventricular hypertrophy and/or microalbuminuria. Left ventricular hypertrophy was assessed by electrocardiography and/or echocardiography. Left ventricular hypertrophy assessed by electrocardiography was defined as a Sokolow–Lyon index >3.5 mV; left ventricular hypertrophy assessed by echocardiography was defined as a left ventricular mass index >115 g/m^2 for men and >95 g/m^2 for women; microalbuminuria was defined as a 24 h urinary albumin between 30–300 mg or by an albumin to creatinine ratio of 30–300 mg/g. In the training cohort, all the results for LVH were determined by echocardiography. In the validation cohort, LVH were determined by echocardiography in XX patients (the specify number of patients with electrocardiography/ electrocardiography in Torino and Munich is required). Medical history of diabetes was defined according to the 2015 American Diabetes Association criteria (31) as a fasting plasma glucose level greater than 7.8 mmol/L and/or a postprandial 2h plasma glucose level greater than 11.1 mmol/L. Hypokalemia was defined as serum concentration of potassium lower than 3.5 mmol/L.

Definition of biochemical outcome and clinical outcome

Biochemical and clinical outcomes were classified as complete, partial, or absent success and were defined according to the PASO criteria (10).

Blood pressure measurement

In both cohorts, blood pressure of UPA patients were measured in the office, as refer to European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension (32,33). The detail methods were previously described (26,34) and is available in the Supplementary Materials (29).

Development and validation of the nomogram and the nomogram-based predictive score

Univariate and multivariate logistic regression analysis were used to identify predictors of hypertension remission in UPA. A nomogram was formulated based on the results of multivariate logistic regression analysis and by using the *rms* and *forign* package of R, version 3.6.1 (http://www.r-project.org/). The nomogram was established by proportionally converting each regression coefficient in the multivariate logistic regression to a 0- to 100-point scale. The variable with the highest β coefficient (absolute value) was assigned 100 points. The predictive performance of the nomogram was evaluated by concordance index (C index) and calibrated by the bootstrap method, the higher a C index of a nomogram, the better a predictive performance it would achieve (35,36). A nomogram-based predictive score (NBPS) was established. In the NBPS, the continuous variables, were firstly categorized into low, medium or high levels based on data from the entire cohort with the cut-offs of each

category determined by tertiles,) and all the variables were weighted according to its weight in the nomogram.

Statistical Analysis

Data distributions were analyzed by Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation (SD) and were analyzed by the student *t* test. Skewed distributed variables were expressed as median (quartile range) and analyzed after a Z logarithm transformation. Categorical variables (sex, target organ damage) were expressed as absolute numbers and proportions (%) and analyzed by a chi-square test. All variables significantly associated with hypertension remission were candidates for stepwise multivariate analysis (forward). All above analyses were performed using SPSS (version 21.0). Receiver operating characteristic (ROC) curve analysis was used to calculate the predictive performance of the NBPS, ARS, PASO score and the nomogram established by the Japanese team and were performed using MedCalc software 8.1.1.0. In all analyses, *p*< 0.05 was considered statistically significant.

Results

A total of 315 cases of UPA with post-surgical complete biochemical success were enrolled in the present study, with the training cohort comprising 150 cases and the validation cohort comprising 165 cases (Figure 1).

Ninety-seven out of 150 cases (64.7%) achieved complete clinical success after unilateral adrenalectomy in the training cohort after at least 6 months of post-surgical follow-up. In the training cohort, patients with complete clinical success were younger

(43.6±12.8 *vs*. 48.9±10.6, p=0.011), more frequently female (78.4% *vs*. 43.4%, p<0.001), had a shorter duration of hypertension [3.0 (1.0, 8.0) *vs*. 8.0 (3.0, 13.5), p=0.001] and a lower BMI (22.7±2.7 *vs*. 24.8±3.5, p<0.001) compared with patients in the partial plus absent clinical success group. Patients with complete clinical success also had a lower systolic blood pressure (153.4±17.6 vs. 160.7±17.4, p=0.016), a higher pre-operative ARR [293.5 (95.8, 487.1) *vs*. 89.8 (43.1, 195.4), p<0.001], a higher PAC post-SIT [288.0 (180.5, 465.0) *vs*. 208.0 (133.0, 308.0), p=0.013] and a lower incidence of medical history of diabetes (8.2% *vs*. 28.3%, p=0.002). As for target organ damage (TOD), the prevalence of left ventricular hypertrophy (LVH) was lower in those with post-surgical complete clinical success (40.2% vs 77.4%, *p*<0.001), but the incidence of microalbuminuria was not significantly different between the two groups (47.9% vs 57.1%, *p*=0.483). The overall prevalence of TOD was lower in those with post-surgical complete clinical success (56.7% *vs*. 86.8%, p<0.001). The prevalence of family history of hypertension, the defined daily dose (DDD) of anti-hypertensive drugs and the largest adrenal nodule size at imaging were not significantly different between the two groups (Table 1).

In the validation cohort, 57 of 165 cases (34.5%) achieved complete clinical success after unilateral adrenalectomy after at least 6 months of post-surgical follow-up. In line with the training cohort, UPA patients with complete clinical success in the validation cohort were also younger (44.9±10.4 *vs*. 52.9±10.3, p<0.001), more frequently female (64.9% *vs*. 32.4%, p<0.001), had a shorter duration of hypertension [5.1 (1.3, 7.6) *vs*. 8.0 (3.0, 13.5), p<0.001] and a lower BMI (25.0±4.3 *vs*. 28.3±4.5, p<0.001) compared with patients with partial plus absent clinical success. Patients with complete clinical success in the validation cohort also

had a lower systolic blood pressure (155.2±20.9 *vs*. 164.8±26.2, p=0.019) and a higher

pre-operative ARR [178.3 (84.2, 291.0) *vs*. 56.3 (15.0, 145.5), p<0.001]. As for TOD, the

prevalence of LVH was lower in those with post-surgical complete clinical success (42.1% vs

71.3%, *p*<0.001), but the incidence of microalbuminuria was not significantly different

between the two groups (34.0% vs 41.7%, *p*=0.483). The overall prevalence of TOD was

lower in those with post-surgical complete clinical success (50.9% *vs*. 81.5%, p<0.001). In

contrast to the training cohort, UPA patients with complete clinical success in the validation

cohort had a lower defined daily dose (DDD) of anti-hypertensive drugs [2.1 (1.5, 4.2) *vs*. 4.0

(2.0, 5.6), p=0.001] and a larger nodule size at imaging [15.1 (10.0, 21.5) *vs*. 14.0 (9.0, 16.7),

p=0.014] compared with the partial plus absent clinical success group (Supplemental Table

1)(29).

We also compare the clinical and biochemical parameters between the training cohort

and the validation cohort. UPA patients in the training cohort were more frequently female

(66.0% vs. 43.6%, p<0.001), had a higher incidence of complete clinical success (64.7% *vs*.

34.5%, p<0.001) and a higher ARR [201.6 (56.6, 445.6) *vs*. 87.4 (27.8, 219.2), p<0.001]. In

addition, UPA patients in the training cohort were younger (45.5±12.3 *vs*. 50.2±11.0, p<0.001),

had a lower duration of hypertension [4.0 (1.0, 10.0) *vs*. 7.4 (3.2, 14.6), p<0.001)], a lower

BMI (23.5±3.2 *vs*. 27.2±4.8, p<0.001), a lower systolic blood pressure (156.0±17.9 vs.

161.5±24.9, p=0.026), a lower DDD of anti-hypertensive medication [2.0 (1.0, 2.7) *vs*. 3.3

(2.0, 5.0), p<0.001)] (Supplemental Table 2)(29).

Univariate and multivariate logistic regression analysis were used to identify predictors

of hypertension remission in UPA in the training cohort. univariate analysis showed that age

[OR, 0.964 (95% CI, 0.937-0.992), p=0.012], duration of hypertension [OR, 0.938 (95% CI, 0.891-0.986), p=0.012], female sex [OR, 4.720 (95% CI, 2.282-9.766), p<0.001], BMI [OR, 0.794 (95% CI, 0.705-0.895), p<0.001], systolic blood pressure [OR, 0.977 (95% CI, 0.958-0.996), p=0.018], ARR [OR, 1.788 (95% CI, 1.328-2.407), p<0.001], PAC post-SIT [OR, 1.723 (95% CI, 1.154-2.574), p=0.008], absence of medical history of diabetes [OR, 0.228 (95% CI, 0.089-0.582), p=0.002] and absence of TOD [OR, 0.199 (95% CI, 0.082-0.486), p<0.001] were associated with complete clinical success in UPA (Table 2). All variables significantly associated with hypertension remission (P<0.05) in the univariate analysis were candidates for stepwise multivariate analysis (forward). Four variables were independent predictors of complete clinical success in the multivariate analysis (Table 3). Female sex was the strongest independent predictor [OR, 5.374 (95% CI, 2.257-12.792), p<0.001], followed by ARR [OR, 2.183 (95% CI, 1.503-3.169), p<0.001], and duration of hypertension [OR, 0.910 (95% CI, 0.854-0.970), p=0.004] and absence of TOD [OR, 0.278 (95% CI, 0.099-0.783), p=0.015].

A nomogram was established by incorporating the four significant parameters from the multivariate analysis (sex, ARR, duration of hypertension and TOD) (Figure 2A). The nomogram demonstrated a good accuracy in predicting hypertension remission in UPA, with a bootstrap-corrected C-index of 0.842 (95% CI, 0.774-0.897). In addition, calibration plots showed good agreement between the actual status of hypertension remission and the probability of hypertension remission estimated by the nomogram (Figure 2B). In the validation cohort, the nomogram also displayed a well C-index of 0.833 (95% CI, 0.767-0.886) for the prediction of hypertension remission in UPA and a good agreement in the calibration

plots (Figure 2C).

To facilitate routine clinical use, a nomogram-based predictive score (NBPS) was established. In the model of NBPS, four predictors were weighted according to their weight in the nomogram. Categorical variables of sex and TOD were weighted 3.5 (for female) and 2.5 (for absence of TOD) points, respectively. The continuous variables, ARR and duration of hypertension, were categorized into low, medium or high levels according to the nomogram. In the NBPS, low, medium or high levels of ARR ($pg\cdot ml^{-1}/mIU\cdot l^{-1}$) were defined as ≤ 60, 60.1-180 or > 180 and were weighted 0, 5, 10 points, respectively. The duration of hypertension (years) was categorized as ≤ 5, 5.1-10, > 10 and weighted 6, 3, 0 points, respectively (Table 4).

We then compared the predictive performance of NBPS to the previously established ARS and PASO score in predicting hypertension remission in UPA. The ARS and PASO score of all UPA patients were calculated as previously described (16,21). In the training cohort, compared with those without complete clinical success (partial plus absent clinical success), patients with complete clinical success had a higher ARS and PASO score [4.0 (3.0-5.0) *vs*. 3.0 (2.0-4.0), p<0.001] and [19.0 (16.0-21.0) *vs*. 15.0 (12.5-17.0), p<0.001], respectively. The NBPS in patients with complete clinical success was also significantly higher than the partial plus absent clinical success group [16.5 (13.5-19.5) *vs*. 8.5 (6.0-12.5), p<0.001]. In the validation cohort, those with complete clinical success also had a higher ARS and PASO score compared with those in the partial plus absent complete clinical success group [3.00 (2.00-4.50) *vs*. 1.00 (0.00-2.00), p<0.001] and [18.00 (14.50, 21.75) *vs*. 12.00 (9.13, 14.38), p<0.001], respectively. The NBPS in patients with complete clinical success was also

significantly higher than the partial plus absent clinical success group [14.5 (10.5-17.0) *vs*. 6.0 (3.5-10.5), p<0.001] (Supplemental Table 3) (29). In the training cohort, ROC curve analysis revealed that NBPS could accurately predict hypertension remission in UPA, with an area under ROC curve (AUC) of 0.853(0.786-0.905), which was superior to that of ARS [0.745(95% CI 0.667-0.812), p=0.019] and PASO score [0.747(95% CI 0.670-0.815), p=0.012] (Figure 3A). In the validation cohort, the AUC of NBPS was 0.830 (0.764-0.884), which was superior to that of ARS [0.745 (95% CI, 0.672-0.810), *p*=0.045], but not significantly different from the PASO score [0.825 (95% CI, 0.758-0.880), *p*=0.911] (Figure 3B). We also compared our NBPS to the nomogram established by the Japanese team (20), and found that the AUC of the NBPS is superior to that of the nomogram developed by the Japanese team in the training cohort [0.853 (0.786-0.905) *vs*. 0.731 (95% CI, 0.653-0.800), p=0.005], though no significant difference was found in the validation cohort [0.830 (0.764-0.884) *vs*. 0.770 (95% CI, 0.698-0.832), p=0.157] (Supplemental Figure 1)(29).

The optimal cut-off of NBPS for the prediction of hypertension remission was $\geq$11.5, with a sensitivity of 85.6% (77.0%-91.9%) and a specificity of 71.7% (57.7%-83.2%) in the training cohort and a sensitivity of 68.4% (54.8%-80.1%) and a specificity of 78.7% (69.8%-86.0%) in the validation cohort (Table 5). If we use a cut-off of NBPS≥16.5, the specificity of NBPS is increased to 94.3%; while usingNBPS≥8.5, the sensitivity of NBPS is increased to 95.9% (Supplemental Table 4) (29).

Discussion

In the present study, we found the ARR to be a robust predictor of hypertension remission in UPA patients and established a nomogram-based preoperative score (NBPS) for

the prediction of clinical outcome for UPA patients in a large international multi-ethnic cohort. Our newly developed NBPS was useful in predicting hypertension remission for UPA patients following adrenal surgery, especially in Asian patients.

Efforts have been made to establish an outcome-prediction model (16,21) in UPA. Both ARS and PASO score performed well in predicting the likelihood of hypertension remission following the surgical treatment of UPA. However, these scores did not incorporate several recently reported predictors of hypertension remission (22,23) whereas the present study comprehensively evaluated all the relevant clinical and biochemical parameters. Consistent with the previously developed ARS and PASO score, our NBPS presented herein also employed female sex, duration of hypertension and absence of TOD as predictors of hypertension remission in UPA. However, BMI was excluded because its correlation with hypertension remission only appeared in the univariate analysis. Additionally, the preoperative number of anti-hypertensive drugs (DDD) and adrenal nodule size were also excluded because these variables were not significantly different between those with complete clinical success and those without. The difference in parameters between NBPS and PASO score could be attributed to the relatively lower predictive performance of BMI and adrenal nodule size, as shown by the borderline odds ratio in the study of PASO score (21). The DDD of anti-hypertensive drugs was excluded because its association with hypertension remission may be directly related to the duration of hypertension and ARR.

Besides three abovementioned clinical characteristics, we also found the ARR to be a robust predictor of hypertension remission in UPA patients. The difference in ARR between training and validation cohorts (201.6 vs 87.4) could be partially attributed to referral bias, as

there is a lower level of awareness of PA case detection in China compared to Japan and Italy, so the majority of PA patients has a more pronounced hyperaldosteronism in the hypertension referral center in China. The role of the ARR in predicting hypertension remission in UPA has been investigated in several studies. In a Taipei cohort, Chan et al. found that the ARR in those with complete clinical success were significantly higher than those without (21). Sawka et al. also reported an association of a higher preoperative ARR with hypertension remission in UPA, but the association was only found in univariate analysis (23). Though there were significant differences in the ARR between the training and validation cohorts, our results demonstrated that the ARR in those with complete clinical success was significantly higher than those without in the training and validation cohorts alike. A multivariate analysis also confirmed the ARR as a strong independent predictor of hypertension remission in UPA. We speculate that UPA patients with a higher ARR at the time of screening were more likely to have severe disease (such as higher blood pressure and hypokalemia), and were therefore diagnosed and treated in a timely manner, enabling better clinical outcomes after surgery.

In the present study, by incorporating the selected components of ARS and PASO score in addition to the ARR into the NBPS, we developed a useful clinical outcome prediction tool for UPA patients. Further analyses reveal that the AUC of the NBPS is higher than that of ARS and PASO in the training cohort, and not significantly different from PASO score in the validation cohort. We think the NBPS provide additional value to the PASO score in some ways. On the one hand, the NBPS was developed in an Asian cohort, and its AUC is significantly higher than PASO [0.85 (0.79-0.91) vs. 0.75 (0.67-0.82), p=0.012]. The validation of NBPS was conducted in a Caucasian cohort, and the AUC was similar to PASO.

It should be noted that the characteristics of UPA (i.e. KCNJ5 mutation rate and tumor size) were different between Caucasian and Asian patients (37). Our analyses indicated that the NBPS is applicable to both Caucasian and Asian patients, with a superior performance in the Asian population. On the other hand, the use of less variables (4 in NBPS vs. 6 in PASO) and visualized scoring of the nomogram ensures that the NBPS is user-friendly.

Utsumi T et al. also used a nomogram to estimate hypertension remission in UPA by incorporating age, female sex, duration of hypertension and number of anti-hypertensive drugs (20). Our newly developed nomogram, after multi-ethnic training and validation, excluded parameters of age and the number of antihypertensive drug and additionally included ARR and target organ damage. Furthermore, we converted our nomogram into a more user-friendly score which should facilitate its wide clinical use. A comparison of our NBPS with the nomogram established by the Japanese team (21) revealed that the AUC of the NBPS performed better than the nomogram in the training cohort, although no significant difference was found in the validation cohort. Taken together, our results indicated that the newly developed NBPS offers an improvement over the previously published nomogram.

The rate of complete clinical success differed between the training and validation cohorts, being much higher in the training cohort (64.7% vs. 34.5%). The difference could partially be explained by ethnic differences. According to our unpublished data, the somatic mutation rate of KCNJ5 in UPA patients in the training cohort is 76.7%, which is much higher than reported 35% in Caucasian population (37). It is reported that UPA patients with KCNJ5 mutation has a higher probability of complete clinical success after adrenal surgery (38). The shorter duration of hypertension, higher prevalence of female patients and younger age in the training

cohort could also explain the higher clinical remission rate.

Our study has several strengths. Firstly, we comprehensively evaluated clinical and biochemical predictors of hypertension remission in UPA and all the parameters enrolled in the NBPS were subjected by stepwise selection. Secondly, the NBPS was developed and validated in different ethnic cohorts, with a very low overfitting bias. Furthermore, the current study excluded UPA patients with partial or absent biochemical success, as the lack of complete biochemical success (largely due to wrong judgment of lateralization or incompletely excised aldosterone producing tissues) would confound the main outcome. Thus, eliminating those patients may increases the reproducibility of our results. A potential limitation of the NBPS is the inability to differentiate patients with partial clinical success from those with absent clinical success. In addition, not all UPA patients in hypertension referral centers underwent echocardiography and microalbuminuria measurement, and this may be a limiting factor with the current nomogram. However, it is feasible for the majority of PA referral centers to pursue these investigations and fully utilize our NBPS.

Conclusions

In conclusion, we found the ARR to be a robust predictor of hypertension remission in UPA and established a nomogram-based preoperative score (NBPS) for the prediction of clinical outcomes following unilateral adrenalectomy for UPA patients in a large international multi-ethnic cohort. The NBPS could accurately predict hypertension remission for UPA patients, especially in the Asian population. Patients with a higher NBPS preoperatively are more likely to achieve complete resolution of their hypertension after unilateral

adrenalectomy. In contrast, patients with a lower NBPS were more likely to experience ongoing hypertension and should be closely monitored following surgery with a low threshold for re-initiating antihypertensive therapy.

Reproducible Research Statement: Study protocol and statistical code: Available from Dr. Jinbo Hu, (e-mail: hujinbo_568@163.com)

Data Availability Statement: Available to approved persons through written agreements with the authors and the data partner.

Requests for Single Reprints: Jinbo Hu, MD, PhD, Department of Endocrinology, the First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Street, Chongqing 400016, China, e-mail: hujinbo_568@163.com

Current Authors Addresses: Drs Yi Yang, Jinbo Hu, Ying Song, Wenwen He, Qingfeng Cheng, Linqiang Ma, Ting Luo, Shumin Yang, Qifu Li: Department of Endocrinology, the First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

Drs Jun Yang: Cardiovascular Endocrinology Laboratory, Hudson Institute of Medical Research, Clayton, Vic, Australia; Department of Medicine, Monash University, Clayton, VIC, Australia.

Drs Tracy Ann Williams and Martin Reincke: Medizinische Klinik und Poliklinik IV, Klinikum der Universität, Ludwig-Maximilians-Universität München, Munich, Germany.

Drs Jacopo Burrello and Paolo Mulatero: Division of Internal Medicine and Hypertension Unit, Department of Medical Sciences, University of Torino, Italy.

All authors have read the journal's authorship agreement and that the manuscript has been reviewed by and approved by all named authors.

References

1. **Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, Ganzaroli C, Giacchetti G, Letizia C, Maccario M, Mallamaci F, Mannelli M, Mattarello MJ, Moretti A, Palumbo G, Parenti G, Porteri E, Semplicini A, Rizzoni D, Rossi E, Boscaro M, Pessina AC, Mantero F, Investigators PS** 2006 A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. Journal of the American College of Cardiology 48:2293-2300

2. **Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffolo F, Gabetti L, Mengozzi G, Williams TA, Rabbia F, Veglio F, Mulatero P** 2017 Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. Journal of the American College of Cardiology 69:1811-1820

3. **Loh KC, Koay ES, Khaw MC, Emmanuel SC, Young WF, Jr** Prevalence of primary aldosteronism among asian hypertensive patients in singapore 2000 The Journal of clinical endocrinology and metabolism 85:2854-2859

4. **Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P** 2002 Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 40:892-896

5. **Rossi GP, Sechi LA, Giacchetti G, Ronconi V, Strazzullo P, Funder JW** 2008 Primary aldosteronism: Cardiovascular, renal and metabolic implications. Trends in endocrinology and metabolism: TEM 19:88-90

6. **Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, Mulatero P** 2018 Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: A systematic review and meta-analysis. The lancet. Diabetes & endocrinology 6:41-50

7. **Meyer A, Brabant G, Behrend M** 2005 Long-term follow-up after adrenalectomy for primary aldosteronism. World journal of surgery 29:155-159

8. **Rossi GP, Cesari M, Cuspidi C, Maiolino G, Cicala MV, Bisogni V, Mantero F, Pessina AC** 2013 Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. Hypertension 62:62-69

9. **Steichen O, Zinzindohoue F, Plouin PF, Amar L** 2012 Outcomes of adrenalectomy in patients with unilateral primary aldosteronism: A review. Hormone and metabolic research 44:221-227

10. **Williams TA, Lenders JWM, Mulatero P, Burrello J, Rottenkolber M, Adolf C, Satoh F, Amar L, Quinkler M, Deinum J, Beuschlein F, Kitamoto KK, Pham U, Morimoto R,**

Umakoshi H, Prejbisz A, Kocjan T, Naruse M, Stowasser M, Nishikawa T, Young WF, Jr., Gomez-Sanchez CE, Funder JW, Reincke M 2017 Outcomes after adrenalectomy for unilateral primary aldosteronism: An international consensus on outcome measures and analysis of remission rates in an international cohort. The lancet Diabetes & endocrinology 5:689-699

11. van der Linden P, Steichen O, Zinzindohoue F, Plouin PF 2012 Blood pressure and medication changes following adrenalectomy for unilateral primary aldosteronism: A follow-up study. Journal of hypertension 30:761-769

12. Celen O, O'Brien MJ, Melby JC, Beazley RM 1996 Factors influencing outcome of surgery for primary aldosteronism. Archives of surgery 131:646-650

13. Citton M, Viel G, Rossi GP, Mantero F, Nitti D, Iacobone M 2015 Outcome of surgical treatment of primary aldosteronism. Langenbeck's archives of surgery 400:325-331

14. Sawka AM, Young WF, Thompson GB, Grant CS, Farley DR, Leibson C, van Heerden JA 2001 Primary aldosteronism: Factors associated with normalization of blood pressure after surgery. Annals of internal medicine 135:258-261

15. Zhou Y, Zhang M, Ke S, Liu L 2017 Hypertension outcomes of adrenalectomy in patients with primary aldosteronism: A systematic review and meta-analysis. BMC endocrine disorders 17:61

16. Zarnegar R, Young WF, Jr., Lee J, Sweet MP, Kebebew E, Farley DR, Thompson GB, Grant CS, Clark OH, Duh QY 2008 The aldosteronoma resolution score: Predicting complete resolution of hypertension after adrenalectomy for aldosteronoma. Annals of surgery 247:511-518

17. Aronova A, Gordon BL, Finnerty BM, Zarnegar R, Fahey TJ, 3rd 2014 Aldosteronoma resolution score predicts long-term resolution of hypertension. Surgery 156:1387-1392; discussion 1392-1383

18. Utsumi T, Kawamura K, Imamoto T, Kamiya N, Komiya A, Suzuki S, Nagano H, Tanaka T, Nihei N, Naya Y, Suzuki H, Tatsuno I, Ichikawa T 2012 High predictive accuracy of aldosteronoma resolution score in japanese patients with aldosterone-producing adenoma. Surgery 151:437-443

19. Pasquier L, Kirouani M, Fanget F, Nomine C, Caillard C, Arnault V, Finel JB, Christou N, Mathonnet M, Tresallet C, Hamy A, de Calan L, Brunaud L, Menegaux F, Lifante JC, Hardouin JB, Drui D, Mirallie E, Blanchard C 2017 Assessment of the aldosteronona resolution score as a predictive resolution score of hypertension after adrenalectomy for aldosteronoma in french patients. Langenbeck's archives of surgery 402:309-314

20. Utsumi T, Kamiya N, Endo T, Yano M, Kamijima S, Kawamura K, Imamoto T, Naya Y, Ichikawa T, Suzuki H 2014 Development of a novel nomogram to predict hypertension cure after laparoscopic adrenalectomy in patients with primary aldosteronism. World journal of surgery 38:2640-2644

21. Burrello J, Burrello A, Stowasser M, Nishikawa T, Quinkler M, Prejbisz A, Lenders JWM, Satoh F, Mulatero P, Reincke M, Williams TA 2019 The primary aldosteronism surgical outcome score for the prediction of clinical outcomes after adrenalectomy for unilateral primary aldosteronism. Annals of surgery

22. Chan CK, Kim JH, Chueh E, Chang CC, Lin YF, Lai TS, Huang KH, Lin YH, Wu VC, Group TS 2019 Aldosterone level after saline infusion test could predict clinical outcome in

primary aldosteronism after adrenalectomy. Surgery 166:362-368

23. **Morisaki M, Kurihara I, Itoh H, Naruse M, Takeda Y, Katabami T, Ichijo T, Wada N, Yoshimoto T, Ogawa Y, Sone M, Tsuiki M, Shibata H, Kawashima J, Fujita M, Watanabe M, Matsuda Y, Kobayashi H, Suzuki T, Group JS** 2019 Predictors of clinical success after surgery for primary aldosteronism in the japanese nationwide cohort. Journal of the Endocrine Society 3:2012-2022

24. **Sawka AM, Young WF, Thompson GB, Grant CS, Farley DR, Leibson C, van Heerden JA** 2001 Primary aldosteronism: Factors associated with normalization of blood pressure after surgery. Annals of internal medicine 135:258-261

25. **Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF, Jr** 2016 The management of primary aldosteronism: Case detection, diagnosis, and treatment: An endocrine society clinical practice guideline. The Journal of clinical endocrinology and metabolism 101:1889-1916

26. **Song Y, Yang S, He W, Hu J, Cheng Q, Wang Y, Luo T, Ma L, Zhen Q, Zhang S, Mei M, Wang Z, Qing H, Bruemmer D, Peng B, Li Q** 2018 Chongqing Primary Aldosteronism Study G 2018 Confirmatory tests for the diagnosis of primary aldosteronism: A prospective diagnostic accuracy study. Hypertension 71:118-124

27. **Lim V, Guo Q, Grant CS, Thompson GB, Richards ML, Farley DR, Young WF, Jr 2014** Accuracy of adrenal imaging and adrenal venous sampling in predicting surgical cure of primary aldosteronism. Journal of clinical endocrinology and metabolism 99:2712–2719.

28. **Yang Y, Xiao M, Song Y, Tang Y, Luo T, Yang S, He W, Cheng Q, Ma L, Zhang Y, He Y, Cao Y, Yang J, Peng B, Hu J, Li Q** 2019 H-score of 11beta-hydroxylase and aldosterone synthase in the histopathological diagnosis of adrenocortical tumors. Endocrine 65:683-691

29. **Jinbo Hu.** Data from: Nomogram-Based Preoperative Score for Predicting Surgical Outcome in Unilateral Primary Aldosteronism. Figshare 2020. Deposited 3 June 2020. https://doi.org/10.6084/m9.figshare.12415958.v1

30. **Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU** 2015 Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the american society of echocardiography and the european association of cardiovascular imaging. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 28:1-39 e14

31. **American Diabetes Association** 2018 Classification and diagnosis of diabetes: Standards of medical care in diabetes-2018 2018 Diabetes care 41:S13-S27

32. **Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F** 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 34:2159-219

33. **Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A,**

Schmieder RE, Struijker Boudier HA, Zanchetti A 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 28: 1462-536

34. Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffolo F, Gabetti L, Mengozzi G, Williams TA, Rabbia F, Veglio F, Mulatero P 2017 Prevalence and Clinical Manifestations of Primary Aldosteronism Encountered in Primary Care Practice. J Am Coll Cardiol 69: 1811–20

35. Lei Z, Li J, Wu D, Xia Y, Wang Q, Si A, Wang K, Wan X, Lau WY, Wu M, Shen F 2016 Nomogram for preoperative estimation of microvascular invasion risk in hepatitis b virus-related hepatocellular carcinoma within the milan criteria. JAMA surgery 151:356-363

36. van der Naalt J, Timmerman ME, de Koning ME, van der Horn HJ, Scheenen ME, Jacobs B, Hageman G, Yilmaz T, Roks G, Spikman JM 2017 Early predictors of outcome after mild traumatic brain injury (upfront): An observational cohort study. The Lancet. Neurology 16:532-540

37. Lenzini L, Rossitto G, Maiolino G, Letizia C, Funder JW, Rossi GP 2015 A meta-analysis of somatic KCNJ5 K(+) channel mutations in 1636 patients with an aldosterone-producing adenoma. Journal of Clinical Endocrinology and Metabolism 100: E1089–E1095

38. Leticia A. P. Vilela, Marcela Rassi-Cruz, Augusto G. Guimaraes, Caio C. S. Moises, Thais C. Freitas, Natalia P. Alencar, Janaina Petenuci, Tatiana S. Goldbaum, Ana Alice W. Maciel, Maria Adelaide A. Pereira, Giovanio V. Silva, Andrea P. Abreu, Maria Claudia N. Zerbini, Aline C. B. S. Cavalcante, Francisco C. Carnevale, Bruna Pilan, Fernando Yamauchi, Vitor Srougi, Fabio Y. Tanno, Jose L. Chambo, Ana Claudia Latronico, Berenice B. Mendonca, Maria Candida B. V. Fragoso, Luiz A. Bortolotto, Luciano Drager, Madson Q. Almeida 2019 KCNJ5 somatic mutation is a predictor of hypertension remission after adrenalectomy for unilateral primary aldosteronism. Journal of Clinical Endocrinology and Metabolism 104:4695-4702

Figure Legends:

Figure 1. Flow chart.

Figure 2. Nomogram for preoperative estimation of complete clinical success in UPA patients and predictive performance.

A, Nomogram to estimate complete clinical success in UPA patients. To use the nomogram, find the position of each variable on the corresponding axis, draw a line to the points axis for the number of points, add the points from all of the variables, and draw a line from the total

points axis to determine the possibility of complete clinical success at the lower line of the nomogram. B, Validation of the predictive performance of the nomogram in estimating complete clinical success in the training cohort (n = 150) by calibrating with 1000 bootstrap samples to decrease the overfit bias. C, Validation of the predictive performance of the nomogram in estimating the possibility of complete clinical success in the validation cohort (n = 165) by calibrating with 1000 bootstrap samples to decrease the overfit bias. ARR: aldosterone to renin ratio; HT: hypertension; TOD: target organ damage; C index: concordance index; ROC: receiver operating characteristic curve.

Figure 3. Comparison of NBPS with ARS and PASO score for preoperative estimation of hypertension remission in UPA patients in the training cohort (A) and the validation cohort (B).

ROC curve analysis was used to compare NBPS with ARS and PASO score for the estimation of hypertension remission in the training cohort (A) and the validation cohort (B). The AUC is indicated. ROC curve, receiver operating characteristic curve; NBPS, nomogram-based preoperative score; ARS, aldosteronoma resolution score; PASO, primary aldosteronism surgical outcome; AUC, the area under the ROC curve.

Table 1. Preoperative clinical and biochemical characteristics of UPA patients in the training cohort.

	Complete Clinical Success(n=97)	Partial + Absent Clinical Success(n=53)	*P* Value
Age (years)	43.6±12.8	48.9±10.6	0.011
Sex (M/F)	21/76 (78.4%)	30/23 (43.4%)	<0.001
Duration of hypertension (years)	3.0 (1.0,8.0)	8.0 (3.0,13.5)	0.001
Familial history of hypertension (Yes/No)	50/47 (51.5%)	27/26 (50.9%)	1.000
History of hypokalemia (Yes/No)	83/14 (85.6%)	45/8 (84.9%)	1.000
BMI (kg/m2)	22.7±2.7	24.8±3.5	<0.001
SBP (mmHg)	153.4±17.6	160.7±17.4	0.016
DBP (mmHg)	95.2±13.0	98.0±13.8	0.219
TC (mmol/L)	4.0±0.8	3.9±0.8	0.914
TG (mmol/L)	1.2±1.5	1.3±0.6	0.775
Serum K^+(mmol/L)	3.0±0.6	3.1±0.5	0.217
PAC (pg/ml)	349.0 (248.5, 547.0)	314.0 (218.5, 488.5)	0.237
ARR (pg·ml^{-1}/mIU·l^{-1})	293.5 (95.8, 487.1)	89.8 (43.1, 195.4)	<0.001
PAC post-SIT (pg/ml)	288.0 (180.5, 465.0)	208.0 (133.0, 308.0)	0.013
DDD of anti-hypertensive medication	1.8±1.0	2.1±1.0	0.117
Target organ damage (Yes/No)	55/42 (56.7%)	46/7 (86.8%)	<0.001
Left Ventricular Hypertrophy (Yes/No)	40.2%	77.4%	<0.001
Microalbuminuria (Yes/No)	47.9%	57.1%	0.483
Medical history of diabetes (Yes/No)	8/89 (8.2%)	15/38 (28.3%)	0.002
Size of largest nodule at imaging (mm)	13.9±4.7	14.0±5.4	0.921

Data were expressed as mean ± SD, median (interquartile range) and proportion (%), proportions indicate females, presence of familial history of hypertension, presence of hypokalemia, presence of diabetes and presence of target organ damage. HT, hypertension; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; Serum K^+, concentration of serum potassium; PAC, plasma aldosterone concentration; ARR, aldosterone to renin ratio; SIT, saline infusion test; DDD, defined daily dose.

Table 2. Univariate logistic regression analysis of predictors of hypertension remission in UPA patients based on preoperative data in the training cohort.

Variable	OR (95% CI)	*P* Value
Age (years)	0.964 (0.937-0.992)	0.012
Female sex	4.720 (2.282-9.766)	<0.001
Duration of hypertension (years)	0.938 (0.891-0.986)	0.012
BMI (kg/m2)	0.794 (0.705-0.895)	<0.001
SBP (mmHg)	0.977 (0.958-0.996)	0.018
ARR (pg$^.$ml^{-1}/mIU$^.$l^{-1})	1.788 (1.328-2.407)	<0.001
PAC post-SIT(Pg/ml)	1.723 (1.154-2.574)	0.008
DDD of anti-hypertensive medication	0.779 (0.569-1.066)	0.118
Absence of target organ damage	0.199 (0.082-0.486)	<0.001
Absence of medical history of diabetes	0.228 (0.089-0.582)	0.002
Size of largest nodule at imaging (mm)	0.997 (0.932-1.066)	0.921

Data were expressed as OR (95% CI). HT, hypertension; BMI, body mass index; SBP, systolic blood pressure; PAC, plasma aldosterone concentration; ARR, aldosterone to renin ratio; SIT, saline infusion test; DDD, defined daily dose.

Table 3. Stepwise selection (forward) of predictors of hypertension remission in UPA patients.

Position in model	Variable	OR (95% CI)	*P* Value
First	Female sex	5.374 (2.257-12.792)	<0.001
Second	ARR	2.183 (1.503-3.169)	<0.001
Third	Duration of hypertension	0.910 (0.854-0.970)	0.004
Fourth	Absence of target organ damage	0.278 (0.099-0.783)	0.015

Data were expressed as OR (95% CI). ARR, aldosterone to renin ratio; TOD, target organ damage.

Table 4. Nomogram-based preoperative score: 4 variable model.

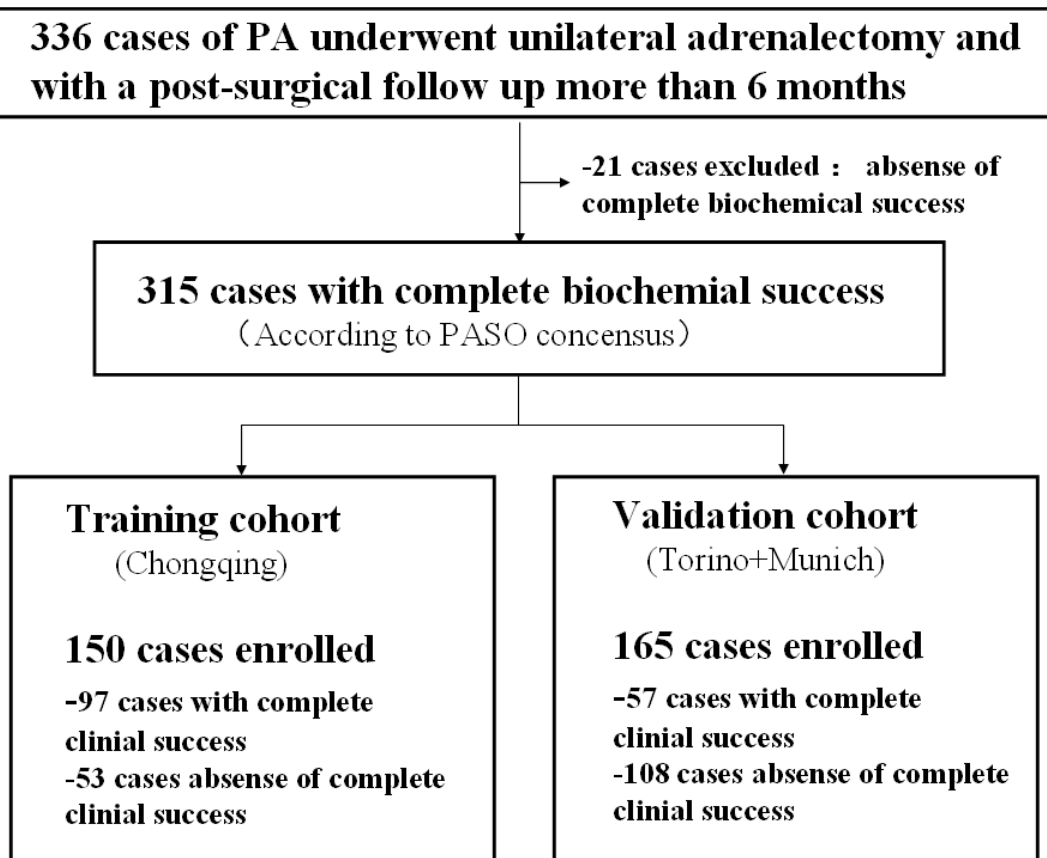| Variables	Category	Points
ARR (pg·ml⁻¹/mIU·l⁻¹)	≤60	0
	60.1-180	5
	＞180	10
Duration of hypertension (years)	≤5	6
	5.1-10	3
	＞10	0
Sex	Male	0
	Female	3.5
Target organ damage	Yes	0
	No	2.5

Possible score ranges from 0 to 22. ARR: aldosterone to renin ratio.

1 **Table 5. Comparing NBPS with ARS and PASO score for the preoperative estimation of hypertension remission in UPA patients in the training and**
2 **the validation cohorts.**

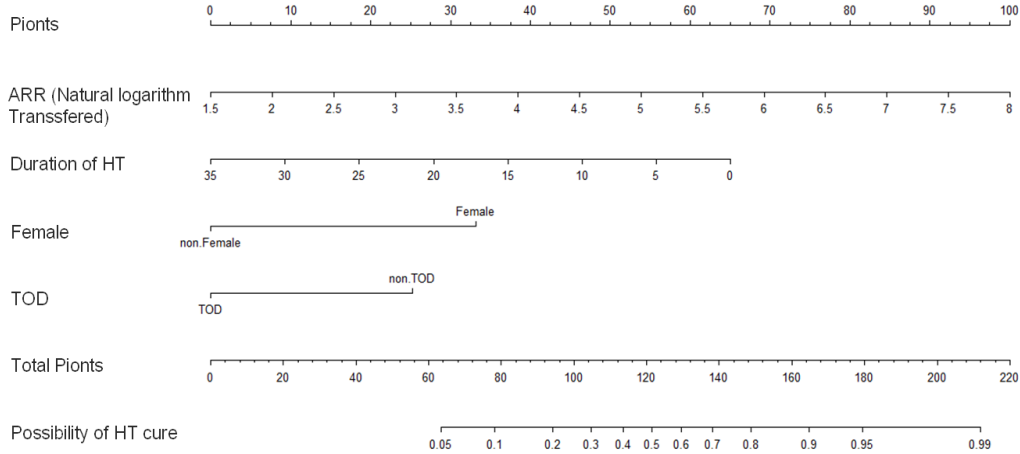|	Value (95% CI)					
Variable	**Training cohort**			**Validation cohort**		
Predictive model	**NBPS**	**ARS**	**PASO score**	**NBPS**	**ARS**	**PASO score**
Cutoff score	**≥11.5**	**≥4**	**≥16**	**≥11.5**	**≥4**	**≥16**
AUC	**0.853 (0.786-0.905)**	**0.745 (0.667-0.812)**	**0.747 (0.670-0.815)**	**0.830 (0.764-0.884)**	**0.745 (0.672-0.810)**	**0.825 (0.758-0.880)**
Sensitivity%	**85.6 (77.0-91.9)**	**72.1 (62.1-80.8)**	**71.1 (61.0-79.9)**	**68.4 (54.8-80.1)**	**40.4 (27.6-54.2)**	**70.1 (56.6-81.6)**
Specificity%	**71.7 (57.7-83.2)**	**71.7 (57.7-83.2)**	**66.0 (51.7-78.5)**	**78.7 (69.8-86.0)**	**92.6 (85.9-96.7)**	**83.3 (74.9-89.8)**

3 Data were expressed as value (95% CI). NBPS, nomogram-based preoperative score; ARS, aldosteronoma resolution score; PASO, primary aldosteronism

4 surgical outcome; AUC, the area under the receiver operating characteristic curve.
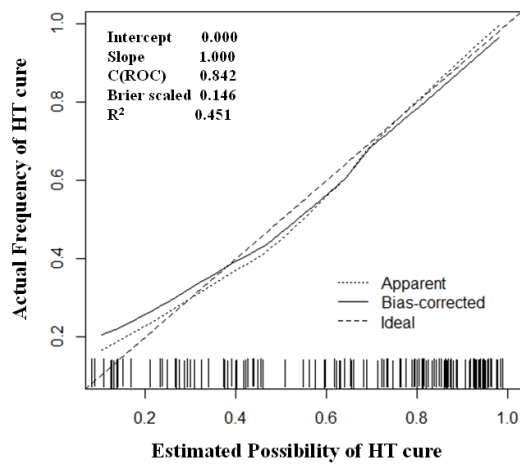
Figure 1.

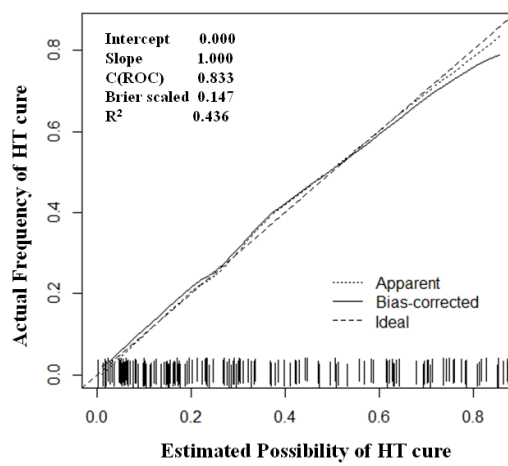336 cases of PA underwent unilateral adrenalectomy and with a post-surgical follow up more than 6 months

→ -21 cases excluded : absense of complete biochemical success

315 cases with complete biochemial success
（According to PASO concensus）

Training cohort
(Chongqing)

150 cases enrolled

-97 cases with complete clinial success
-53 cases absense of complete clinial success

Validation cohort
(Torino+Munich)

165 cases enrolled

-57 cases with complete clinial success
-108 cases absense of complete clinial success

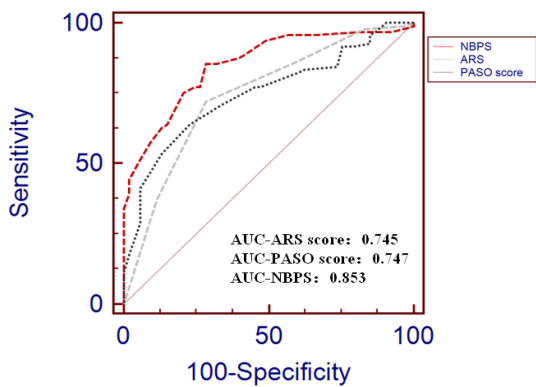# Figure 2.

A: Nomogram

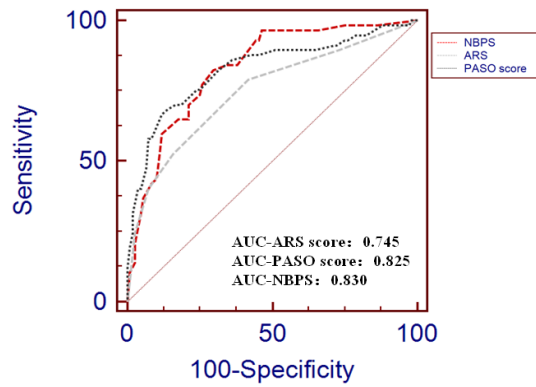## B: Taining corhot

C: Validating corhot

Figure 3.

A: Training Cohort

B: Validating Cohort

<<<<<