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

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

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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 ⩾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.

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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.

Author Contributions:

Conception and design: Q.F. Li, S.M. Yang, J.B. Hu and Y. Yang,

Analysis and interpretation of the data: J.B. Hu and Y. Yang.

Drafting of the article: Y. Yang, J. Yang, S.M. Yang and K.R. Wang.

Critical revision of the article for important intellectual content: J.B. Hu, Q.F. Li, J. Burrello, P. Mulatero, T. A. Williams and M. Reincke.

Statistical expertise: J.B. Hu.

Obtaining of funding: Q.F. Li, S.M. Yang, Y. Song and J.B. Hu.

Administrative, technical, or logistic support: Y. Song, Ting Luo and W.W. He.

Collection and assembly of data: W.W. He, Q.F. Cheng, L.Q. Ma, J. Burrello, P. Mulatero, T. A. Williams and M. Reincke.

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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 ($pg \cdot ml^{-1}/mIU \cdot l^{-1}$)	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 ($pg \cdot ml^{-1}/mIU \cdot l^{-1}$)	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 ($pg \cdot ml^{-1}/mIU \cdot l^{-1}$)	≤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.

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

Variable	Value (95% CI)					
	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)**

Data were expressed as value (95% CI). NBPS, nomogram-based preoperative score; ARS, aldosteronoma resolution score; PASO, primary aldosteronism surgical outcome; AUC, the area under the receiver operating characteristic curve.

Figure 1.

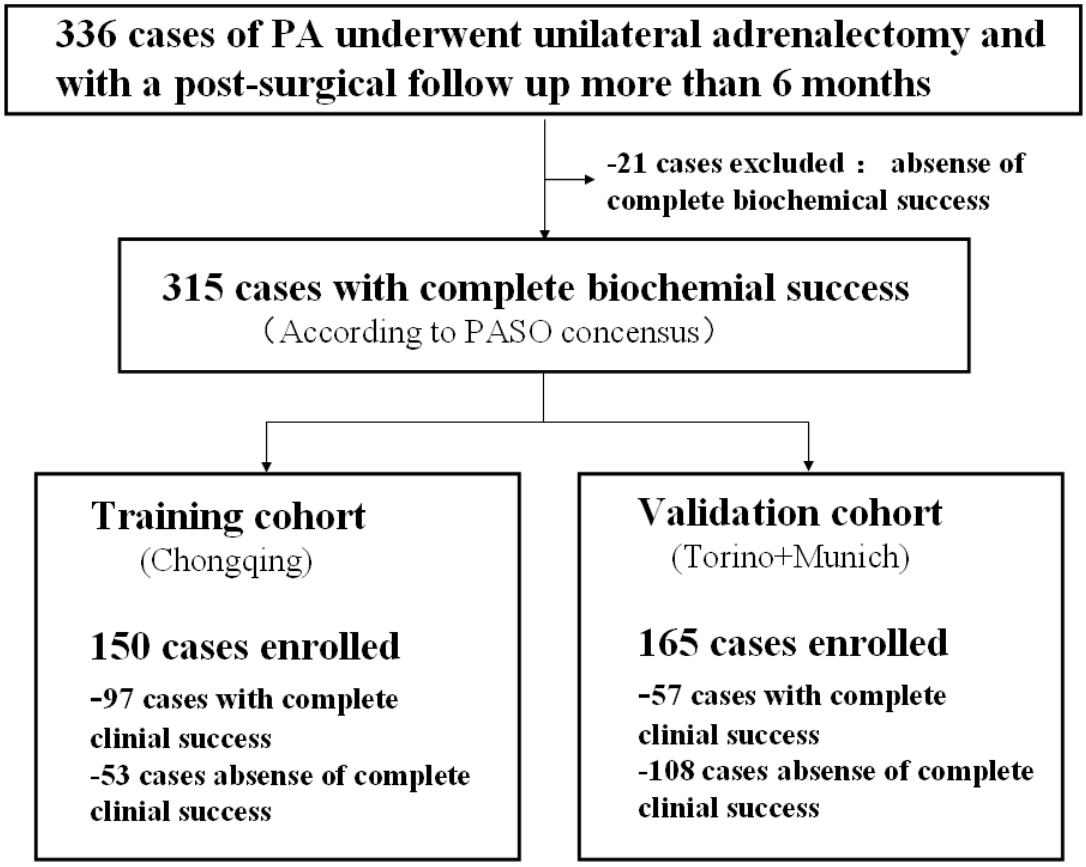

336 cases of PA underwent unilateral adrenalectomy and with a post-surgical follow up more than 6 months
-21 cases excluded： absense of complete biochemical success
315 cases with complete biochemial success
（According to PASO concensus）
Training cohort
(Chongqing)
150 cases enrolled
-97 cases with complete 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.

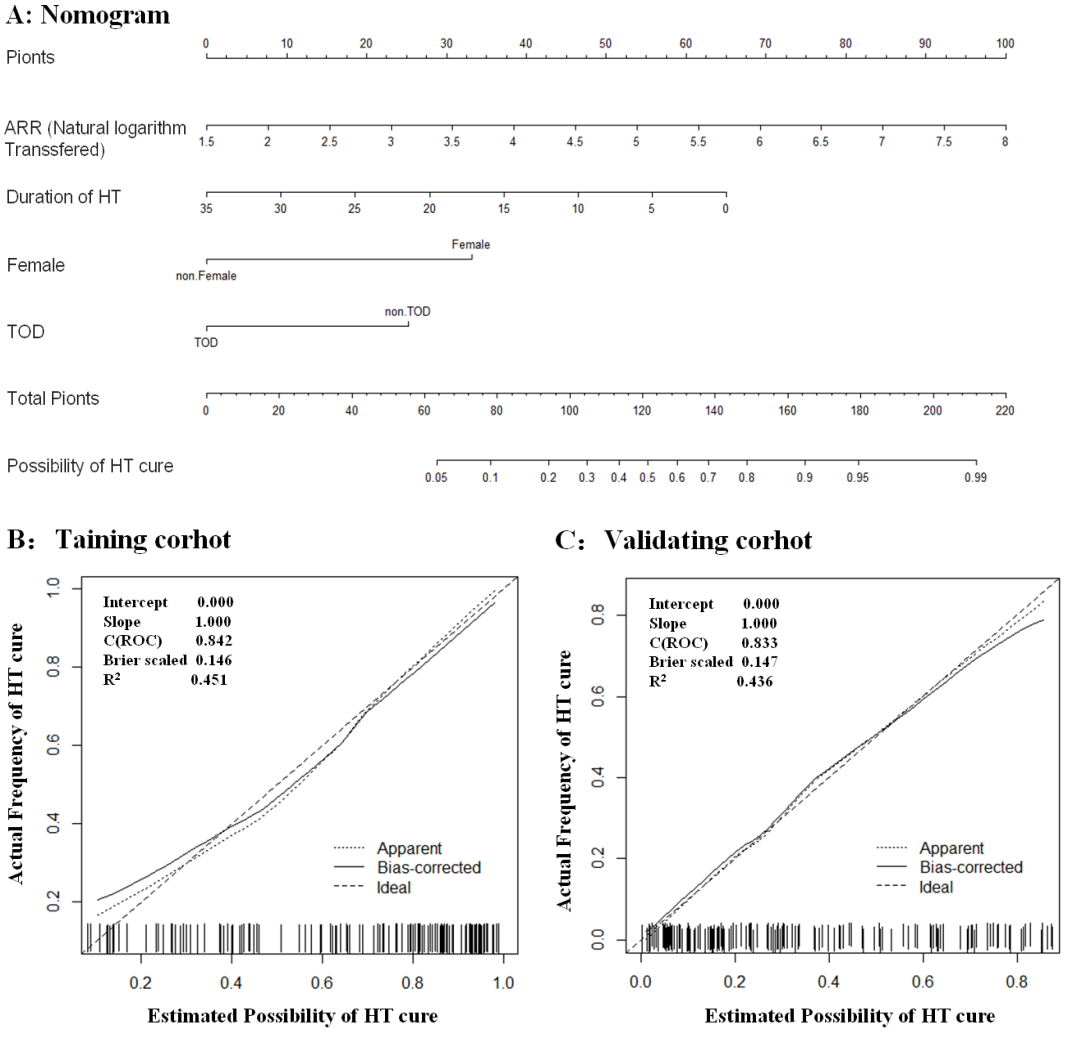
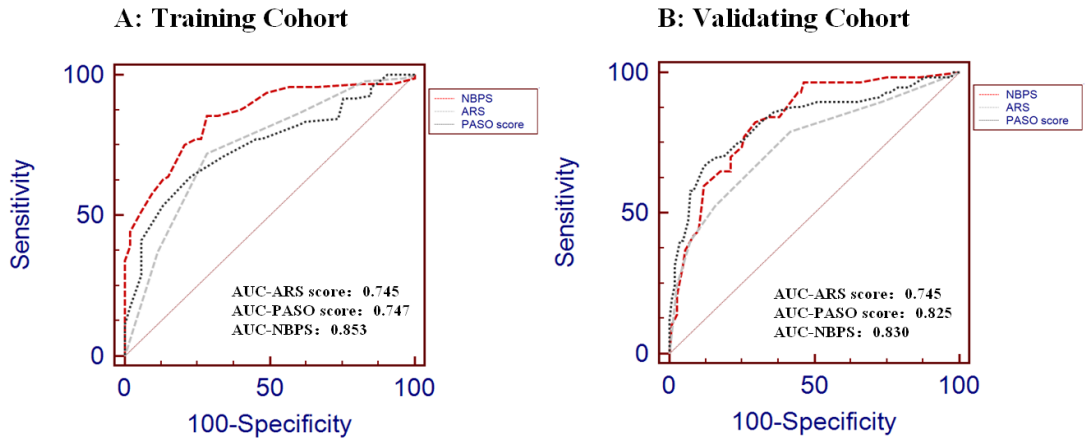


Figure 3.



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