Original Article

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Aldosterone–potassium ratio predicts primary aldosteronism subtype

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Objective: Prediction models have been developed to predict either unilateral or bilateral primary aldosteronism, and these have not been validated externally. We aimed to develop a simplified score to predict both subtypes and validate this externally.

Methods: Our development cohort was taken from 165 patients who underwent adrenal vein sampling (AVS) in two Asian tertiary centres. Unilateral disease was determined using both AVS and postoperative outcome. Multivariable analysis was used to construct prediction models. We validated our tool in a European cohort of 97 patients enrolled in the SPARTACUS trial who underwent AVS. Previously published prediction models were also tested in our cohorts.

Results: Backward stepwise logistic regression analysis yielded a final tool using baseline aldosterone-to-lowest-potassium ratio (APR, ng/dl/mmol/l), with an area under receiver-operating characteristic curve of 0.80 (95% CI 0.70–0.89). In the Asian development cohort, probability of bilateral disease was 90.0% (with APR <5) and probability of unilateral disease was 91.4% (with APR >15). Similar results were seen in the European validation cohort. Combining both cohorts, probability of bilateral disease was 76.7% (with APR <5), and probability for unilateral was 91.7% (with APR >15). Other models had similar predictive ability but required more variables, and were less sensitive for identifying bilateral PA.

Conclusion: The novel aldosterone-to-lowest-potassium ratio is a convenient score to guide clinicians and patients of various ethnicities on the probability of primary aldosteronism subtype. Using APR to identify patients more likely to benefit from AVS may be a cost-effective strategy to manage this common condition.

Keywords: adrenal venous sampling, adrenalectomy, clinical prediction score, endocrine hypertension, subtyping

Abbreviations: ARR, aldosterone–renin ratio; AUROC, area under receiver-operating characteristic; AVS, adrenal vein sampling; CT, computed tomography; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PASO, Primary Aldosteronism Surgical Outcomes; PRA, plasma renin activity; SLT, saline-loading test

INTRODUCTION

About 50% of patients with primary aldosteronism have unilateral disease and can be cured with laparoscopic adrenalectomy [1,2]. However, AVS is required to identify unilateral primary aldosteronism, and this is technically difficult with often poor success rates [3]. Prediction models have been developed to identify either unilateral [4–6], or bilateral primary aldosteronism [7–9]. These models have either not been validated externally, or shown variable results when applied externally [9–11]. Due to differences in renin assays and confirmatory tests (captopril, oral salt or intravenous salt loading used worldwide) [7,12,13], current prediction models may not be applicable for use in other centres. Furthermore, a prediction model, which utilizes fewer variables will be easier for clinical use.

Although AVS has been used as a gold standard to determine subtype of primary aldosteronism, there is currently no international consensus on the protocol or optimal cut-off of lateralization ratio that should be used [14,15]. In addition, lateralization ratio between 3 and 4 is often considered an indeterminate result [1,16]. As patients who undergo unilateral adrenalectomy should be cured of primary aldosteronism, the postsurgery outcome as determined by the Primary Aldosteronism Surgical Outcomes (PASO) criteria [17,18] will be better for assessing subtype of primary aldosteronism.

Hence, we aimed to create a prediction model to predict both unilateral and bilateral primary aldosteronism, as assessed using both AVS and postsurgery outcomes

Journal of Hypertension 2020, 38:1375–1383

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Received 2 August 2019 **Revised** 12 November 2019 **Accepted** 2 December 2019

DOI:10.1097/HJH.0000000000002348

determined by PASO criteria in our Asian development cohort. This model was then externally validated in an European cohort enrolled in the AVS arm of SPARTACUS study. Finally, we assessed the utility of available published models (and our models) in our cohorts to predict unilateral and bilateral primary aldosteronism.

METHODS

Asian development cohort

We conducted a retrospective study of all patients who underwent AVS in two Asian tertiary centres in Singapore (Changi General Hospital and Singapore General Hospital) from January 2003 to December 2018. Patients with successful AVS were included. The study was approved by the local ethics committee who waived requirement for informed consent.

Baseline clinical characteristics and medical history was collected for all patients from medical records, and this included demographics, plasma aldosterone concentration (PAC), plasma renin activity (PRA), subtyping tests, and postoperative follow-up. Lowest potassium was defined as the lowest ever recorded serum potassium taken from either the referring physician records, or hospital records. Potential factors predisposing to hypokalemia, such as medications or gastrointestinal losses, were noted.

Diagnosis of primary aldosteronism

All patients fulfilled the diagnostic criteria recommended by The Endocrine Society guidelines [1]. Before screening, antihypertensive medications (including ACE-inhibitors, diuretics) that interfere with the renin–angiotensin–aldosterone system were discontinued at least 2 weeks in most patients, and potassium-sparing diuretics stopped at least 6 weeks in all patients. Patients with precedent hypokalemia were prescribed potassium supplementation to aim for serum potassium of at least 3.5 mmol/l before baseline aldosterone was measured. Confirmatory tests were performed with intravenous saline infusion test (SLT), and all patients had a post-SLT PAC at least 140 pmol/l. Postoperative outcomes were assessed using the PASO criteria [18].

Computed tomography and adrenal vein sampling

All patients underwent thin-slice computed tomography (CT) scan. Unilateral adenoma was defined as a unilateral nodule with diameter at least 8 mm, with the contralateral gland appearing smooth and not enlarged. A subgroup analysis of lesions at least 10 mm was also used to compare with Kobayashi [9] and Umakoshi [19] models. In both Asian centres, sequential AVS under continuous corticotropin stimulation was performed by an experienced interventional radiologist. AVS was successful if plasma cortisol concentrations were at least five times higher in both adrenal veins compared with peripheral vein. Lateralization ratio was calculated using the aldosterone/cortisol ratio between both adrenal veins. AVS results were used to determine primary aldosteronism subtype. A lateralization ratio of at least 4 was taken to be consistent with unilateral primary aldosteronism, and lateralization ratio less than 2 was taken to be consistent with bilateral primary aldosteronism. In patients with lateralization ratios between 2 and 4, two authors (T.P. and L.W.J) reviewed the clinical data (which included contralateral suppression on AVS, CT findings), treatment recommendation and postoperative outcomes to determine unilateral primary aldosteronism. Patients deemed to have unilateral primary aldosteronism were required to have resolution of hypokalemia, normalization of aldosterone–renin ratio (ARR) postsurgery and/or improvement of hypertension. Patients recommended for medical treatment were classified as bilateral primary aldosteronism.

Primary Aldosteronism Surgical Outcomes criteria

As complete clinical cure, or complete biochemical cure, postadrenalectomy is a better assessment of unilateral primary aldosteronism, we did a secondary analysis using the PASO criteria [18]. We included only patients with unilateral primary aldosteronism who had undergone surgery, and had either complete clinical cure (normotensive without antihypertensive medications), or complete biochemical cure (resolution of hypokalemia and normalization of aldosterone–potassium ratio) (Supplementary Figure 1, http://links.lww.com/HJH/B225). Patients recommended for medical treatment based on AVS results were classified as bilateral primary aldosteronism.

Biochemical parameters

PAC and PRA were determined in all patients. In Changi General Hospital, PAC was measured using a solid-phase 125-I RIA (Siemens Medical Solutions Diagnostics, Los Angeles, California, USA). In Singapore General Hospital, PAC was measured by RIA (ZenTech, RIAZENco, Belgium). In both centres, PRA was measured by quantifying angiotensin I, generated after incubation of plasma, by standard RIA (DiaSorin, Stillwater, Minnesota, USA) as previously described [20]. The lower analytical limit for PRA was 0.2 ng/ml/h. From 2017, PRA and PAC were sent to Mayo Clinic Laboratories, Rochester, Minnesota, USA, for determination using LC-MS/MS, and the reference ranges were 0.6–3.0 ng/ml/h and 21 pmol/l or less, respectively. PAC measurements in pmol/l were converted to ng/dl by dividing by 27.7. As PAC measurements done using LC-MS/MS are lower than those using conventional immunoassay methods, LC-MS/MS values were multiplied by 1.3896 to correlate with PAC done using RIA, as suggested by a recent article comparing LC-MS/MS with chemiluminescent immunoassay [21].

Validation European cohort

European patients who previously enrolled into the SPARTACUS trial were used for the validation cohort [22]. The SPARTACUS trial was a randomized controlled trial evaluating using a CT-only approach, versus an AVS approach to diagnose unilateral primary aldosteronism. As CT findings alone may lead to inaccurate lateralization of adrenal disease in primary aldosteronism [1], only patients in the AVS arm were included, with the methods as described previously [22]. Patients included in the study were 18 years or older, and had hypertension needing at least three antihypertensive drugs in adequate doses, or hypertension

accompanied by hypokalemia [22]. The European patients underwent similar diagnostic tests as the Asian cohort, including oral or intravenous salt-loading test for confirmation in accordance to the Endocrine Society guidelines [1]. Plasma aldosterone and renin were measured by the referring centre. Patients subsequently underwent sequential AVS with continuous corticotropin stimulation. AVS was successful if plasma cortisol were at least three times higher in both adrenal veins compared with peripheral vein. Patients with lateralization ratios greater than 4 were classified as unilateral and underwent surgery, whereas those less than 4 were treated with medications.

Statistics

Statistical analysis was performed using SPSS Version 20.0 (IBM Corp., Armonk, New York, USA). Continuous variables were expressed as median (IQR) and compared using the Mann–Whitney *U*-test. Chi-square test was used for categorical variables. Statistical significance was set at P less than0.05.

Variables associated with unilateral primary aldosteronism in the univariate analysis and those included in previous models were entered into the multivariate logistic regression model. We conducted backwards stepwise selection process. We assessed for collinearity between variables. For variables with significant correlation, backwards stepwise selection process was repeated while excluding correlated variables. For each regression model, we reduced the variables to as few as possible while retaining good performance.

Continuous variables significant in the logistic models were categorized using the Youden index, which was calculated as (sensitivity + specificity) − 1. To generate the clinical prediction scores, we either used the variables weighted according to their regression coefficients or utilized a mathematical formula. Model discrimination was assessed using the Hosmer–Lemeshow goodness-of-fit test, and the scores' predictive performances were assessed using the area under receiver-operating characteristic (AUROC). We determined cut-offs with more than 90% probability to predict unilateral and bilateral primary aldosteronism.

Our models and previously published models were tested in our development and validation cohorts by calculating the AUROC, Hosmer–Lemeshow goodness-of-fit test, and probability for unilateral and bilateral primary aldosteronism. For previously published models, we used the suggested cut-offs by the authors for determining unilateral and bilateral primary aldosteronism. If not available, optimal cut-offs were determined using the original publication data, and our data.

RESULTS

Baseline characteristics

For the development cohort, 165 Asian patients underwent AVS in two tertiary centres. We excluded 51 with unsuccessful AVS, and 11 patients with incomplete AVS data (Fig. 1). Patients with unsuccessful AVS did not differ greatly from those with successful AVS (Supplementary Table 1, http://links.lww.com/HJH/B225). In total, 103 patients had complete AVS data, median age 52.0 (46.0–61.4) years, 38 women (36.9%). Sixty patients had lateralization ratio greater than 4 (unilateral primary aldosteronism) and 24 patients had lateralization ratio less than 2 (bilateral primary aldosteronism). In the remaining 19 patients with lateralization ratios between 2 and 4, nine patients were classified as bilateral, and 10 as unilateral. Nine of the 10 unilateral patients underwent surgery with resolution of primary aldosteronism postop (Supplementary Table 2, http://links.lww.com/HJH/B225). Using AVS criteria, 70 of 103 patients (68.0%) had unilateral primary aldosteronism. Baseline characteristics are included in Table 1. AVS was nonconcordant with CT findings in 30 of 103 (29.1%) patients (Supplementary Figure 1, http://links.lww.com/HJH/B225).

Using postoperative PASO criteria, 42 patients had unilateral primary aldosteronism, and 32 had bilateral primary aldosteronism (Supplementary Figure 2, http://links.lww.com/HJH/B225). Seventeen patients were completely cured of hypertension and another 24 had biochemical cure of primary aldosteronism. One patient with a lateralization ratio less than 2 underwent surgery and was cured of hypertension postsurgery. Eighteen patients decided against surgery after

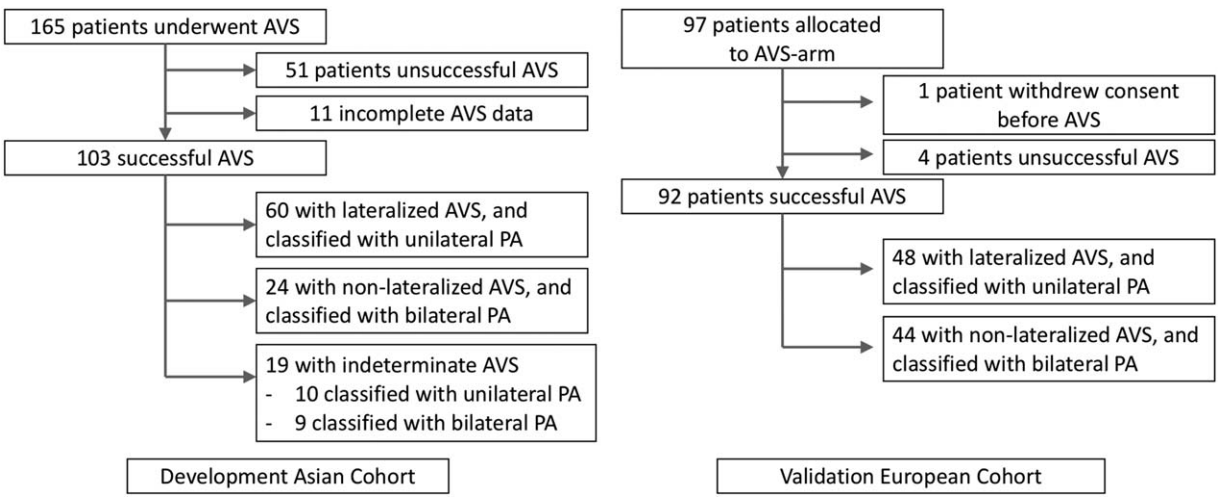

FIGURE 1 Patient selection for Asian development cohort ($n = 103$), and European validation cohort ($n = 92$) taken from patients previously enrolled in SPARTACUS trial.

TABLE 1. Baseline characteristics of all 103 patients with unilateral or bilateral primary aldosteronism classified using AVS and postsurgery outcomes

	Unilateral primary aldosteronism ($N = 70$)	Bilateral primary aldosteronism ($N = 33$)	Total ($N = 103$)	*P*
Age (years)	50.0 (43.2–57.0)	60.2 (50.0–63.4)	52.0 (46.0–61.4)	0.003
Females (%)	26 (37.1%)	12 (36.4%)	38 (36.9%)	0.94
Ethnicity (%)				0.09
Chinese	56 (80.0%)	26 (78.8%)	82 (79.6%)	
Malay	8 (11.4%)	2 (6.1%)	10 (9.7%)	
Indian	1 (1.4%)	4 (12.1%)	5 (4.9%)	
Others	5 (7.1%)	1 (3.0%)	6 (5.8%)	
BMI (kg/m^2)	26.4 (23.7–28.8)	26.2 (23.6–28.5)	26.4 (23.7–28.7)	0.88
SBP	147 (130–164)	150 (139–164)	149 (134–164)	0.37
DBP	84 (76–94)	87 (80–95)	85 (78–94)	0.31
Number of BP Meds	2.0 (1.0–3.0)	1.0 (1.0–2.8)	2.0 (1.0–3.0)	0.44
Lowest serum potassium recorded (mmol/l)	2.5 (2.2–2.9)	3.0 (2.7–3.3)	2.7 (2.3–3.0)	<0.001
Potassium level during AVS (mmol/l)	3.5 (3.3–3.9)	3.7 (3.4–3.9)	3.7 (3.3–3.9)	0.57
Creatinine level during AVS (μmol/l)	73 (59–92)	78 (62–90)	74 (59–91)	0.54
Estimated GFR (MDRD) (ml/min/1.73 m^2)	90.3 (74.6–111.1)	86.1 (69.9–97.7)	88.0 (72.8–104.8)	0.14
Baseline PAC (ng/dl)	36.6 (25.4–50.8)	22.3 (13.8–33.3)	31.0 (20.2–46.2)	<0.001
PRA (ng/ml/h)	0.22 (0.20–0.60)	0.33 (0.20–0.60)	0.22 (0.20–0.60)	0.32
Baseline ARR	124.3 (73.0–194.8)	65.8 (33.0–114.8)	107.5 (56.5–171.6)	<0.001
Post SLT PAC (ng/dl)	25.0 (17.2–41.7)	14.1 (12.2–20.0)	20.0 (13.5–31.8)	<0.001
Duration of hypertension (years)	7 (3–10)	10 (3–15)	8 (3–11)	0.25
Ischemic heart disease	4 (5.7%)	3 (9.1%)	7 (6.8%)	0.53
Chronic kidney disease	5 (7.1%)	3 (9.1%)	8 (7.8%)	0.73
Stroke	5 (7.1%)	2 (6.1%)	7 (6.8%)	0.84
Hyperlipidemia	27 (38.6%)	19 (57.6%)	46 (44.7%)	0.07
Diabetes	15 (21.4%)	9 (27.3%)	24 (23.3%)	0.51
Atrial fibrillation	3 (4.3%)	0 (0.0%)	3 (2.9%)	0.23
Presence of hypokalemia	67 (95.7%)	27 (81.8%)	94 (91.3%)	0.02
Diuretic use during hypokalemia	6 (8.6%)	6 (18.2%)	12 (11.7%)	0.16
Abnormal CT findings				0.001
Unilateral adenoma	61 (87.1%)	17 (51.5%)	78 (75.7%)	
Bilateral abnormal	3 (4.3%)	3 (9.1%)	6 (5.8%)	
Bilateral normal	6 (8.6%)	13 (39.4%)	19 (18.4%)	

Data are median (interquartile range) or number (percentage). ARR, aldosterone–renin ratio; AVS, adrenal vein sampling; BP, blood pressure; GFR, glomerular filtration rate; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SLT, saline-loading test.

AVS, whereas seven did not have a repeat ARR postsurgery. Three patients had normalization of hypokalemia but persistently high ARR postsurgery, with PAC between 200 and 300 pmol/l and did not undergo repeat SLT.

For the validation cohort, 97 European patients were allocated to the AVS arm of the SPARTACUS trial, with one patient withdrawing consent before AVS, and four patients having an unsuccessful AVS. Ninety-two patients had a successful AVS, and 48 (52.2%) were identified with unilateral primary aldosteronism and 46 patients underwent surgery (Fig. 1). Using PASO criteria, 41 patients were classified as unilateral primary aldosteronism, with five patients having persistently high ARR postsurgery as described in the study [23].

In the Asian cohort, comparing patients with unilateral to bilateral primary aldosteronism, baseline PAC was higher, 36.6 vs. 22.3 ng/dl, $P < 0.001$, and lowest recorded serum potassium was lower, 2.5 vs. 3.0 mmol/l, $P < 0.001$. Post-SLT PAC was also higher in unilateral patients, 25 versus 14.1 ng/dl, but 15 patients did not undergo SLT. In addition, patients with unilateral primary aldosteronism were younger, had higher ARR, and were more likely to harbour a unilateral adenoma. Baseline PRA was lower in patients with unilateral primary aldosteronism but this was not statistically significant.

Development of prediction models

For multivariate analysis, variables included were age, sex, estimated glomerular filtration rate, presence of hypokalemia, lowest potassium, baseline PAC, baseline ARR, post-SLT PAC and CT nodule. Using stepwise backward regression, two variables remained for model A: baseline ARR and post-SLT PAC. Cut-off values were determined for each variable to predict unilateral primary aldosteronism: ARR greater than 131 (score 1), and post-SLT PAC greater than 24 ng/dl (score 1) (Supplementary Table 3, http://links.lww.com/HJH/B225). The AUROC for model A was 0.81 (95% CI 0.73–0.90) (Fig. 2).

Collinearity was present between baseline PAC and both variables in model A using Spearman's correlation. Baseline PAC was strongly correlated with ARR, $r_s = 0.648$, $P < 0.001$, and with post-SLT PAC, $r_s = 0.648$, $P < 0.001$. Multivariate analysis was repeated after excluding ARR and post-SLT PAC, leaving three variables: baseline PAC, lowest potassium and CT nodule, with an AUROC of 0.84. After removing CT nodule, AUROC reduced marginally to 0.83. As baseline PAC was positively correlated with unilateral primary aldosteronism, and lowest potassium negatively correlated, we elected to use a ratio of baseline PAC: lowest potassium ratio (aldosterone–potassium ratio, APR). To determine 90% probability of bilateral primary

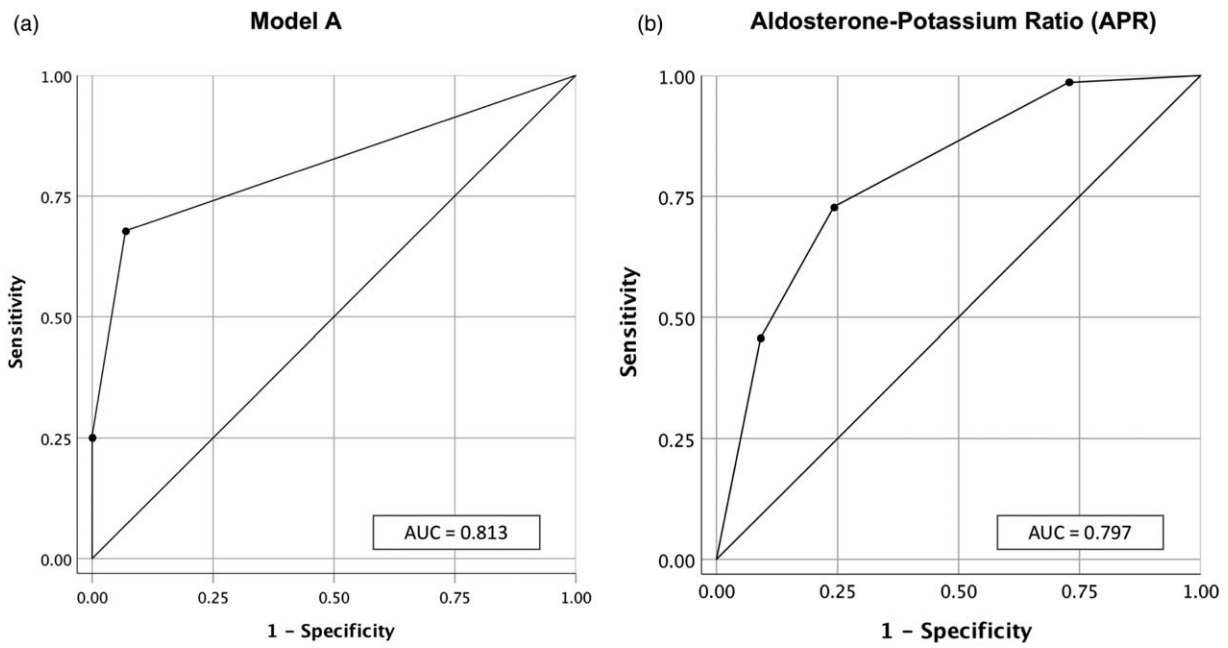

FIGURE 2 Receiver-operating characteristic curve analysis of (a) model A and (b) aldosterone–potassium ratio to diagnose unilateral primary aldosteronism, in Asian development cohort ($n = 103$). (a) Model A: ARR greater than 131 (score 1), and post-SLT PAC greater than 24 ng/dl (score 1). (b) Patients stratified by APR (ng/dl/mmol/l) into less than 5, 5–10, 10–15, greater than 15. APR, aldosterone–potassium ratio.

aldosteronism, the optimal cut-off for APR was less than 5.3. To determine 90% probability of unilateral primary aldosteronism, both cut-offs greater than 11.4 and greater than 14.9 were suitable. For ease of clinical use, we separated patients into four groups using APR: 5, 5–10, 10–15, greater than 15 (Table 2). Using AVS criteria, the final APR had an AUROC of 0.80 (95% CI 0.70–0.89) (Fig. 2). Using PASO criteria, the AUROC was similar, 0.78 (95% CI: 0.71–0.85) (Supplementary Figure 3, http://links.lww.com/HJH/B225). We did a post hoc analysis using the original PAC levels in all patients, without a correction factor for measurements done using LC-MS/MS, and the AUROC was similar, 0.80 (95% CI 0.70–0.89) (Supplementary Figure 4, http://links.lww.com/HJH/B225).

In the Asian development cohort, probability of unilateral primary aldosteronism was 86.4% with APR greater than 10 and increased to 91.4% with APR greater than 15, with respective sensitivities of 72.9 and 45.7%. With low APR less than 5, probability for bilateral primary aldosteronism was 90%, and sensitivity of 27.3%. With model A, a score of at least 1 had a 95.2% probability of unilateral primary aldosteronism and sensitivity of 67.8%, whereas a score of 0 had a 58.7% probability of bilateral primary aldosteronism and sensitivity of 93.1%.

In the European validation cohort, renin was measured differently, using direct renin concentration. Hence, model A and other models were not applicable in this cohort. Probability for unilateral primary aldosteronism was 80.6% (APR >10), increasing to 92.3% (APR >15), whereas probability for bilateral primary aldosteronism was 70% (APR <5). Combining the data of the Asian and European patient cohorts, the probability of unilateral primary aldosteronism was 84.4% (95% CI: 75.6–90.5%) with APR greater than 10, and increased to 91.7% (95% CI 80.5–96.7%) with APR greater than 15. Probability of bilateral primary aldosteronism was 76.7% (95% CI 59.1–88.2%) with APR less than 5 (Fig. 3). Using PASO criteria and combining both cohorts, the probability of unilateral primary aldosteronism 78.3% with APR greater than 10, and increased to 88.9% with APR greater than 15. Probability of bilateral primary aldosteronism was 82.1% with APR less than 5 (Supplementary Figure 5, http://links.lww.com/HJH/B225).

Previously published models were tested in our Asian cohort. Using Kobayashi's recommended score of at least 8 to predict bilateral primary aldosteronism [9], three of three (100%) patients in our cohort were correctly identified. Using a score 1 or less, the probability for unilateral primary aldosteronism was 83.6%, and sensitivity was 65.7%. Forty-five of 103 patients (43.7%) were in the indeterminate range. Using Umakoshi's model [19], 56 of 72 (77.8%) patients with unilateral nodule and hypokalemia had unilateral primary aldosteronism, and four of five (80.0%) patients with bilaterally normal adrenals and normokalemia had bilateral primary aldosteronism. Five patients with bilateral nodules were excluded. Kamemura's [8] model applies only to patients without adrenal tumors. None of our 24 patients without tumors fulfilled the recommended score of 3. Amongst patients with a score at least 1, six of six (100%) had bilateral primary aldosteronism, but a score of 0 was not useful to predict unilateral primary aldosteronism (probability 61.1%). Using Kuper's model [4], a score more than 5 had a 80% probability for unilateral primary aldosteronism (sensitivity 85.7%), whereas a score 1 or less identified only two of two patients (100%) with bilateral primary aldosteronism.

Although both the models proposed by Kobayashi and Kuper accurately identified patients with bilateral primary aldosteronism, they only identified three and two patients,

TABLE 2. Prevalence of subtype of primary aldosteronism in the Asian ($N = 103$) and European ($N = 92$) cohorts using aldosterone–potassium ratio, model A, and other prediction models

Asian cohort	Score	Unilateral primary aldosteronism [$N = 70$ (%)]	Percent of score with unilateral	Bilateral primary aldosteronism [$N = 33$ (%)]	Percent of score with bilateral	Total	Area under ROC curve, 95% CI	Hosmer–Lemeshow good-of-fit statistics, *P*
Aldosterone–potassium ratio, APR	< 5	1 (1.4%)	10.0%	9 (27.3%)	90.0%	10 (9.7%)	0.797 (0.704–0.890)	0.592
	5–10	18 (25.7%)	52.9%	16 (48.5%)	47.1%	34 (33.0%)		
	10–15	19 (27.1%)	79.1%	5 (15.2%)	20.8%	24 (23.3%)		
	> 15	32 (45.7%)	91.4%	3 (9.1%)	8.6%	35 (34.0%)		
Model A	0	19 (32.2%)	41.3%	27 (93.1%)	58.7%	46 (44.7%)	0.813 (0.725–0.901)	0.795
	1	25 (42.4%)	92.6%	2 (6.9%)	7.4%	27 (26.2%)		
	≥2	15 (25.4%)	100.0%	0 (0.0%)	0.0%	15 (14.6%)		
Kobayashi *et al.* [9]	≥8	0 (0.0%)	0.0%	3 (9.1%)	100.0%	3 (2.9%)	0.708 (0.598–0.817)	0.220
	2–7	24 (34.3%)	53.3%	21 (63.6%)	46.7%	45 (43.7%)		
	≤1	46 (65.7%)	83.6%	9 (27.3%)	16.4%	55 (53.4%)		
Umakoshi *et al.*[a] [20]	Group 1	56 (83.6%)	77.8%	16 (51.6%)	22.2%	72 (73.5%)	0.673 (0.549–0.796)	0.215
	Group 2	0 (0.0%)	0.0%	2 (6.5%)	100.0%	2 (2.0%)		
	Group 3	10 (14.'9%)	52.6%	9 (29.0%)	47.4%	19 (19.4%)		
	Group 4	1 (1.5%)	20.0%	4 (12.9%)	80.0%	5 (5.1%)		
Kanemura [8]	3	0 (0.0%)	0.0%	0 (0.0%)	0.0%	0 (0.0%)	0.731 (0.526–0.935)	NA
	1–2	0 (0.0%)	0.0%	6 (46.2%)	100.0%	6 (25.0%)		
	0	11 (100%)	61.1%	7 (53.8%)	38.9%	18 (75.0%)		
Kupers [4]	≤1	0 (0.0%)	0.0%	2 (6.1%)	100.0%	2 (1.9%)	0.706 (0.590–0.821)	0.661
	2–4	10 (14.3%)	38.5%	16 (48.5%)	61.5%	26 (25.2%)		
	≥5	60 (85.7%)	80.0%	15 (45.5%)	20.0%	75 (72.8%)		

European cohort	Score	Unilateral primary aldosteronism [$N = 48$ (%)]	Percent of score with unilateral	Bilateral primary aldosteronism [$N = 44$ (%)]	Percent of score with bilateral	Total	Area under ROC curve, 95% CI	Hosmer–Lemeshow good-of-fit statistics, *P*
Aldosterone–potassium ratio, APR	<5	6 (12.5%)	30.0%	14 (31.8%)	70.0%	20 (21.7%)	0.726 (0.623–0.829)	0.165
	5–10	17 (35.4%)	41.5%	24 (54.5%)	58.5%	41 (44.6%)		
	10–15	13 (27.1%)	72.2%	5 (11.4%)	27.8%	18 (19.6%)		
	>15	12 (25.0%)	92.3%	1 (2.3%)	7.7%	13 (14.1%)		

CT, computed tomography; NA, not applicable; ROC, receiver-operating characteristic
[a]Umakoshi: group 1 (unilateral nodule on CT with hypokalemia); group 2 (unilateral nodule on CT with normokalemia); group 3 (bilateral normal adrenals on CT with hypokalemia); group 4 (bilateral normal adrenals on CT with normokalemia).

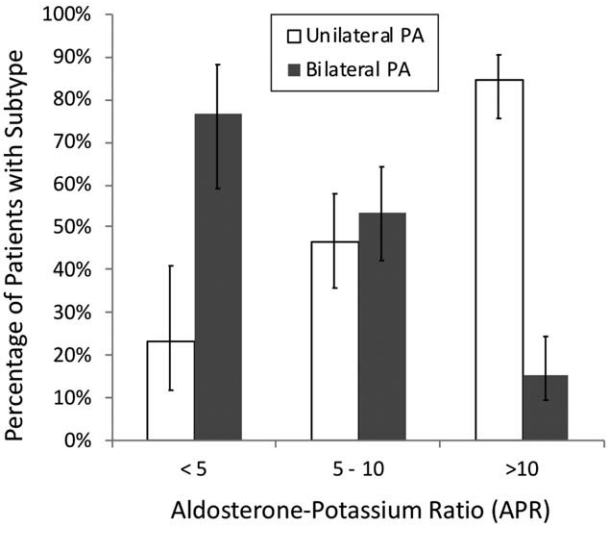

FIGURE 3 Patients stratified by baseline aldosterone-to-lowest potassium ratio (ng/dl/mmol/l), and the underlying subtype of primary aldosteronism (unilateral versus bilateral), with 95% confidence interval, in Asian ($N = 103$) and European ($N = 92$) cohorts combined ($N = 195$).

respectively. Both models were able to predict patients with a more than 80% probability of unilateral primary aldosteronism. Hosmer–Lemeshow goodness-of-fit statistics supported model fit for all prediction score models to predict unilateral primary aldosteronism (Table 2).

DISCUSSION

We identified APR as a convenient and accurate tool to guide clinicians to predict both unilateral and bilateral primary aldosteronism. In addition, we externally validated the APR and demonstrated its utility in both Asian and European patients with confirmed primary aldosteronism. With primary aldosteronism estimated to affect up to 10% of all hypertensive patients, sending all patients worldwide for AVS may be costly, logistically challenging and will benefit only those with unilateral primary aldosteronism. Hence, the APR conveniently stratifies the likelihood of unilateral primary aldosteronism and is ideal for routine clinical use. It can also help to more effectively utilize resources, particularly in places where AVS expertise may not be readily available.

We found a low APR (<5) to be predictive of bilateral primary aldosteronism, whereas a high APR (>10) predictive of unilateral primary aldosteronism. Using a higher cutoff of more than 15, probability of unilateral primary aldosteronism increased to more than 90% in both the Asian and European cohorts, with a 95% CI of 80.5–96.7%. Importantly, APR requires only two widely available variables. Patients with unilateral primary aldosteronism often have higher baseline PAC, higher baseline ARR and higher PAC postconfirmatory tests [4,5,7,9,12,13,23,24], similar to our findings. Patients with primary aldosteronism often have undetectable renin levels, and higher ARR is contributed mainly by an elevated aldosterone. As both ARR and postsuppression PAC were strongly correlated to baseline PAC, we elected to use baseline PAC. Centres worldwide use different renin assays and different confirmatory tests for the diagnosis of primary aldosteronism [25,26]. The advantage of baseline PAC in this prediction model is that it is available in patients with confirmed primary aldosteronism, regardless of the renin assay or confirmatory test used. Importantly, aldosterone measurements may still be prone to interassay variability depending on the method used, and standardization of aldosterone assays will help to address that [1]. We found that using the uncorrected aldosterone measurements with LC-MS/MS or RIA methods did not lead to differences in our final results, and this suggests that the APR is useful regardless of the aldosterone assay, and improves the generalizability of our findings.

Patients with unilateral primary aldosteronism also exhibit more severe hypokalemia than bilateral primary aldosteronism [11,23,24]. Potassium levels can be altered by potassium supplementation [13], medication use, or gastrointestinal losses. Hence, we used the lowest recorded potassium level, prior to oral supplementation. This was possible as we had comprehensive records from both primary and tertiary care in our Asian cohort. Similar to aldosterone–renin ratio (ARR) used for screening of primary aldosteronism, a low denominator can inflate the ratio. Fortunately, potassium levels are rarely undetectable, and its measurements are accurate and consistent worldwide. It is important to note that serum and plasma potassium levels may differ by up to 0.4 mmol/l, especially in the presence of marked thrombocytosis [27]. Of note, we used plasma potassium for measurement, and none of our patients in our study cohort had a platelet count greater than 500 000/μl. Of note, one patient with bilateral primary aldosteronism had severe hypokalemia while on diuretic, resulting in APR of more than 15 (falsely classified as unilateral). As aldosterone levels can be affected by hypokalemia, we corrected hypokalemia with supplementation prior to baseline PAC measurements.

Although adrenal nodules on CT imaging was included in some prediction models [4,7,9], we found this variable to add little value. This is likely because CT was discordant with AVS in 29.1% of our patients, which is consistent with reported discordance rates of 37.8% [28] and 41.4% [29]. Although AVS is the current reference test, it has its limitations [30]. Lateralization ratios between 3 and 4 are considered indeterminate, but some patients harbour unilateral primary aldosteronism [16]. Hence, we elected to include postoperative outcomes, which more accurately classifies primary aldosteronism subtype [18]. Nine patients with lateralization ratios less than 4 underwent surgery with clinical improvement in all. Although postsurgery ARR was not available in five patients, three of these five patients had complete cure of hypertension and hypokalemia, which strongly supports cure of primary aldosteronism postsurgery. Furthermore, unlike previous studies, which only utilized AVS results to determine primary aldosteronism subtype, we utilized the PASO criteria in our secondary analysis, which is regarded as a more accurate determinant of unilateral primary aldosteronism [18]. It is worthwhile to note that PASO criteria only applied to patients with unilateral primary aldosteronism who underwent surgery, whereas bilateral primary aldosteronism was based on a clinical diagnosis using AVS results. Some patients in the Asian cohort were excluded as they elected not to undergo surgery, or did not undergo repeat biochemical assessment postsurgery. Importantly, using PASO criteria, we still had 158 patients from both cohorts determined to have unilateral and bilateral primary aldosteronism, and APR was equally predictive of both unilateral and bilateral patients, with the likelihood of unilateral disease 88.9% with APR more than 15, and bilateral disease 82.1% with APR less than 5.

Another strength of our study was the external validation in a large European cohort. The European patients represented a different ethnic cohort diagnosed over a similar time period. They were recruited in a clinical trial SPARTACUS [22], which juxtaposes with the Asian 'real-world' cohort. In the European cohort, six of 20 patients with APR less than 5 had unilateral primary aldosteronism (falsely classified as bilateral). This was likely because several patients were already on potassium supplementation when referred to the tertiary centre, resulting in higher potassium and lower APR. Interestingly, one patient failed to have resolution of primary aldosteronism postsurgery, suggesting that APR had correctly predicted bilateral primary aldosteronism.

Applying previously published models to our Asian cohort, we found consistent findings with the previous studies. Using Kobayashi's model [9], only three of 33 (9.1%) patients with bilateral primary aldosteronism were identified using the recommended score at least 8. With a score of 1 or less, 83.6% of our patients had unilateral primary aldosteronism, similar to 84.7% reported in that study. Using Küper's model [4], 80% of our patients with score at least 5 had unilateral primary aldosteronism, similar to two other studies reporting 82% [11], and 85% [31], and lower than the 100% reported in the original study. We also found similar findings using Umakoshi's model [19], that the probability of unilateral primary aldosteronism was high (77.8% in our cohort versus 70.6%) in the presence of unilateral nodules and hypokalemia, and low (20 versus 6.2%) with normal adrenals and normokalemia. Our cohort had a lower proportion of women (37%) than men, which was seen in some studies [4,7], but not others [9]. This may be because of postmenopausal women electing for spironolactone treatment, which is generally tolerable, and avoiding AVS and surgery. We found that sex was not predictive of disease subtype, which is consistent with

previous studies [4,7,12]. Overall, APR performed better than the other published models with a higher AUROC of 0.797, despite including few variables. Our choice of utilizing a ratio of the actual values, instead of dichotomizing the variables improves its performance. Greater weightage is conferred for a lower potassium 2 versus 3 mmol/l in predicting unilateral primary aldosteronism.

In addition to prediction models, other noninvasive methods have been proposed to predict primary aldosteronism subtype, such as postural test [1], or measurements of hybrid hormones [32,33]. More recently, ^{11}C-metomidate PET/CT imaging offers a noninvasive alternative to AVS [34]. ^{11}C-metomidate PET/CT may possibly identify more zona glomerulosa-like adenomas with ATP or Ca channel mutations [35], compared with the typical zona fasciculata-like adenomas harbouring KCNJ5 mutations [36]. As patients with KCNJ5 mutations have higher baseline aldosterone [37] and lower potassium levels [38], APR may be a better marker for detecting patients with underlying KCNJ5 mutations. Furthermore, Asians have been shown to have a higher prevalence of KCNJ5 mutations than Caucasians [37,39]. Reassuringly, we found APR to be equally accurate in both our Asian and European cohorts for predicting unilateral primary aldosteronism.

This present study has several limitations. Firstly, using the lowest potassium level may be confounded by diuretic use or concomitant gastrointestinal losses. Less than 5% of our development cohort were using diuretics, and none had gastrointestinal losses at presentation. Secondly, about a third of our development cohort failed AVS, which may have affected our findings. This further highlights the limitations faced by most world-wide centres performing AVS. However, we did not find any significant differences between patients with failed and successful AVS. Furthermore, our findings were supported by the European validation cohort, where AVS were done in high-volume centres, with 92 of 96 (95.8%) patients having a successful AVS. Thirdly, both our Asian and European cohorts had a higher proportion of patients with unilateral primary aldosteronism, although recent studies have shown that bilateral primary aldosteronism is more common [40]. This likely reflects a selection bias with physicians advising patients with more severe phenotype to undergo AVS. Reassuringly, previously developed prediction models performed similarly in our development cohort. Finally, we had a relatively small sample size and our findings can be validated in a large, multicentre prospective cohort. Using a larger sample size, more factors may have been elucidated in our model. However, this will also add to the complexity of the final model, and reduce its convenience for clinical use. Using only two variables allows for parsimony, and lowers the probability of over-fitting.

Having externally validated the APR, we could consider utilizing it in a decision-making algorithm, and prospectively assessing the cost-effectiveness of this strategy. Patients with a high APR and more likely to have unilateral primary aldosteronism may be recommended for subtype testing, whereas those with low APR may be considered for medical treatment. The threshold to pursue subtyping may vary between different centres and countries. In centres where expertise of AVS and laparoscopic surgery are easily available, and costs less prohibitive, a lower threshold may be chosen with more patients undergoing subtyping. In other centres, where these facilities are not available, then AVS may be reserved only for those with very likely unilateral primary aldosteronism. Other clinical factors should also be considered. Patients who are young, women, and have a short duration of hypertension are more likely to benefit from surgery [18]. Furthermore, surgery has been shown to have better outcomes compared with medical treatment [41,42]. Hence, these patients may still consider pursuing AVS despite a low APR. Finally, the APR may also guide decision-making in patients with a failed AVS. If likelihood of unilateral disease is high based on high APR, patients should then be referred to a centre with greater expertise for repeat AVS, or even ^{11}C-metomidate PET/CT imaging.

In conclusion, we have demonstrated that the APR is a simple and useful tool to predict primary aldosteronism subtype in patients with confirmed primary aldosteronism. An APR less than 5 is predictive of bilateral primary aldosteronism, and APR greater than 10 is predictive of unilateral primary aldosteronism. Further prospective studies using this tool to identify patients with unilateral primary aldosteronism may be done to assess its cost-effectiveness for clinical practice.

ACKNOWLEDGEMENTS

The authors thank the study team from the original SPARTACUS trial.

Conflicts of interest

There are no conflicts of interest.

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