Urine pH and Female Gender are Better Screening Markers of Primary Aldosteronism than Hypokalemia in First-Visited Hypertensive Patients.

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BACKGROUND

Although early diagnosis of primary aldosteronism (PA) is important for prevention of irreversible organ damages, **it is not cost effective** to perform a screening test in every hypertensive patients.

- The Endocrine Society (ENDO) and the Japanese Society of Hypertension (JSH) **recommend the case detection of PA** in patient groups with relatively high prevalence of PA such as hypokalemia (1-2).
- On the other hands, hypokalemia develops in only 9-37% of patients with PA. Therefore, the Japan Endocrine Society (JES) **recommends to screen all hypertensive patients** (3).

A high sensitive clinical prediction rule for the diagnosis of PA will help us to achieve a good balance between early diagnosis and medical cost.

In the present study, we hypothesized that a combination of clinical features of PA is useful for detecting patients with high probability of PA.

As such clinical features of PA, we selected urine pH (U-pH), an index of metabolic alkalosis, serum uric acid (S-UA), sex, age and severity of hypertension (2-14).

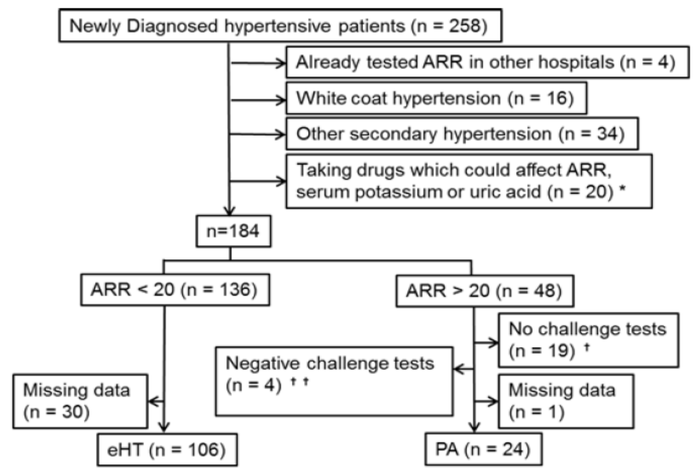
OBJECTIVE

To examine whether combination of clinical features of PA that had been reported is useful for screening PA in newly diagnosed hypertensive patients.

METHODS

- DESIGN: **Cohort study**
- SETTING: **JR Sapporo Hospital, a private hospital not specializing endocrinology.** Approximately 90% of patients with hypertension were referred from health checkup services and approximately 10% were from family clinics for screening of secondary hypertension. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of JR Sapporo Hospital.
- PARTICIPANTS (Figure 1): **Consecutive adult outpatients with newly diagnosed hypertension.** Patients at age under 75 years old with untreated hypertension and presence of data on serum PAC (ng/dL) and PRA (ng/mL/hr) measured at our hospital were included.
  <Exclusion criteria> (i) Patients in whom ARR was measured in other hospitals before referring to our hospital, (ii) white coat hypertension and secondary hypertension except for PA, (iii) Use of drugs that might have strongly affected ARR such as NSAIDs (n=1) and drugs that potentially decreased serum potassium or uric acid such as steroids (n=10) or traditional Chinese medicine containing licorice (n=6), (iv) Patients with ARR over 20 who did not revisit for further examination and who did not agree to be hospitalized for challenge tests (†), (v) Patients who had negative results of some challenge tests but had not undergone all of four challenge tests (††).
- PROCEDURE OF PA DIAGNOSIS:
  At the first visit, patients with hypertension were measured for PAC, PRA and routine blood tests after at least 15 minutes bed rest. To patients with ARR 20 or above, further endocrine examinations for PA was recommended. If they agreed, they were hospitalized and examined by at least two tests out of the four challenge tests: saline loading test, upright furosemide-loading test captopril challenge test, and ACTH stimulation test. We defined **the reference standard of PA as ARR 20 or above and at least one positive results of these four challenge tests.** The cutoff values of each challenge test are following; saline-loading test: post-loading PAC 6 ng/dL or above, upright furosemide-loading test: PRA below 2.0 ng/mL/hr after loading, captopril-challenge test: ARR 20 or above 60 and / or 90 minutes after administration, ACTH stimulation test: PAC to cortisol ratio 0.85 or above 30 and / or 60 minutes after ACTH 250μg intravenous injection.
- POTENTIAL DETECTIVE MARKERS OF PA AND CUTOFFS:
  We defined **potential detective markers and their cutoffs from literatures and primary care viewpoints**: hypokalemia as potassium below 3.5 mEq/L, metabolic alkalosis as sodium minus chloride 40 or above, high U-pH as 7 or above, low S-UA as below 4.0 mg/dL, female sex, moderate to severe hypertension and age under 40 years old.
- STATISTICAL METHODS:
  Dataset and univariate analysis: Dataset was used to examine clinical variables for association of diagnosis of PA. In the univariate analysis, we compared each of continuous variables by using Student's t test and categorical variables by Pearson's chi-squared test.
  Development of scoring system: Candidate variables, which were selected from the potential detective markers based on the results of univariate analyses, were all entered into multivariable logistic regression analysis (full model) and the area under the receiver operating characteristic curve (AUC) was calculated. To evaluate the influence of each independent variable, we assessed **the difference between AUC of the full model and AUC which was calculated without that variable in the logistic regression and calculated its 95% confidence interval (CI) via 1,000 bootstrap samples**. A scoring system for the diagnosis of PA was developed based on coefficients from the multivariable logistic regression. We chose hypokalemia, the most well-known clinical feature of PA, and the variables which has changed the point estimate of AUC more than hypokalemia as the detective markers. A simple scoring system was developed with the markers. We assigned **the nearest integer point based on the coefficient to each detective marker.**
  Calibration and Discrimination of scoring system: Patients were categorized according to their score and the observed prevalence of PA in each score were compared. Discriminatory performance of the scoring system was assessed by ROC curve and AUC calculated its 95% CI and AUC of the scoring system.
  All statistical analysis were conducted using Stata12.1. P-values equal to or under 0.05 were considered statistically significant.

Figure 1. Participants' flow diagram



RESULTS

Table 1. Patient Characteristics

		Total (n=130)	PA (n=24)	eHT (n=106)	P※
Female	n (%)	33 (25.4)	11 (45.8)	22 (20.8)	0.01†
Age	y.o.	54± 11	56± 12	54± 11	0.27
Age below 40	n (%)	15 (11.5)	1 (4.1)	14 (13.2)	0.21
BMI	kg/m2	25.2± 3.7	25.5± 3.4	25.1± 3.8	0.63
BMI 25 or above	n (%)	68 (52.3)	13 (54.1)	55 (51.9)	0.83
Duration of HT ≧ 6	n (%)	24 (18.5)	7 (29.2)	17 (16.0)	0.13
Moderate to severe HT	n (%)	82 (63.1)	15 (62.5)	67 (63.2)	0.95
SBP	mmHg	159± 16	164± 18	158± 16	0.11
DBP	mmHg	95± 13	94± 11	95± 13	0.74
Dyslipidemia	n (%)	73 (56.1)	15 (62.5)	58 (54.7)	0.49
Diabetes mellitus	n (%)	9 (6.9)	1 (4.2)	8 (7.6)	0.56
PAC	ng/dL	11.0± 4.3	13.1± 5.3	10.5± 3.9	0.008†
PRA	ng/mL/hr	1.4± 1.8	0.3± 0.2	1.7± 1.9	<0.001†
ARR		17.2± 23.1	53.8± 34.7	9.0± 4.3	<0.001†
Adrenal mass	n (%)	9 (6.9)	9 (37.5)	0 (0)	<0.001†
K^+	mEq/L	3.7± 0.3	3.6± 0.3	3.7± 0.3	0.12
K^+ < 3.5mEq/L	n (%)	21 (16.1)	6 (25.0)	15 (14.2)	0.19
Na^+	mEq/L	140.7± 1.7	140.8± 1.3	140.8± 1.7	0.88
Cl^-	mEq/L	105.2± 1.9	105.0± 2.0	105.2± 1.9	0.66
Na^+ minus Cl^-	mEq/L	35.6± 2.0	35.6± 2.5	35.5± 1.9	0.76
Na^+ minus Cl^- ≧ 40	n (%)	3 (2.3)	1 (4.2)	2 (1.9)	0.50
BUN	mg/dL	13.6± 3.1	14.1± 3.5	13.4± 3.1	0.33
Cr	mg/dL	0.76± 0.17	0.76± 0.18	0.76± 0.17	0.96
eGFR	ml/min	81.8± 17.4	75.5± 13.6	83.2± 17.9	0.048†
S-UA	mg/dL	6.0± 1.5	5.7± 1.3	6.1± 1.5	0.32
S-UA < 4.0 mg/dL	n (%)	11 (8.5)	3 (12.5)	8 (7.6)	0.43
Urinalysis					
U-pH		6.41± 0.70	6.80± 0.78	6.33± 0.68	0.007†
U-pH ≧ 7.0		49 (37.7)	15 (62.5)	34 (32.1)	0.006†

Variables are described as mean ± SD and number (percentage).
* Student's t-test (continuous variables) or Pearson's chi-square test (categorical variables) comparing patients with PA group and eHT group.
† P<0.05.

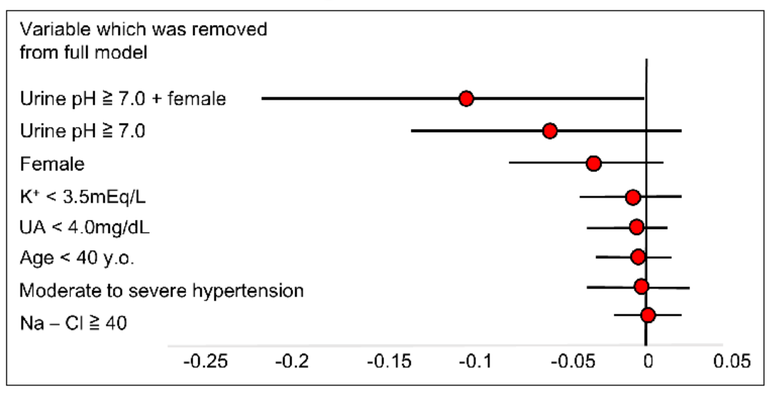
PA group had higher U-pH and higher proportion of female compared with eHT group. There was no significant different between the two groups in other potential markers of PA including hypokalemia.

Table 2. Multivariable potential detective markers of diagnosis PA.

Characteristic	Regression β-coefficient (95% CI)	Odds ratio (95% CI)
Female	1.00 (-0.51 to 2.06)	2.73 (0.95 to 7.84)
Age below 40	-0.92 (-3.08 to 1.24)	0.40 (0.05 to 3.44)
Moderate to severe hypertension	-0.14 (-1.15 to 0.87)	0.87 (0.32 to 2.38)
K^+ below 3.5mEq/L	0.67 (-0.56 to 1.91)	1.96 (0.57 to 6.73)
Na^+ minus Cl^- 40mEq/L or above	-0.80 (-3.63 to 2.03)	0.45 (0.27 to 7.59)
S-UA below 4.0mg/dL	-0.69 (-2.28 to 0.89)	0.50 (0.1 to 2.43)
U-pH 7.0 or above	1.30 (0.30 to 2.30)	3.67 (1.35 to 10.0)*
		*; P < 0.05

U-pH 7.0 or above was independently associated with PA (OR 3.67, 95%CI 1.35 to 10.0).

Figure 2. Difference between AUC of full model and AUC removing each detective marker



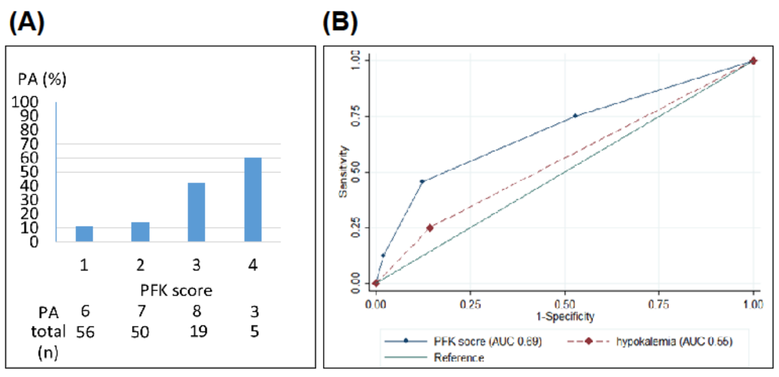
Values indicates point estimates and 95% CI

To evaluate the influence of each detective marker on the diagnosis of PA, we assessed AUC of all detective markers and then removed a detective marker individually from the full model.

AUC of the logistic regression with all potential detective markers (full model) was 0.73 (95%CI 0.61 to 0.85).

Removing high U-pH, female gender and hypokalemia decreased AUC by 0.059, 0.035 and 0.0011, respectively. When both high u-pH and female gender were removed, AUC was decreased by 0.11 (95%CI 0.0025 to 0.22, p=0.045).

Figure 3. Prevalence of PA in each score of PFK score and ROC analysis.



Since U-pH and female gender affected AUC more than hypokalemia, we selected U-pH, female and hypokalemia to combine in a scoring system for assessing probability of PA.

(A) We attributed one point to each of these three detective markers and developed a scoring system named PFK score from those acronyms of pH, female and K+.
The prevalence of PA in patients with 0, 1, 2 and 3 points in PFK score were 11, 14, 42 and 60 %, respectively.

(B) AUC of PFK score with 0.69 (95%CI 0.56 to 0.81) was significantly higher than that of hypokalemia with 0.55 (95%CI 0.46 to 0.65, p= 0.022).

DISCUSSION

Summary: We observed three important clinical points using data from **consecutive patients with newly diagnosed hypertension**.

1)Combination of urinary pH, sex and K^+, *compared with hypokalemia only, is useful for selection of patients suitable for the endocrine examination to diagnose PA.*
2)Only U-pH 7.0 or above was adopted as the single detective marker for PA *and other potential markers including hypokalemia wasn't.*
3)Patients with PA had higher proportion of female compared with those with eHT.

Strength:
1)Setting: This study was performed in **hospital not specializing in endocrinology** and the records of **consecutive adult patients** who visited **Department of Internal Medicine**. Therefore, it was considered to have little possibility of selection bias than studies performed in hospitals specialized in endocrinology.
2)Scoring system: **PFK score is the first scoring system** to detect whose ARR should be measured. In addition, PFK score is **simple** and the variables are **available in daily practice**.

Limitation:
1) This study was performed in a single hospital in Japan.
2) Cutoffs of ARR and challenge tests were different between JES and ENDO.

Therefore, our results might not directly apply in other countries. To conquer the potential difference of race, countries and guidelines, further studies are expected to confirm the external validity of PFK score.

CONCLUSION

Urine pH and female gender are better screening markers of PA than hypokalemia in first-visited hypertensive patients.

PFK score is a novel easy-to-use clinical prediction rule in screening for PA .

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52 ERA 88--FP

F2) Hypertension. Clinical.

Tomohisa Yamashita

DOI: 10.3252/pso.eu.52era.2015

ePosters supported by F. Hoffmann- La Roche Ltd.

52nd ERA-EDTA CONGRESS LONDON 2015 UNITED KINGDOM MAY 28 '15

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