Original Article

Subtype-specific trends in the clinical picture of primary aldosteronism over a 13-year period

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Objective: Primary aldosteronism has two main clinically and biologically distinct subtypes: unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH). We aimed to evaluate the changes of each subtype's clinical characteristics over a 13-year period.

Methods: This retrospective study involved time-trend analyses to identify changes in the clinical features of APA and BAH at diagnosis (2006–2018). A nationwide database from 41 Japanese referral centers was searched, which identified 2804 primary aldosteronism patients with complete baseline information and adrenal venous sampling (AVS) data.

Results: The proportion of patients with APA decreased from 51% in 2006–2009 to 22% in 2016–2018. Among the 1634 patients with BAH, trend analyses revealed decreases in hypertension duration (median 7–3 years; $P < 0.01$) and hypokalemia prevalence (18–11%; $P < 0.01$). However, among the 952 patients with APA, there were no significant changes in hypertension duration (median 8 years) and hypokalemia prevalence (overall 70%). Furthermore, the APA group had a trend towards increased use of multiple hypertensive drugs at diagnosis (30–43%; $P < 0.01$). When subtypes were reclassified according to the precosyntropin stimulation AVS data, APA patients tended to be diagnosed earlier and at milder forms, consistent with the trend in overall primary aldosteronism patients.

Conclusion: During 2006–2018, we identified marked subtype-specific trends in the clinical findings at the diagnosis of primary aldosteronism. Our results suggested that the emphasis on the implementing cosyntropin stimulation during AVS might lead to under-identification of APA, especially in patients with mild or early cases.

Keywords: aldosterone, blood pressure, hyperaldosteronism, hypertension

Abbreviations: APA, unilateral aldosterone-producing adenoma; ARR, aldosterone-to-renin ratio; AVS, adrenal venous sampling; BAH, bilateral adrenal hyperplasia; CT, computed tomography scan; eGFR, estimated glomerular filtration rate; JPAS/JRAS, Japan Primary Aldosteronism Study/Japan Rare Intractable Adrenal Diseases Study; PAC, plasma aldosterone concentration; PRA, plasma renin activity; Q1, first study quarter (2006–2009); Q2, second study quarter (2010–2012); Q3, third study quarter (2013–2015); Q4, fourth study quarter (2016–2018); UDM, undetermined primary aldosteronism subtypes

INTRODUCTION

Primary aldosteronism is one of the most common causes of secondary hypertension. Mineralocorticoid receptors are excessively activated by primary

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aldosteronism, which causes severe cardiovascular events and increases the occurrence of various comorbidities, such as cerebrovascular disease, renal dysfunction, diabetes mellitus, and metabolic syndrome [1–3]. The two main subtypes of primary aldosteronism are unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH) [4]; adrenal venous sampling (AVS) is the gold standard modality for determining primary aldosteronism subtype. Adrenalectomy is a potentially curative treatment for APA, and the patient's duration of hypertension is considered an important predictor of whether adrenalectomy will resolve their hypertension [5–8].

On the basis of these factors, primary aldosteronism is now widely recognized as an important disease in the field of hypertension, and various clinical guidelines have been developed. The American Endocrine Society published the first primary aldosteronism guidelines in 2008 [9], followed by the Japanese Scientific Societies' primary aldosteronism guidelines in 2009 [10,11]. The screening and diagnostic guidelines have subsequently been updated to reflect the fact that mild cases are more common than initially thought [4]. Thus, the current guidelines recommend screening for patients who present with symptoms that support a suspicion of primary aldosteronism, such as young-onset hypertension, hypokalemia, or hypertension that is resistant to multiple drug treatments. However, despite the increased understanding of the need to screen for primary aldosteronism, many patients with hypertension may have undiagnosed primary aldosteronism, especially in the primary care setting [12–14], which has become a major public health issue [15].

A few recent reports have suggested that patients with primary aldosteronism who are referred to specialized facilities now tend to have milder forms of the disease, which may be related to increased disease awareness and screening [16,17]. Furthermore, the proportion of patients with the BAH subtype has rapidly increased and now exceeds the proportion of patients with the APA subtype [16], and this phenomenon has also been observed in Asian countries [17,18]. However, despite the two primary aldosteronism subtypes being clinically and biologically distinct, few studies have evaluated the temporal changes in their clinical features [19–22]. Therefore, we aimed to investigate the temporal changes in the clinical characteristics of the two main subtypes (APA and BAH) of primary aldosteronism over a 13-year period.

METHODS

Study design and population

This study evaluated data from the Japan Primary Aldosteronism Study/Japan Rare Intractable Adrenal Diseases Study (JPAS/JRAS). The JPAS/JRAS was a nationwide multicenter study that involved 41 referral centers (22 university hospitals and 19 city hospitals). We used the JPAS/JRAS dataset, which was collected using an online registry system and was last validated in March 2019. Other studies using this dataset have recently been reported [23–25]. Patients were included if they were 20–90 years old and had been diagnosed with primary aldosteronism. The system's construction and maintenance were performed by EPS Corporation (Tokyo, Japan).

We performed a retrospective time-series trend analysis over a 13-year period using the JPAS/JRAS dataset to identify temporal changes in the clinical characteristics of APA and BAH at diagnosis. The present study ultimately included 2804 patients who were diagnosed with primary aldosteronism, had complete data regarding baseline variables, and underwent AVS between 1 January 2006 and 31 December 2018. We excluded patients in whom AVS was not performed ($n = 37$), those with no information on comprehensive clinical judgment of subtype ($n = 233$), and those with incomplete data on baseline variables ($n = 574$).

Diagnosis of primary aldosteronism and subtyping

The diagnosis of primary aldosteronism was made according to the criteria of the national guidelines [10,11]. Patients were screened based on the plasma aldosterone-to-renin ratio (ARR), which was measured while the patient was in supine position. An ARR value of more than 200 pg/ml per ng/ml h prompted confirmatory tests. The primary aldosteronism diagnosis was confirmed based on at least one positive confirmatory test result, including the captopril challenge test, isotonic saline infusion test, and oral salt-loading test. During the diagnostic tests, the patient's antihypertensive medications were replaced with calcium channel antagonists and α-adrenergic blockers, if possible. A lateralization index after cosyntropin stimulation, an index for determining lateralization, had a cut-off value of lateralization index greater than 4. When the lateralization index was in the borderline range of 2–4, lateralization was comprehensively determined by clinical endocrinologists based on the patient's AVS data and clinical features, such as contralateral ratio, age, plasma potassium concentration, plasma aldosterone concentration (PAC), and adrenal imaging findings. We also created a subgroup of undetermined primary aldosteronism subtypes (UDM) for patients who were considered 'unclassifiable' by clinicians after a comprehensive evaluation.

Furthermore, for subtype classification, we created an alternative model to address the recommended criteria from the AVIS-2 study [26]. This model included patients with AVS data that were collected before cosyntropin stimulation, and the primary aldosteronism subtypes were retrospectively reclassified using a selectivity index (selectivity index ≥ 1.4 for successful cannulation without cosyntropin stimulation) and the lateralization index (>2 for lateralization). The lateralization index was calculated by dividing the aldosterone-to-cortisol ratio on the dominant side by that on the nondominant side, while the selectivity index was calculated as the ratio of the cortisol concentrations in the adrenal vein over the inferior vena cava [27].

Data collection and definitions

Baseline characteristics at diagnosis included sex, age, duration of hypertension, BMI, SBP, DBP, estimated glomerular filtration rate (eGFR), PAC, plasma renin activity (PRA), ARR, and primary aldosteronism-related complications, which included hypokalemia, cardiovascular diseases, cerebrovascular diseases, diabetes mellitus,

dyslipidemia, and the use of at least two antihypertensive drugs. Data were also collected regarding cosyntropin use during AVS, performance of adrenal computed tomography (CT) scan before AVS, and the prevalence of unilateral adrenal mass on CT. Blood pressure was measured with the patient in a seated position. Hypokalemia was defined as a serum potassium concentration of less than 3.5 mEq/l and/or the use of potassium supplementation at primary aldosteronism diagnosis. Diabetes mellitus was identified based on the Japanese criteria (fasting blood sugar concentration ≥126 mg/dl and glycated hemoglobin concentration ≥6.5%) and/or the use of antidiabetic drugs at primary aldosteronism diagnosis [28]. Dyslipidemia was also identified based on the Japanese criteria (fasting triglyceride concentration ≥150 mg/dl, low-density lipoprotein concentration ≥140 mg/dl, and high-density lipoprotein concentration ≤40 mg/dl) and/or the use of antidyslipidemic drugs at primary aldosteronism diagnosis [29]. Cardiovascular diseases, including myocardial infarction, heart failure, and angina pectoris, were confirmed by cardiologists. Cerebrovascular diseases, including cerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage, were confirmed by neurologists. eGFR (ml/min per 1.73 m^2) was calculated as $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ pi re 3j× 0.739 (if female) [30].

Laboratory testing

Commercially available radioimmunoassay kits were used to measure PAC (SPAC-S Aldosterone kits; Fuji Rebio, Co, Ltd, Tokyo, Japan). PRA was measured using radioimmunoassay kits (Fuji Rebio, Inc, Tokyo, Japan, and Yamasa Co, Ltd, Choshi, Japan) or enzyme immunoassay kits (Yamasa, Co, Ltd). Plasma active renin concentration was measured using immunoradiometric assays (Renin IRMA-FR; Fuji Rebio, Inc), which were divided by 5 and converted to PRA according to the Japan Endocrine Society guidelines [11].

Statistical analysis

Continuous variables were reported as median [interquartile range], and categorical variables were reported as number (percentage). Intergroup comparisons of the patients' baseline characteristics were performed using the Mann–Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Trends and changes in the clinical characteristics of primary aldosteronism at diagnosis were evaluated by dividing the 13-year study period into 3-to-4-year quarters (Q1, 2006–2009; Q2, 2010–2012; Q3, 2013–2015; Q4, 2016–2018). For the trend analysis, we used the Jonckheere–Terpstra trend test for quantitative variables and the Cochran–Armitage test for categorical variables. We used multivariable linear and logistic regression models for age adjustment. Variables with nonnormal distributions were log-transformed in the linear regression analysis and the normality of residual distributions was visually assessed using the Q–Q plots. Differences were considered statistically significant at two-tailed *P* values of less than 0.05. All statistical analyses were performed using the R software version 3.6.3 (The R Foundation for Statistical Computing; Vienna, Austria) [31]. Figures and tables were generated using the Microsoft Excel version 2019 (Microsoft Corp, Redmond, Washington, USA).

Ethical considerations

The study was conducted in accordance with the guidelines for clinical studies from the Japanese Ministry of Health and Labor, as well as the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. The retrospective study protocol was approved by the Ethics Committee of the National Hospital Organization Kyoto Medical Center (as the lead project center) and by each participating center's institutional ethics committee. The requirement for informed consent was waived because of the study's retrospective nature. The study protocol was registered at the University Medical Information Network (#18756 and #32525).

RESULTS

Overall trends before stratification

During the 13-year study period and before the stratification into primary aldosteronism subtypes, there was a trend toward a younger age at diagnosis (*P* for trend <0.01), a higher prevalence of the use of cosyntropin stimulation during AVS (age-adjusted *P* for trend <0.01), a higher prevalence of CT findings of unilateral adrenal mass (age-adjusted *P* for trend <0.01), a lower prevalence of hypokalemia (age-adjusted *P* for trend <0.01), and lower values for PAC and ARR (both age-adjusted *P* for trend <0.01) (Supplemental Digital Content 1, http://links.lww.com/HJH/B685). The duration of hypertension decreased significantly throughout the four study quarters without age adjustment (*P* for trend <0.01), although the difference was not statistically significant with age adjustment.

Patient characteristics of each primary aldosteronism subtype at diagnosis

The subtype diagnoses were APA for 952 patients (34%), BAH for 1634 patients (58%), and UDM for 218 patients (8%). Relative to patients with BAH at baseline, patients with APA at baseline were more likely to be men (56 vs. 46%; $P < 0.01$), had a lower BMI (23.9 kg/m^2 [21.3–27.3 kg/m^2] vs. 24.7 kg/m^2 [22.4–27.4 kg/m^2]; $P < 0.01$), and had a longer duration of hypertension (8 years [3–15 years] vs. 4 years [1–10 years]; $P < 0.01$). Furthermore, patients with APA had a higher PAC (283 pg/ml [175–443 pg/ml] vs. 155 pg/ml [115–212 pg/ml]; $P < 0.01$), a lower PRA (0.3 ng/ml h [0.2–0.4 ng/ml h] vs. 0.3 ng/ml h [0.2–0.5 ng/ml h]; $P < 0.01$), and a higher ARR (1070 pg/ml per ng/ml h [560–2226 pg/ml per ng/ml h] vs. 426 pg/ml per ng/ml h [290–689 pg/ml per ng/ml h]; $P < 0.01$). Moreover, patients with APA had higher prevalence of CT findings of unilateral adrenal mass (90 vs. 46%; $P < 0.01$), hypokalemia (70 vs. 14%; $P < 0.01$) and cerebrovascular disease (9 vs. 5%; $P < 0.01$), and more likely used multiple antihypertensive drugs (35 vs. 17%; $P < 0.01$) (Table 1).

Trends in the clinical characteristics of each primary aldosteronism subtype at diagnosis

The proportion of patients diagnosed with APA decreased substantially throughout the four study quarters (Q1: 51%, Q2: 39%, Q3: 34%, Q4: 22%; *P* for trend <0.01) (Fig. 1a). In

TABLE 1. Patient characteristics for each primary aldosteronism subtype

N	APA ($n = 952$)	BAH ($n = 1634$)	*P* value[a]
Female sex (%)	438 (46)	907 (56)	**<0.01**
Age (years)	57 [47–66]	55 [47–65]	0.08
Duration of hypertension (years)	8 [3–15]	4 [1–10]	**<0.01**
Cosyntropin stimulation during AVS (%)	897 (94)	1558 (95)	0.24
Performance of CT (%)	942 (99)	1619 (99)	0.90
Unilateral adrenal mass on CT (%)	844 (90)	740 (46)	**<0.01**
BMI (kg/m^2)	23.9 [21.3–27.3]	24.7 [22.4–27.4]	**<0.01**
SBP (mmHg)	140 [130–154]	140 [129–150]	**0.03**
DBP (mmHg)	87 [79–96]	87 [78–96]	>0.99
eGFR (ml/min per 1.73 m^2)	77 [65–92]	78 [67–90]	0.27
Plasma aldosterone concentration (pg/ml)	283 [176–433]	155 [115–212]	**<0.01**
Plasma renin activity (ng/ml h)	0.3 [0.2–0.4]	0.3 [0.2–0.5]	**<0.01**
Aldosterone-to-renin ratio (pg/ml per ng/ml h)	1070 [560–2226]	426 [290–689]	**<0.01**
Use of ≥2 antihypertensive drugs (%)	333 (35)	275 (17)	**<0.01**
Hypokalemia (%)	669 (70)	236 (14)	**<0.01**
Cardiovascular disease (%)	34 (4)	31 (2)	**<0.01**
Cerebrovascular disease (%)	90 (9)	79 (5)	**<0.01**
Diabetes mellitus (%)	147 (15)	245 (15)	0.80
Dyslipidemia (%)	267 (28)	478 (29)	0.54

Data are presented as median [interquartile range] or number (%). APA, unilateral aldosterone-producing adenoma; AVS, adrenal venous sampling; BAH, bilateral adrenal hyperplasia; CT, computed tomography; eGFR, estimated glomerular filtration rate.
[a]The Mann–Whitney *U* test was used for continuous variables. The χ^2 test was used for categorical variables. Values in bold indicate a significant difference.

addition, we analyzed the trends in the baseline characteristics of patients with APA and BAH throughout the four study quarters. Among patients with BAH, the results showed a trend towards a younger age at primary aldosteronism diagnosis (*P* for trend <0.01), a shorter duration of hypertension (age-adjusted *P* for trend <0.01), and a lower prevalence of hypokalemia (age-adjusted *P* for trend <0.01) (Fig. 1b and c, Table 2). Among patients with APA, there was also a trend towards a younger age at primary aldosteronism diagnosis (*P* trend <0.01), although the duration of hypertension was prolonged and the prevalence of hypokalemia remained high with no significant temporal changes. Furthermore, APA patients had a trend towards an increased use of multiple hypertensive drugs at primary aldosteronism diagnosis over the four study quarters (age-adjusted *P* for trend <0.01). The trends observed among patients with UDM are shown in the Supplemental Digital Content 2, http://links.lww.com/HJH/B686.

Stratified analyses according to subtype using the alternative criteria

In both groups of APA and BAH, there was a trend toward an increased cosyntropin use during AVS (both age-adjusted *P* for trend <0.01), whereas the proportion of APA cases decreased and that of BAH cases increased. On the basis of previous reports, we suspected that mild APA may have been inaccurately identified because of the stringent criteria with cosyntropin stimulation [26,32]. Therefore, we conducted stratified analyses according to the reclassified subtypes that were assigned using different criteria and the AVS results before cosyntropin stimulation (the alternative model).

Of the 2804 patients included, we identified 2362 patients with available AVS data before cosyntropin stimulation. Of the 2362 identified patients, there were 2213 with AVS data before and after cosyntropin stimulation and 149 with only precosyntropin stimulation data. A total of 1943 patients had successful cannulation during AVS in a precosyntropin stimulated condition (i.e. selectivity index of ≥1.4) and were re-classified as APA (1241 patients, 64%: lateralization index of >2.0) or BAH (702 patients, 36%: lateralization index of ≤2.0). The patients' baseline characteristics in the alternative model are shown in Supplemental Digital Content 3, http://links.lww.com/HJH/B687. The differences between the APA and BAH subtypes in the alternative model were generally similar to those listed above that were identified in the original model, which is shown in the Table 1.

Comparing results of trend analyses between the original and alternative models

The trends observed among patients with APA and BAH in the alternative model are shown in the Supplemental Digital Content 4, http://links.lww.com/HJH/B688. Both models revealed a significant decrease in the proportion of patients with APA between Q1 and Q4, although the decrease was smaller in the alternative model (alternative model: 72–60%, *P* for trend <0.01) (Fig. 1d). In contrast with the results of the original model, the alternative model also showed that the APA group had a significant decrease in the duration of hypertension (Q1: 7 years [2–17 years], Q2: 7 years [3–13 years], Q3: 5 years [2–12 years], Q4: 4 years [1–10 years]; age-adjusted *P* for trend <0.05) and in the prevalence of hypokalemia (Q1: 53%, Q2: 46%, Q3: 40%, Q4: 28%; age-adjusted *P* for trend <0.01) (Fig. 1e and f). Meanwhile, in the BAH group, the duration of hypertension decreased significantly without age adjustment (Q1: 7 years [3–11 years], Q2: 5 years [2–12 years], Q3: 4 years [1–11 years], Q4: 3 years [1–10 years]; *P* for trend <0.01), although the difference was not statistically significant with age adjustment.

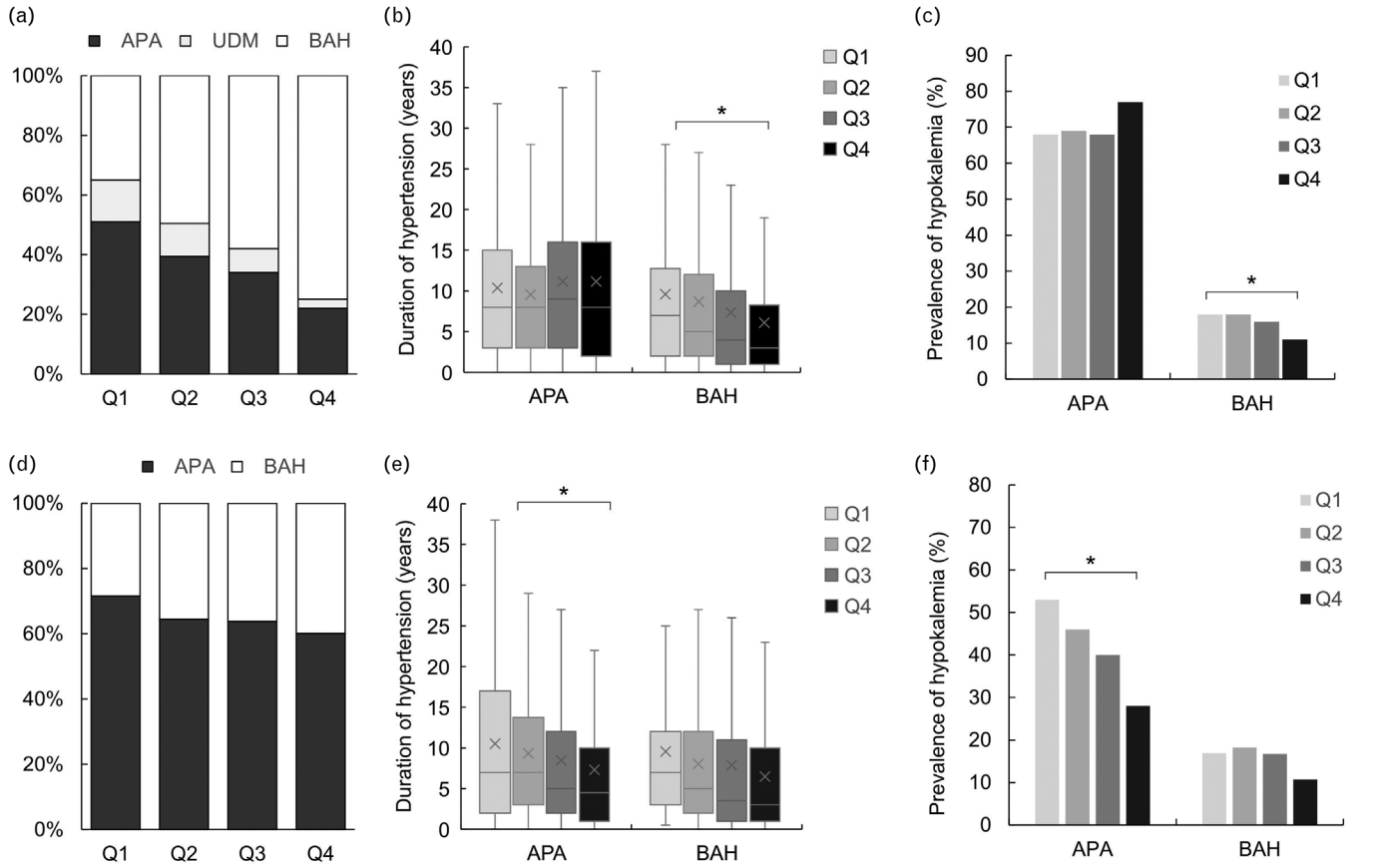

FIGURE 1 Trends during the four study quarters among patients with aldosterone-producing adenoma and bilateral adrenal hyperplasia. (a–c) Original model of primary aldosteronism subtypes classified according to the criteria of national guidelines [10,11]. (d–f) Alternative model of primary aldosteronism subtypes based on results of adrenal vein sampling before cosyntropin stimulation according to the previously published AVIS-2 study [26]. (a and d) Prevalences of APA and BAH in the total population (both P for trend <0.01). (b and e) Durations of hypertension (presented with box-and-whiskers plots, years). (c and f) Prevalences of hypokalemia (median, percentage). *Age-adjusted P for trend less than 0.05. Duration of hypertension was log-transformed because of nonnormal distributions in the linear regression analysis. APA, unilateral aldosterone-producing adenoma; BAH, bilateral adrenal hyperplasia; Q1, 2006–2009; Q2, 2010–2012; Q3, 2013–2015; Q4, 2016–2018; UDM, undetermined primary aldosteronism subtype.

DISCUSSION

There are limited data regarding the temporal changes in the clinical features of the two main primary aldosteronism subtypes, namely APA and BAH. This retrospective multicenter study found that, prior to stratification into primary aldosteronism subtypes, Japanese patients with primary aldosteronism exhibited an overall trend toward milder forms at diagnosis between 2006 and 2018. This trend was also evident in the BAH group after stratification. Moreover, the BAH group had a shorter duration of hypertension at primary aldosteronism diagnosis. However, the APA group exhibited no significant changes in the key clinical findings regarding primary aldosteronism severity during the study period. These APA patients tended to have a longer duration of hypertension before the diagnosis of primary aldosteronism. Several studies have shown that the duration of hypertension is significantly associated with prognosis after adrenalectomy in patients with APA [5–8]. Therefore, this study's findings suggest that the current guidelines may be inadequate in terms of improving surgical outcomes among patients with APA who undergo adrenalectomy. Further research is needed to clarify how the current clinical strategies for primary aldosteronism can be improved to achieve accurate and early diagnosis of APA.

Previous studies also used datasets from referral centers to evaluate long-term changes in the clinical characteristics of patients with primary aldosteronism [16,17]. For instance, a multicenter retrospective study of data between 2008 and 2016 from the German Conn's Registry [16] revealed a trend toward a milder clinical picture of primary aldosteronism, which was attributed by the authors to be related to enhanced screening and early diagnosis. Their results were consistent with our findings. The same study [16] also revealed a significant temporal decrease in the proportion of unilateral cases (67–43%). A similar trend was observed in a retrospective single-center Korean study that compared patients during 1986–2005 and 2006–2012 [17]. However, these studies did not evaluate temporal trends in the clinical presentation of each primary aldosteronism subtype, while the present study identified distinctive differences between the two main primary aldosteronism subtypes in Japan over a 13-year period.

The gold-standard modality for diagnosing the primary aldosteronism subtype is AVS, although there are no uniform criteria for determining successful cannulation and lateralization [33,34]. Cosyntropin stimulation has been

TABLE 2. Trends in the clinical characteristics at diagnosis of each primary aldosteronism subtype

	APA					BAH				
	Q1 2006–2009	Q2 2010–2012	Q3 2013–2015	Q4 2016–2018	Trend *P* value	Q1 2006–2009	Q2 2010–2012	Q3 2013–2015	Q4 2016–2018	Trend *P* value
n	184	247	330	191		128	311	557	638	
Female sex (%)	93 (51)	119 (48)	145 (44)	81 (42)	0.06	75 (59)	158 (51)	339 (61)	335 (53)	0.51
Age (years)	62 [52–68]	57 [47–66]	57 [46–65]	53 [44–63]	**<0.01**	63 [54–70]	59 [51–68]	55 [47–64]	52 [45–60]	**<0.01**
Duration of hypertension (years)	8 [3–15]	8 [3–13]	9 [3–16]	8 [2–16]	0.85[b]	7 [2–12]	5 [2–12]	4 [1–10]	3 [1–8]	**<0.01**[a,b]
Cosyntropin stimulation during AVS (%)	152 (83)	224 (91)	330 (100)	191 (100)	**<0.01**[a]	93 (73)	271 (87)	557 (100)	637 (100)	**<0.01**[a]
Performance of CT (%)	183 (99)	241 (98)	328 (99)	190 (99)	0.43	126 (98)	309 (99)	553 (99)	631 (99)	0.92
Unilateral adrenal mass on CT (%)	166 (90)	222 (90)	292 (88)	164 (86)	0.16	72 (56)	198 (64)	229 (41)	241 (38)	**<0.01**[a]
BMI (kg/m^2)	23.9 [21.2–27.2]	23.5 [21.1–26.1]	24.2 [21.3–27.90]	23.70 [21.5–27.40]	0.77	24.5 [21.8–27.4]	24.3 [21.9–26.8]	24.6 [21.8–27.7]	24.5 [22.2–27.3]	0.42
SBP (mmHg)	140 [130–153]	139 [128–152]	142 [129–154]	144 [132–155]	0.95	140 [132–152]	139 [124–150]	140 [129–152]	140 [130–150]	0.89
DBP (mmHg)	88 [80–97]	86 [78–94]	86 [78–95]	88 [79–97]	0.58	89 [80–94]	84 [77–92]	87 [78–97]	88 [79–97]	>0.99
eGFR (ml/min per/1.73 m^2)	75 [62–93]	80 [68–93]	76 [65–91]	76 [63–90]	0.38	75 [66–90]	79 [68–92]	77 [67–90]	79 [67–90]	0.67
Plasma aldosterone concentration (pg/ml)	284 [170–404]	262 [161–415]	273 [181–420]	318 [202–472]	>0.99	153 [107–231]	149 [108–194]	156 [113–207]	160 [121–218]	>0.99
Plasma renin activity (ng/ml·h)	0.20 [0.10–0.40]	0.20 [0.10–0.40]	0.30 [0.10–0.40]	0.20 [0.20–0.40]	0.52	0.3 [0.2–0.5]	0.3 [0.2–0.5]	0.3 [0.2–0.5]	0.3 [0.2–0.5]	0.94
Aldosterone-to-renin ratio (pg/ml per ng/ml·h)	1105 [579–2142]	1008 [510–2266]	971 [564–2140]	1370 [655–2268]	0.94	436 [304–727]	410 [272–682]	420 [288–710]	436 [297–660]	0.64
Use of ≥2 antihypertensive drugs (%)	56 (30)	90 (36)	105 (32)	82 (43)	**<0.01**[a]	23 (18)	74 (24)	88 (16)	90 (14)	0.32[a]
Hypokalemia (%)	126 (68)	171 (69)	225 (68)	147 (77)	0.13	23 (18)	56 (18)	87 (16)	70 (11)	**<0.01**[a]
Cardiovascular disease (%)	4 (2)	9 (4)	16 (5)	5 (3)	0.59	4 (3)	5 (2)	12 (2)	10 (2)	0.40
Cerebrovascular disease (%)	20 (11)	19 (8)	32 (10)	19 (10)	>0.99	8 (6)	16 (5)	28 (5)	27 (4)	0.30
Diabetes mellitus (%)	28 (15)	38 (15)	56 (17)	25 (13)	0.76	16 (12)	46 (15)	108 (19)	75 (12)	0.32
Dyslipidemia (%)	37 (20)	66 (27)	107 (32)	57 (30)	**<0.01**[a]	35 (27)	92 (30)	168 (30)	183 (29)	0.99

Data are presented as median [interquartile range] or number (%). Trend analysis before adjustment was performed using the Jonckheere–Terpstra trend test for continuous variables and the Cochran-Armitage trend test for categorical variables. Values in bold indicate a significant trend. APA, unilateral aldosterone-producing adenoma; AVS, adrenal venous sampling; BAH, bilateral adrenal hyperplasia; CT, computed tomography; eGFR, estimated glomerular filtration rate; Q1–Q4, the four quarters of the 13-year study period.
[a]Age-adjusted *P* for trend using multivariable linear and logistic regression models.
[b]Log-transformed variables because of nonnormal distributions in the linear regression analysis.

conventionally used to increase the rate of successful cannulation during AVS [35]. In addition, approximately 40% of facilities worldwide currently use cosyntropin stimulation during AVS [36]. Our results indicated that cosyntropin stimulation during AVS increased substantially over the four study quarters. Furthermore, almost all cases in the most recent quarters (Q3 and Q4) had cosyntropin stimulation. However, some experts recommend unstimulated AVS as previous studies have shown that cosyntropin stimulation may only help identify APA in relatively severe cases [26,32]. Moreover, our alternative model revealed that the duration of hypertension decreased over time among patients with APA before and after age-adjustment, which was consistent with the overall trend toward milder forms. These results indicated that cosyntropin stimulation during AVS might interfere with the identification of APA, especially in those with milder forms of the disease or in those who were detected during the early course of the disease, which were becoming increasingly common because of recent intensification in screening. Nevertheless, we found that cannulation for AVS without cosyntropin stimulation had a failure rate that could not be ignored (419/2362 [18%]), even when using the less stringent cutoff values as recommended in the AVIS-2 study [26]. No consensus has yet been reached on the appropriate selectivity index cutoff without cosyntropin stimulation, posing a challenge for future primary aldosteronism diagnostics. Therefore, it would be useful to develop technologies that can improve the success of cannulation for AVS without relying on cosyntropin stimulation (e.g. intraoperative cortisol measurement [37]). It would also be helpful to evaluate comprehensive localization techniques using new ancillary tools, such as subtype-specific steroid profiles [38].

To the best of our knowledge, this study evaluated the largest cohort of primary aldosteronism cases in the world over one of the longest study periods as compared with previous observational studies. In addition, data were collected from Japanese facilities that were dedicated to treating patients with primary aldosteronism.

The study has several limitations. First, the identified patients included in the study were referred to specialized facilities and may not have been representative of all patients who were encountered in the primary care setting. Second, the patients were mostly Japanese; thus, our results cannot possibly be applied to other ethnic groups. Nevertheless, it is possible that our findings can be generalizable to other specialized centers worldwide as the trends we found are generally consistent with previously reported trends of studies at multiple referral centers. Third, pathological diagnosis is essential for the definitive diagnosis of APA or BAH. However, there was no indication for surgery in BAH cases, which was why pathological diagnosis was not included in the definition of primary aldosteronism subtypes in this study. Finally, the observational study design precludes a conclusion regarding the causality of the relationship between a prolonged duration of hypertension and primary aldosteronism-related complications, such as hypokalemia.

In conclusion, we believe that this was the first large-scale study to evaluate temporal changes in the clinical characteristics of the two main subtypes of primary aldosteronism. There was a trend towards early detection and relatively milder forms of primary aldosteronism in the BAH group. However, the APA group continued to have a prolonged duration of hypertension. Moreover, there were no significant changes towards improvement in the key clinical findings regarding the severity of primary aldosteronism. These results may highlight a need to revise the current guidelines regarding surgical intervention for APA in the early stages of hypertension. In addition, the results from the alternative model for primary aldosteronism subtyping without cosyntropin stimulation suggest that AVS with cosyntropin stimulation may reduce the diagnostic ability to identify APA in mild cases and cases with early detection, which are becoming increasingly common.

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Conflicts of interest

There are no conflicts of interest.

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