Comparison between the clinical characteristics of patients with adrenal incidentalomas and those with hypertension-associated adrenal tumors in a single center in Japan

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Abstract. In the largest retrospective study of adrenal incidentalomas (AIs) in Japan between 1999 and 2004, adrenal tumors detected during secondary hypertension (HT) screening were included. The characteristics of patients with adrenal tumors detected during HT screening may differ from those of patients with AIs. This study aimed to compare the characteristics of patients with AIs with those of patients with adrenal tumors detected during HT screening. We retrospectively analyzed patients referred to our division for detailed examination of adrenal tumors between April 2009 and April 2017. When the purposes of imaging tests included HT screening, we defined adrenal tumors as HT associated, otherwise as strictly defined AIs. We reviewed data on age, sex, purpose and modality of imaging, location of tumor, tumor diameter, and hormonal evaluation. We identified 104 patients with HT-associated adrenal tumors and 413 with AIs. Patients with HT-associated adrenal tumors were younger (54.2 years vs. 61.7 years, \( p < 0.001 \)) and had smaller tumor diameters (1.3 cm vs. 1.9 cm, \( p < 0.001 \)), lower prevalence of nonfunctioning tumors (24.0\% vs. 67.6\%, \( p < 0.001 \)), and higher prevalence of primary aldosteronism (58.7\% vs. 4.8\%, \( p < 0.001 \)) than those with AIs. There were no differences in terms of tumor location and prevalence of subclinical Cushing’s syndrome, Cushing’s syndrome, and pheochromocytoma (18.3\% vs. 16.0\%, 7.7\% vs. 8.0\%, and 2.9\% vs. 4.6\%, respectively). In conclusion, patients with HT-associated tumors were younger and had a smaller tumor with higher prevalence of primary aldosteronism than those with AIs.

Key words: Adrenal incidentaloma, Primary aldosteronism, Subclinical Cushing’s syndrome, Cushing’s syndrome, Pheochromocytoma

AN ADRENAL INCIDENTALOMA (AI) is an adrenal mass detected on imaging not performed for suspected adrenal disease [1]. In a study of 520 chest high-resolution computed tomography (CT) scans performed during 2001, AIs were detected in 4.4\% [2]. With the advancement of imaging technology and the precision of CT, the current prevalence of AIs will be presumably higher than previously reported.

A Japanese national survey of AIs published in 2005 included data from 3,678 patients, based on questionnaires collected from hospitals all over Japan from 1999 to 2004 [3]. In 12\% of all subjects, the purpose of imaging investigation was to determine any etiology for secondary hypertension (HT); however, reasons for including patients with adrenal tumors detected during secondary HT screening were not specified. It is controversial whether patients with adrenal tumors detected during secondary HT screening should be included in the study population since secondary HT screening may indicate the detection of suspected adrenal disease; hence, the inclusion would be contradictory to the definition of AI. It is unclear whether there is any difference between the characteristics of AIs and those of adrenal tumors detected during secondary HT screening. Because both types of tumors have different reasons for being investigated, it is inferable that both types will have different characteristics. However, no studies have described the differences between the characteristics of AIs and those of adrenal tumors detected during secondary HT screening.

Furthermore, there have been few extensive surveys of AIs in Japan since the Japanese national survey was performed. Moreover, the Japanese diagnostic criteria for primary aldosteronism (PA) and subclinical Cushing’s
syndrome (SCS) were revised in 2016 and 2017, respectively [4, 5]. A large-scale study consisting of 150 subjects in Osaka region was conducted in 2016 [6], in which the previous diagnostic criteria for SCS were used; thus, an analysis of patients with AIs using the new criteria is required.

We aimed to compare the characteristics of patients with AIs to those with adrenal tumors detected during secondary HT screening using data from a high-volume hospital in Tokyo. Furthermore, to elucidate the current status of clinical practice and diagnosis of AIs in Japan, we investigated the clinical diagnosis and characteristics of patients with AIs.

**Materials and Methods**

**Patients**

We included patients referred to the Division of Nephrology and Endocrinology, the University of Tokyo Hospital, from April 1, 2009 to April 30, 2017. We selected patients with the following registered diseases in their medical records: AI, adrenal tumor, PA, pheochromocytoma (PC), Cushing’s syndrome (CS), adrenal adenoma, and SCS. Additionally, we included patients with measured urine metanephrines because this measurement is usually performed when physicians investigate adrenal tumors or suspect adrenal functional tumors. We excluded patients using the following criteria: (1) no imaging tests performed, (2) no adrenal tumor in imaging test, (3) no first visit between April 1, 2009 and April 30, 2017, and (4) use of glucocorticoid excluding ointments. Subsequently, we classified the patients with adrenal tumors whose purposes of imaging test included secondary HT screening as patients with “HT-associated adrenal tumors,” which means if the patients had multiple purposes of imaging tests including secondary HT screening, we classified them as patients with HT-associated adrenal tumors. We classified patients with adrenal tumors detected other than secondary HT screening as patients with AIs. Patients with HT-associated adrenal tumors included both patients receiving hormonal evaluations prior to imaging and those receiving imaging tests prior to hormonal evaluations.

**Data collection and definitions**

We retrospectively collected the following data: age, sex, whether patient underwent renal replacement therapy, purpose and modality of imaging, location of tumor, tumor diameter, hormonal evaluation of AIs and HT-associated adrenal tumors, malignant tumor of the adrenal gland, and concomitant diseases (HT, diabetes mellitus [DM], dyslipidemia [DLP], cardiovascular disease, and cerebrovascular disease). Tumor diameters were defined as either the largest diameter of unilateral tumors or the larger diameter of bilateral tumors. HT was defined as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg in the examination room, prescription of antihypertensive agents, or previous diagnosis of HT. DM was defined as fasting blood glucose level of ≥126 mg/dL and HbA1c (National Glycohemoglobin Standardization Program) ≥6.5%, prescription of hypoglycemic medication, or previous diagnosis of DM. DLP was defined as a low-density lipoprotein cholesterol level of ≥140 mg/dL, a high-density lipoprotein cholesterol level of <40 mg/dL, triglyceride level of ≥150 mg/dL, prescription of lipid-modifying medication, or previous diagnosis of DLP. Cardiovascular disease was defined as myocardial infarction or angina pectoris. Cerebrovascular disease was defined as cerebral infarction, cerebral hemorrhage, or transient ischemic attack.

**Modality of imaging**

When adrenal tumors were detected in a general checkup, we included all the modalities of imaging used to confirm the adrenal tumors. For the patients who were suspected of having adrenal tumors based on one modality and confirmed through additional modalities of imaging, we chose all the modalities used until the confirmation of adrenal tumors.

**Diagnostic criteria**

PA was suspected when patients showed plasma aldosterone concentration (pg/mL)/plasma renin activity ratio (ng/mL/h) of >200. When PA was suspected, we performed captopril challenge test, upright furosemide loading test, or saline loading test. In this study, we diagnosed PA biochemically when at least one of the tests has a positive result [4].

In the case of SCS, we used the diagnostic criteria as follows because not all the patients underwent thorough evaluations according to the revised diagnostic criteria for SCS [5]. Patients were diagnosed as having possible SCS when their serum cortisol levels after 1-mg dexamethasone test (DST) were ≥1.8 μg/dL [5] and patients showed normal serum cortisol level at outpatient examination room (normal range of the kit used in our institution, 7.07–19.6 μg/dL in the morning and 2.96–9.77 μg/dL in the afternoon) without Cushingoid features. Possible SCS in this study did not require the fulfillment of the following small standards: (1) low plasma levels of ACTH in the early morning (≤10 pg/mL) and/or decreased ACTH response after CRH stimulation (peak value of ACTH <1.5 times former value), (2) no diurnal changes in serum cortisol levels (serum cortisol at midnight ≥7.5 μg/dL while awake and ≥5.0 μg/dL while sleeping), (3) unilateral uptake and suppression of the
contra-lateral uptake of $^{131}$I-adosterol on adrenal scintigraphy, and (4) low serum levels of dehydroepiandrosterone sulfate (DHEA-S). Patients were diagnosed as having definite SCS when they met all the revised diagnostic criteria for SCS [5].

The diagnosis of CS was required the presence of Cushingoid features, with normal or higher serum cortisol levels that lack suppression following 1-mg DST ($\geq 5.0 \mu g/dL$). In addition, at least one of the following endocrine data needed to be met: (1) suppressed plasma ACTH (10 pg/mL) and/or decreased ACTH response after CRH stimulation (peak value of ACTH <1.5 times former value), (2) loss of diurnal cortisol rhythm (serum cortisol at midnight $\geq 7.5 \mu g/dL$ while awake and $\geq 5.0 \mu g/dL$ while sleeping), (3) decreased serum DHEA-S levels, and (4) unilateral uptake and suppression of the contra-lateral uptake of $^{131}$I-adosterol on adrenal scintigraphy.

PC was diagnosed based on the clinical practice guideline of PC and paraganglioma [7]. PC was suspected when patients showed urine metanephrines $\geq 0.5$ mg/gCre. PC was diagnosed based on positive $^{123}$I- or $^{131}$I-metaiodobenzylguanidine scintigraphy results and/or pathological diagnoses.

Adrenal insufficiency was diagnosed when patients needed glucocorticoid replacement therapy. Adrenal cortical carcinoma was pathologically diagnosed. Lymphoma and metastases included both pathological and clinical diagnoses.

The term “functioning tumors” used in this study was defined as hormonal hypersecreting tumors including PA, possible SCS, CS, and PC.

**Hormonal measurements**

Plasma renin activity was measured with radioimmunoassay using Renin RIA Bead on Gamma Counter ARC-950 (Hitachi Aloka Medical, Ltd., Tokyo, Japan) before 2016 and with enzyme immunoassay using Renin Activity Kit YAMASA (Yamasa Co., Chiba, Japan) on AP-X (Kyowa Medex Co., Ltd., Tokyo, Japan) since 2016. PAC was measured with radioimmunoassay using SPAC-S Aldosterone Kit (TFB Inc., Tokyo, Japan) on Gamma Counter ARC-950 (Hitachi Aloka Medical, Ltd., Tokyo, Japan). Serum cortisol was measured with chemiluminescent enzyme immunoassay using Access Cortisol (Beckman Coulter, Inc., California, United States) before 2012, electrochemiluminescence immunoassay using Eclecsys® Cortisol (Roche Diagnostics GmbH, Mannheim, Germany) from 2012 to 2015 and Eclecsys® Cortisol II (Roche Diagnostics GmbH, Mannheim, Germany) since 2016. Serum ACTH was measured with electrochemiluminescence immunoassay using Eclecsys® ACTH (Roche Diagnostics GmbH, Mannheim, Germany). Catecholamines in the plasma were measured with high-performance liquid chromatography using CA test TOSOH Reaction solution D, E (TOSOH Corporation, Tokyo, Japan) on HPLC system L-6200 (Hitachi, Ltd., Tokyo, Japan). Urine metanephrines were measured with high-performance liquid chromatography using WAKOSIL-II RS (FUJIFILM Wako Pure Chemical Corporation, Tokyo, Japan) on HPLC system L-6200 (Hitachi, Ltd., Tokyo, Japan) and Intelligent Fluorescence Detector (JASCO Corporation, Tokyo, Japan). All measurements were performed in the Department of Clinical Laboratory, the University of Tokyo Hospital, and reliability and reproducibility of values obtained with each reagent and machine were confirmed periodically and anytime the type of reagent or machine was changed.

**Statistical analysis**

Age is presented as average ± standard deviation (SD). Median with 25th and 75th percentiles is given for tumor diameters. Categorical data are shown as numbers with percentage. We compared the characteristics of AIs with those of HT-associated adrenal tumors. Subsequently, we excluded patients with adrenal insufficiency and compared the characteristics of nonfunctioning tumors with those of functioning tumors in patients with AIs and in those with HT-associated adrenal tumors.

We analyzed continuous data with normal distribution using the Student’s $t$-test, and the Mann-Whitney $U$ test was used for the evaluation of non-normally distributed data. Categorical data were analyzed using chi-squared test and Fisher’s exact test accordingly. A $p$ value of $<0.05$ was considered statistically significant in this study.

Sensitivity analyses were performed as follows: (1) determine the prevalence of PA in patients with $\geq 1$ cm diameter for AIs and HT-associated adrenal tumors, (2) examine the prevalence of definite SCS in patients with AIs and HT-associated adrenal tumors, (3) examine the prevalence of PA and SCS defined using the previous diagnostic criteria in patients with AIs and HT-associated adrenal tumors, (4) define the term “functioning tumors” as hormonal hypersecreting tumors including PA, definite SCS, CS, and PC and the term “nonfunctioning tumors” as adrenal tumors other than “functioning tumors,” and after excluding patients with adrenal insufficiency compare the characteristics of nonfunctioning tumors and those of functioning tumors in patients with AIs and in those with HT-associated adrenal tumors, respectively, (5) examine the performing rate of adrenal vein sampling (AVS) and the concordance rate of AVS...
lateralization with imaging tests in patients with PA. All analyses were performed using SPSS statistics version 25 (SPSS Inc., Chicago, IL, USA).

**Ethics statement**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee where the studies were conducted (the Ethics Committee of the University of Tokyo Hospital, Approval No. 2879-5) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was a retrospective observational study using existing data from medical records. The institutional review board waived the requirement for informed consent from the patients according to the ethical guidelines for medical and health research involving human subjects in Japan.

**Results**

**Patients with adrenal incidentalomas and hypertension-associated adrenal tumors**

We identified a total of 2,582 patients who had adrenal glands diseases registered or their urinary metanephrine values measured during the period. We excluded 2,065 patients who met the exclusion criteria, and finally, 413 patients were classified as those with AIs and 104 patients as those with HT-associated adrenal tumors (Fig. 1).

The characteristics of the 413 patients with AIs and 104 patients with HT-associated adrenal tumors are shown in Table 1. The average age was 61.7 $\pm$ 12.3 years in patients with AIs. Of the 413 patients with AIs, 212 (51.3%) were males. The most frequent purpose of imaging was general checkup (23.0%). A total of 279 patients (67.6%) were diagnosed as having nonfunctioning tumors, 66 (16.0%) as having possible SCS, 20 (4.8%) as having PA, 33 (8.0%) as having CS, 19 (4.6%) as having PC, and 3 (0.7%) as having adrenal insufficiency in patients with AIs. Nineteen patients were found to have both PA and SCS or CS at the same time among all patients. Patients with HT-associated adrenal tumors were younger than those with AIs (54.2 $\pm$ 12.4 vs. 61.7 $\pm$ 12.3, \(p < 0.001\)). Tumors on the left side were detected most frequently regardless of the purpose of imaging. The tumor diameters were smaller in patients with HT-associated adrenal tumors than in those with AIs (1.3 [1.0, 1.8] vs. 1.9 [1.4, 2.6], \(p < 0.001\)). The prevalence of nonfunctioning tumors (24.0% vs. 67.6%, \(p < 0.001\)) was lower and that of PA was higher (58.7% vs. 4.8%, \(p < 0.001\)) in patients with HT-associated adrenal tumors than in those with AIs. The prevalence of possible SCS, CS, and PC in patients with HT-associated adrenal tumors was almost the same as those in patients with AIs.

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**Fig. 1** Patients’ flow diagram
**Clinical data of patients with nonfunctioning and functioning tumors**

Table 2 shows the comparison of the clinical data between patients with functioning tumors and those without functioning tumors, stratified into patients with AIs and those with HT-associated adrenal tumors. After the exclusion of the patients with adrenal insufficiency, we identified a total of 514 patients: 410 patients with

| Characteristics                      | Adrenal incidentaloma | Hypertension-associated adrenal tumor | p     |
|--------------------------------------|-----------------------|--------------------------------------|-------|
| Age, years                           | 61.7 (12.3)           | 54.2 (12.4)                          | <0.001* |
| Male, n (%)                          | 212 (51.3)            | 48 (46.2)                            | 0.35  |
| Location of the tumor, n (%)         |                       |                                      | 0.50  |
| Right                                | 131 (31.7)            | 30 (28.8)                            |       |
| Left                                 | 234 (56.7)            | 65 (62.5)                            |       |
| Bilateral                            | 48 (11.6)             | 9 (8.7)                              |       |
| Tumor diameter, cm                   | 1.9 (1.4, 2.6)        | 1.3 (1.0, 1.8)                       | <0.001* |
| Modality of imaging*, n (%)          |                       |                                      |       |
| CT                                   | 374 (90.6)            | 89 (85.6)                            | 0.14  |
| MRI                                  | 64 (15.5)             | 26 (25.0)                            | 0.022* |
| US                                   | 77 (18.6)             | 7 (6.7)                              | 0.003* |
| PET                                  | 27 (6.5)              | 0 (0.0)                              | 0.007* |
| Others                               | 1 (0.2)               | 0 (0.0)                              | 0.99  |
| Hormonal evaluation*, n (%)          |                       |                                      |       |
| Nonfunctioning tumor                 | 279 (67.6)            | 25 (24.0)                            | <0.001* |
| Possible SCS                         | 66 (16.0)             | 19 (18.3)                            | 0.57  |
| PA                                   | 20 (4.8)              | 61 (58.7)                            | <0.001* |
| CS                                   | 33 (8.0)              | 8 (7.7)                              | 0.92  |
| PC                                   | 19 (4.6)              | 3 (2.9)                              | 0.59  |
| Adrenal insufficiency                | 3 (0.7)               | 0 (0.0)                              | 0.99  |
| Malignant tumor, n (%)               |                       |                                      |       |
| Adrenal cortical carcinoma           | 4 (1.0)               | 0 (0.0)                              | 0.59  |
| Lymphoma                             | 3 (0.7)               | 0 (0.0)                              | 0.99  |
| Metastasis                           | 6 (1.5)               | 0 (0.0)                              | 0.61  |
| Purpose of imaging*, n (%)           |                       |                                      |       |
| General checkup                      | 95 (23.0)             | —                                    |       |
| Preoperative evaluation              | 55 (13.3)             | —                                    |       |
| Hepatobiliary disease                | 44 (10.7)             | —                                    |       |
| Respiratory symptoms/abnormality on chest imaging | 39 (9.4)              | —                                    |       |
| Chest, abdominal, or low back pain   | 34 (8.2)              | —                                    |       |
| Follow-up after operation            | 26 (6.3)              | —                                    |       |
| Cancer staging                       | 24 (5.8)              | —                                    |       |
| Others                               | 164 (39.7)            | —                                    |       |
| Renal replacement therapy, n (%)     | 8 (1.9)               | 1 (1.0)                              | 0.70  |

Age is shown as mean (SD) and tumor diameter as median (25th percentile, 75th percentile).

* The numbers are duplicated.

CT, computed tomography; MRI, magnetic resonance imaging; US, abdominal ultrasonography; PET, positron emission tomography; PA, primary aldosteronism; SCS, subclinical Cushing’s syndrome; CS, Cushing’s syndrome; PC, pheochromocytoma

The duplicated cases in adrenal incidentaloma: 3 subjects with CS + PA, 4 subjects with possible SCS + PA

The duplicated cases in hypertension-associated adrenal tumor: 12 subjects with possible SCS + PA

*p < 0.05
Approximately 90% of AIs were detected using CT. Among 410 patients with AIs, patients with functioning tumors were less likely to be males (35.1% vs. 58.8%, p < 0.001) and more likely to have larger tumor diameters (2.4 [1.8, 3.2] vs. 1.7 [1.3, 2.3], p < 0.001) and had higher prevalence of HT (73.3% vs. 58.1%, p = 0.003) and DLP (59.5% vs. 47.0%, p = 0.017) than those with nonfunctioning tumors. In 104 patients with HT-associated adrenal tumors, patients with functioning tumors were younger (58.8 ± 12.2, p = 0.008), less likely to be male (27.3% vs. 58.8%, p < 0.001), and more likely to have larger tumor diameters (2.5 [2.0, 3.5] vs. 1.7 [1.3, 2.4], p < 0.001) and had a higher prevalence of HT (76.8% vs. 58.5%, p = 0.001) and DLP (61.6% vs. 47.6%, p = 0.017) than those with nonfunctioning tumors. In 104 patients with HT-associated adrenal tumors, patients with functioning tumors were younger (52.4 ± 11.2 vs. 58.4 ± 14.2, p = 0.041) than those with nonfunctioning tumors. These results were shown in Supplementary Table 3.

Of the 20 PA patients with AIs, 5 underwent AVS. Of the 61 PA patients with HT-associated adrenal tumors, 41 underwent AVS. The laterality of AVS was ipsilateral sides of the imaging tests in 60% of PA patients with AIs receiving AVS and 61.0% of those with HT-associated adrenal tumors receiving AVS.

**Discussion**

In this single-center survey, AIs were more frequently located on the left side of the adrenal gland, and general checkup was the most frequent purpose of imaging. Approximately 90% of AIs were detected using CT. Patients with HT-associated adrenal tumors were younger

| Table 2  | Clinical data of 410 patients with adrenal incidentaloma and 104 patients with hypertension-associated adrenal tumor with or without function |
|----------|-------------------------------------------------------------------------------------------------------------------------------------|
|          | Adrenal incidentaloma                                                                                                              |
|          | Nonfunctioning tumor | Functioning tumor | p  | Hypertension-associated adrenal tumor |
|          | 279 (68.0%) | 131 (32.0%) |  | Nonfunctioning tumor | Functioning tumor | p  |
| Age, years | 62.4 (12.3) | 59.9 (11.9) | 0.050 | 55.9 (14.6) | 53.7 (11.7) | 0.60 |
| Male, n (%) | 164 (58.8) | 46 (35.1) | <0.001 | 8 (32.0) | 40 (50.6) | 0.10 |
| Location of the tumor, n (%) | 0.091 | 0.61 |
| Right | 89 (31.9) | 42 (32.1) | 7 (28.0) | 23 (29.1) |
| Left | 165 (59.1) | 68 (51.9) | 17 (68.0) | 48 (60.8) |
| Bilateral | 25 (9.0) | 21 (16.0) | 1 (4.0) | 8 (10.1) |
| Tumor diameter, cm | 1.7 (1.3, 2.3) | 2.4 (1.8, 3.2) | <0.001 | 1.0 (0.8, 1.5) | 1.5 (1.0, 2.0) | 0.015 |
| Concomitant disease*, n (%) | | | | | | |
| Hypertension | 162 (58.1) | 96 (73.3) | 0.003 | 25 (100) | 79 (100) |
| Diabetes mellitus | 59 (21.1) | 36 (27.5) | 0.16 | 6 (24.0) | 8 (10.1) | 0.077 |
| Dyslipidemia | 131 (47.0) | 78 (59.5) | 0.017 | 15 (60.0) | 39 (49.4) | 0.35 |
| Cardiovascular disease | 16 (5.7) | 9 (6.9) | 0.65 | 0 (0.0) | 1 (1.3) | 0.99 |
| Cerebrovascular disease | 22 (7.9) | 8 (6.1) | 0.52 | 2 (8.0) | 8 (10.1) | 0.99 |

Age is shown as mean (SD) and tumor diameter as median (25th percentile, 75th percentile).

* The numbers are duplicated.

p < 0.05

Sensitivity analyses

When we used the inclusion criteria of ≥1 cm diameter for AIs, the number of eligible patients was 470, and the prevalence of PA in patients with AIs and in patients with HT-associated adrenal tumors were 4.9% and 59.3%, respectively. These results are shown in Supplementary Table 1.

The prevalence of definite SCS were 8.0% in patients with AIs and 1.9% in patients with HT-associated adrenal tumors (Supplementary Table 2).

The prevalence of PA diagnosed using the previous diagnostic criteria were 1.7% in patients with AIs and 0.5% in patients with HT-associated adrenal tumors (Supplementary Table 2).

The prevalence of SCS diagnosed using the previous diagnostic criteria were 7.3% in patients with AIs and 1.7% in patients with AIs receiving AVS, and 1.9% in patients with HT-associated adrenal tumors (Supplementary Table 2).
and had tumors with smaller diameters than patients with AIs. The prevalence of nonfunctioning tumors was lower and that of PA was higher in patients with HT-associated adrenal tumors than in those with AIs. Additionally, tumor diameters of functioning tumors were larger than those of nonfunctioning tumors in both patients with AIs and those with HT-associated adrenal tumors. To the best of our knowledge, this is the first and largest retrospective study comparing the clinical characteristics of patients with HT-associated adrenal tumors to those with AIs.

There have been few surveys about hormonal evaluations of patients with HT-associated adrenal tumors. Our study revealed that patients with adrenal tumors detected during secondary HT had a higher prevalence of PA than those with AIs, which may be attributable to the different prevalence of HT between the two types of tumors. The prevalence of PA is reportedly 1.4%–12.7% in patients with HT [8-12]; therefore, the hypertensive population is more likely to have PA than the non-hypertensive population. In our study, the prevalence of HT was higher in patients with adrenal tumors detected during secondary HT screening than in those with AIs, so our result was consistent with these facts. The prevalence of possible and definite SCS in patients with HT-associated adrenal tumors was similar to that in patients with AIs. This is partly due to the low prevalence of SCS in patients with secondary HT.

The tumor diameters were smaller in patients with HT-associated adrenal tumors than in those with AIs, and the higher prevalence of PA in patients with HT-associated adrenal tumors might have affected this result. In previous studies [3, 6, 13, 14], the tumor diameters of functioning tumors other than PA were larger than those of nonfunctioning tumors, while the tumor diameters of PA were smaller than those of nonfunctioning tumors. Additionally, when imaging tests for patients suspected of having PA were performed, clinicians and radiologists often over-diagnosed small adrenal nodules. Over-diagnosis of small adrenal nodules for patients with AIs might have affected the smaller diameter in patients with AIs detected during secondary HT screening.

The prevalence of nonfunctioning tumors was lower in the patients with HT-associated adrenal tumors than in those with AIs, and the patients with HT-associated adrenal tumors were younger than those with AIs. These were partly due to the fact that the patients with HT-associated adrenal tumors had examinations for secondary HT because they had uncontrolled HT or HT inappropriate for their age. Among patients with AIs, those with nonfunctioning tumors had an HT prevalence of ≥50%, which is compatible with 60 s in Japan [15]. This result was appropriate because the average age was 62.4 years in patients with nonfunctioning tumors among the patients with AIs.

The prevalence of PA in patients with AIs (4.8%) was comparable to that reported in three previous studies (1.6%–6.1%) [16-18], which excluded patients who underwent imaging investigations for secondary HT. In this study, the prevalence of PA using the previous diagnostic criteria (1.7%) was lower than when using the current diagnostic criteria; thus, the revision of diagnostic criteria for PA led to the higher prevalence of PA. We speculate that the inclusion of <1-cm AIs, which were excluded in several previous studies [14, 18-20], had little effect on the prevalence of PA because the prevalence of PA did not change substantially during sensitivity analysis (4.8% (Table 1) vs. 4.9% (Supplementary Table 1)).

The diagnostic criteria for PA in the previous studies [3, 6, 14, 16-23] did not require the confirmation of the functional localization and pathological diagnosis [24]; thus, some nonfunctioning tumors were possibly misdiagnosed as PA. Radiographically identified adrenal tumors are not always the source of PA, even when ipsilateral with adrenal vein sampling lateralization [25]. Since our diagnosis of PA did not require adrenal vein sampling either, the accurate prevalence of PA might have been lower. To determine the accurate prevalence of PA, we need to perform AVS and identify subtype of PA including unilateral and bilateral aldosterone-producing adenoma, idiopathic hyperaldosteronism, unilateral and bilateral aldosterone-producing microadenoma, unilateral adrenal hyperplasia, primary adrenal hyperplasia, and so on.

The prevalence of possible SCS in this study was higher than that of SCS in the national survey in Japan (16.0% vs. 2.5%) [3], and the prevalence of definite SCS, or that of SCS based on the previous diagnostic criteria for SCS in the patients with AIs in this study was also higher than that of SCS in the national survey in Japan (8.0%, 7.3% vs. 2.5%) [3]. These results may be attributed to the fact that physicians attending to patients with adrenal tumors are becoming increasingly knowledgeable about SCS in terms of its diagnosis and related examinations. In fact, the estimated number of patients with SCS has been increasing according to national surveys in Japan [26]. As evidence to support this inference, a national survey performed between 1992 and 1996 reported that the estimated number of patients with SCS was 290, while another survey performed between 2003 and 2007 reported that the estimated number of patients with SCS was 1,829 [26].

The prevalence of possible SCS was higher than that of definite SCS because the latter needed to satisfy more strict criteria (16.0% vs. 8.0%, Supplementary Table 2). Our criteria for possible SCS did not completely meet the revised Japanese diagnostic criteria of SCS [5].
because most AIs in this study were detected and examined before this revision. The diagnostic criteria revised in 2017 for SCS modified the cutoff value from 3.0 μg/dL to 1.8 μg/dL; thus, patients with a cortisol value ≥3 μg/dL (the previous cutoff value) after 1-mg DST underwent hospitalization for examinations to be evaluated for the small standards, while patients with the cortisol value of 1.8–3.0 μg/dL (the current extended cutoff value) after 1-mg DST did not undergo hospitalization. Therefore, in this study, patients were diagnosed as having possible SCS regardless of whether they met the small standards. Based on the above facts, the true prevalence of SCS in patients with AIs was supposed to be between the prevalence of possible SCS (16.0%) and that of definite SCS (8.0%) in this study.

These changes in a detection frequency and diagnostic criteria of SCS, cortisol cutoff value in 1-mg DST of 1.8 μg/dL from 3 μg/dL, may have a beneficial effect on the prognosis of patients with AIs because patients with SCS had reportedly an increased rate of coexistent diseases, such as HT and impaired glucose tolerance [27], as well as an increased risk of cardiovascular events and mortality [28]. The revision of the criteria for SCS may help clinicians to detect adrenal tumors secreting a smaller but nonnegligible amount of cortisol autonomously in patients with AIs, thereby preventing deterioration of concomitant diseases and improving prognosis for those patients.

Some patients were found to have both SCS or CS and PA in this study. Adrenal tumors producing both cortisol and aldosterone are not rare. Some previous studies reported that 10–20% of patients with PA had SCS [29-31]. In this study, there were 3 subjects with CS and PA, and 4 subjects with possible SCS (including 3 definite SCS) and PA among patients with AIs. There were 12 subjects with possible SCS (including 1 definite SCS) and PA among patients with HT-associated adrenal tumors. The prevalence of PA with CS or SCS in this study was similar to that in previous studies [29-31]. There were no adrenal tumors producing both catecholamines and cortisol or aldosterone in this study.

In this study, the proportion of left-sided tumors was greater than that of the right-sided tumors which is consistent with the results in several recent studies [3, 6, 17-22, 32]. However, more right-sided tumors were detected in the previous studies [14, 16]. This might be because the imaging modality could partly affect the locations of the tumors. In the study by Mantero et al. [16], AIs were detected using abdominal ultrasonography (US) in 71% of cases and using CT in 28% of cases. The left adrenal gland was reportedly more difficult to detect using abdominal US [33]. On the contrary, in recent studies, 70%-100% of AIs were detected using CT [3, 6, 17-21, 32]. Additionally, this observation may be due to detection bias attributed to the location of the right adrenal gland [32], as suggested by Hao M et al.

This study had some limitations. First, this was a cross-sectional study in a single center. However, the total population of this study included patients who underwent health checkup in the Center for Epidemiology and Preventive Medicine, the University of Tokyo Hospital, and patients referred by clinics and hospitals located in the Kanto region; therefore, this study may partly represent the clinical characteristics of AIs in the central region of Japan. Second, the patients in this study were not necessarily admitted to the hospital. If the whole population had undergone hospital admission for additional investigations, the prevalence of functioning tumors could have increased, which is considered to be an admission bias. Third, some patients might be misdiagnosed based on the simplified biochemical definition we used in this study and the lack of confirmation through functional localization or pathological diagnosis. Fourth, each endocrinologist established the clinical diagnoses of AIs and HT-associated adrenal tumors in this study, and therefore all patients did not undergo the same examinations. Fifth, we did not select patients with the registered disease name “secondary HT” in the medical records. We did not include all patients with adrenal tumors detected during secondary HT screening in those with HT-associated adrenal tumors. However, as we selected patients with measured urine metanephrines, we might not have significantly missed such patients. Finally, excluding patients with HT-associated adrenal tumors from those with AIs might induce selection bias. Imaging tests for secondary HT screening are performed to detect not only adrenal diseases but also other etiologies, such as renal parenchymal diseases, renal artery stenosis, and coarctation of the aorta, for secondary HT [8].

In conclusion, patients with HT-associated tumors were younger and had tumors with smaller diameters, lower prevalence of nonfunctioning tumors, and higher prevalence of PA than patients with AIs. Otherwise, there were no differences between the two groups. These results would be helpful in understanding the current status of clinical practice and diagnosis of AIs and HT-associated adrenal tumors.

**Disclosure**

None of the authors has any potential conflicts of interest associated with this study.
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