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Original Research

Expert Consensus on the Primary Aldosteronism Severity Classification and its strategic application in indicating adrenal venous sampling

Masanori Murakami,[1,*] Mitsuhide Naruse,[2,*] Hiroki Kobayashi,[3] Mirko Parasiliti-Caprino,[4] Fabio Bioletto,[4] Denise Brüdgam,[5] Isabel Stüfchen,[5] Martin Reincke,[5] Matthieu St-Jean,[6] Ivana Kraljevic,[7,8] Darko Kastelan,[7,8] Pasi I. Nevalainen,[9] Marta Araujo-Castro,[10] Norlela Sukor,[11,12] Michiel F. Nijhoff,[13] Joanna Matrozova,[14] Oskar Ragnarsson,[15,16] Zulfiya Shafigullina,[17] Niina Matikainen,[18] Athina Markou,[19] George Piaditis,[19] Shoichiro Izawa,[20] Takuyuki Katabami,[21] Takamasa Ichijo,[22] Akiyo Tanabe,[23] Mika Tsuiki,[24] Miki Kakutani,[25] Norio Wada,[26] Seizaburo Masuda,[27] Alessandra Violet Bacca,[28] Felix Beuschlein,[5,29,30] Giuseppe Maiolino,[31] Henrik Falhammar,[32,33] Marianne A. Grytaas,[34] Kristian Løvås,[34] Madson Q. Almeida,[35] Raluca Maria Furnica,[36] Troy Puar,[37,38] Piotr Kmieć,[39,40] Stefano Masi,[28] Isabelle Bourdeau,[41] Laurence Amar,[42,43] Michael Conall Dennedy,[44] Francesco Fallo,[31] Jaap Deinum,[45] Sam O'Toole,[46] Tetsuya Yamada,[1] Marcus Quinkler,[47] André Lacroix,[41] and Tomaz Kocjan[48,49]

[1]Department of Molecular Endocrinology and Metabolism, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo, Tokyo 113-8510, Japan
[2]Endocrine Center, Ijinkai Takeda General Hospital, Kyoto 601-1495, Japan
[3]Division of Nephrology, Hypertension, and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine, Tokyo 173-8610, Japan
[4]Division of Endocrinology, Diabetes and Metabolism, Department of Medical Sciences, University of Turin, Turin 10126, Italy
[5]Department of Medicine IV, University Hospital, Ludwig Maximilian University Munich, Munich 80336, Germany
[6]Division of Endocrinology, Department of Medicine, Centre intégré universitaire de santé et de services sociaux de l'Estrie - Centre hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec, Canada J1H 5N4
[7]Department of Endocrinology, University Hospital Centre Zagreb, Zagreb 10 000, Croatia
[8]School of Medicine, University of Zagreb, Zagreb 10 000, Croatia
[9]Endocrine Unit, Department of Internal Medicine, Tampere University Hospital, and Faculty of Medicine and Health Technology, Tampere University, Tampere 33521, Finland
[10]Department of Endocrinology and Nutrition, Hospital Universitario Ramón y Cajal, Madrid 28034, Spain
[11]Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Center (UKMMC), Cheras, Kuala Lumpur 56000, Malaysia
[12]Hospital Canselor Tuanku Muhriz, Jalan Yaacob Latif, Bandar Tun Razak, Kuala Lumpur 56000, Malaysia
[13]Department of Internal Medicine, Division of Endocrinology and Diabetes, Leiden University Medical Center, Leiden 2333 ZA, The Netherlands
[14]University Hospital of Endocrinology, Medical University, Sofia 1431, Bulgaria
[15]Department of Endocrinology, Sahlgrenska University Hospital, Gothenburg 413 45, Sweden
[16]Wallenberg Center for Molecular and Translational Medicine, University of Gothenburg, Gothenburg 405 30, Sweden
[17]Department of Endocrinology, North-Western State Medical University Named After I.I. Mechnikov, St. Petersburg 191015, Russia
[18]Endocrinology, Abdominal Center, Helsinki University Hospital and RPU Clinical and Molecular Medicine, University of Helsinki, Helsinki 00290, Finland
[19]Endocrinology Department and Diabetes Center, 'G. Gennimatas' General Hospital of Athens, Athens 11527, Greece
[20]Division of Endocrinology and Metabolism, Tottori University Faculty of Medicine, Yonago 683-8504, Japan
[21]Department of Metabolism and Endocrinology, St. Marianna University Yokohama Seibu Hospital, Yokohama 241-0811, Japan
[22]Department of Diabetes and Endocrinology, Saiseikai Yokohamashi Tobu Hospital, Yokohama 230-8765, Japan
[23]Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine, Tokyo 162-8655, Japan
[24]Department of Endocrinology and Metabolism, NHO Kyoto Medical Center, Kyoto 612-8555, Japan
[25]Department of Diabetes, Endocrinology and Clinical Immunology, School of Medicine, Hyogo Medical University, Nishinomiya, Hyogo 663-8501, Japan
[26]Department of Diabetes and Endocrinology, Sapporo City General Hospital, Sapporo 060-8604, Japan
[27]Department of Endocrinology and Metabolism, Kashiwa City Hospital, Kashiwa 277-0825, Japan

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[28]Department of Clinical and Experimental Medicine, University of Pisa, Pisa 56126, Italy
[29]Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich (USZ) and University of Zurich (UZH), Zurich 8091, Switzerland
[30]The LOOP Zurich—Medical Research Center, Zurich 8044, Switzerland
[31]Department of Medicine, Clinica Medica 3, University of Padova, Padova 35128, Italy
[32]Department of Endocrinology, Karolinska University Hospital, Stockholm 171 76, Sweden
[33]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm 171 76, Sweden
[34]Department of Medicine, Haukeland University Hospital, Bergen 5021, Norway
[35]Adrenal Unit, Laboratory of Molecular and Cellular Endocrinology LIM/25, Division of Endocrinology and Metabolism, Clinics Hospital & Cancer Institute of Sao Paulo State, University of Sao Paulo Medical School, Sao Paulo 01246-903, Brazil
[36]Department of Endocrinology and Nutrition, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels 1200, Belgium
[37]Department of Endocrinology, Changi General Hospital, Singapore 529889
[38]Medical ACP, Duke-NUS Medical School, Singapore 169857
[39]Department of Endocrinology and Internal Medicine, Medical University of Gdańsk, Gdańsk 80214, Poland
[40]Department of Endocrinology and Internal Medicine, University Clinical Center, Gdańsk 80214, Poland
[41]Endocrine Division, Department of Medicine, Centre hospitalier de l'Université de Montréal (CHUM), Montréal, Canada H2X 3E4
[42]Université Paris Cité, Inserm, PARCC, Equipe Labellisée par la Ligue contre le Cancer, Paris F-75015, France
[43]Hypertension Unit, Hôpital Européen Georges Pompidou, Assistance Publique—Hôpitaux de Paris, Paris F-75015, France
[44]Department of Endocrinology, University Hospital Galway, Galway H91 YR71, Ireland
[45]Department of Internal Medicine, Radboud University Medical Center, Nijmegen 6525 GA, Netherlands
[46]Department of Endocrinology, The Royal Hallamshire Hospital, Sheffield S10 2JF, United Kingdom
[47]Endocrinology in Charlottenburg, Berlin 10627, Germany
[48]Department of Endocrinology, Diabetes, and Metabolic Diseases, University Medical Centre Ljubljana, Ljubljana 1000, Slovenia
[49]Faculty of Medicine, University of Ljubljana, Ljubljana 1000, Slovenia

*Corresponding authors: Department of Molecular Endocrinology and Metabolism, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan. Email: mmurakami.mem@tmd.ac.jp (M.M.); Endocrine Center and Clinical Research Center, Ijinkai Takeda General Hospital, 28-1 Ishida moriminami-cho, Fushimi-ku, Kyoto 601-1495 Japan. Email: mtsnaruse@nifty.com (M.N.).

Abstract

Objective: Severity classifications are essential for many diseases to prioritize patient management tasks such as diagnosis, treatment, and follow-up. Primary aldosteronism (PA), a common cause of secondary hypertension, lacks a standardized severity scale despite generally requiring invasive diagnostics like adrenal venous sampling (AVS). This study aimed to develop a global expert consensus-based classification for PA severity to improve clinical decision-making.

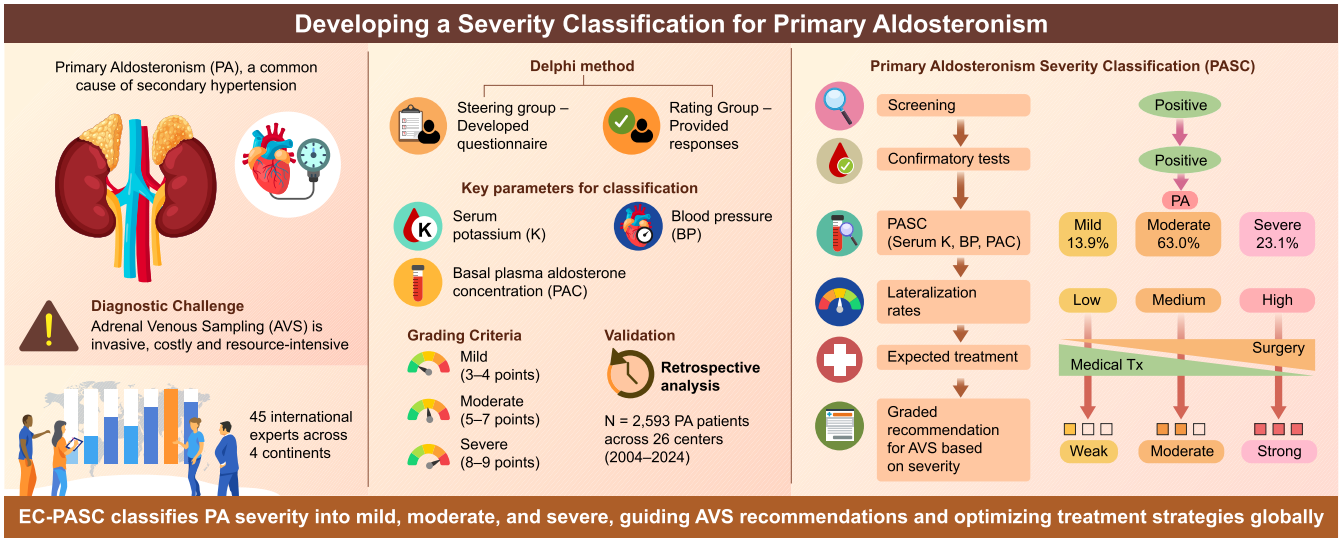
Methods: A panel of 45 international experts from 40 centers across four continents used the Delphi method to create a consensus severity classification for PA. This classification was then applied retrospectively to 2593 PA patients from 26 centers to assess its association with the disease subtype.

Results: After four rounds, the Primary Aldosteronism Severity Classification (PASC), which integrates biochemical and clinical parameters including serum potassium, blood pressure, and basal plasma aldosterone concentration, was established. Primary Aldosteronism Severity Classification classifies PA into mild (3 and 4 points), moderate (5-7 points), and severe (8 and 9 points). Among the cohort from 26 centers, 13.9%, 63.0%, and 23.1% were classified as mild, moderate, and severe, respectively, aligning with lateralized subtype prevalence rates of 14.7%, 44.6%, and 72.6%.

Conclusion: Primary Aldosteronism Severity Classification is a newly developed simplified, semi-quantitative classification of PA severity. The correlation between PASC and lateralized PA subtype supports its potential to provide graded recommendations of AVS prior to surgical indication in each patient.

Keywords: primary aldosteronism, hypertension, expert consensus, severity classification, adrenal venous sampling

Graphical Abstract



Significance Statement

Primary aldosteronism (PA) is a prevalent cause of secondary hypertension, with severity ranging from mild to severe. Adrenal venous sampling (AVS), the gold standard for subtype diagnosis, but faces challenges of patient burden due to invasiveness, cost, and limited availability. Here, we developed the Primary Aldosteronism Severity Classification through a Delphi consensus process involving 45 experts across 40 centers globally. Primary Aldosteronism Severity Classification integrates clinical and biochemical parameters to classify PA severity as mild, moderate, or severe, correlating with the likelihood of a lateralized subtype. We propose a severity-based, graded recommendation for AVS indication: weak for mild, moderate for moderate, and strong for severe cases. This framework could optimize PA management, improve diagnostic efficiency, and reduce patient burden.

Introduction

Primary aldosteronism (PA) is a prevalent cause of secondary hypertension and its manifestations might vary from mild to severe clinical manifestations, occasionally requiring immediate medical attention (ie, in the case of severe hypokalemia or severe blood pressure elevation). Experts in endocrinology or adrenal diseases currently use clinical skills empirically developed from their experience to evaluate the patient's clinical presentation, assess its severity and diagnostic and treatment strategies. Since many hypertensive patients are treated by general physicians, clinical guidelines have been developed to standardize care. These guidelines outline patient screening, confirmatory testing, subtype diagnosis, and treatment options like adrenalectomy or mineralocorticoid receptor antagonists (MRAs)-based medication.[1-4]

Once diagnosis of PA has been reached through confirmatory testing, the subsequent step in the management of the disease is to decide whether the patient would require surgery or only medical therapy. This decision depends on whether aldosterone hypersecretion is caused by lateralized or bilateral adrenal disease. While computed tomography (CT) scans usually help answer this, small adenomas or bilateral hyperplasia may not be detectable. Additionally, CT's diagnostic value is limited due to the high frequency of adrenal incidentalomas.[5] As a result, adrenal venous sampling (AVS) is recommended in almost all cases as the criterion standard for subtype diagnosis.[1-4] However, AVS is an invasive procedure associated with various challenges, including limited availability, technical difficulties, healthcare costs, radiation exposure, and the complexity of result interpretation. Moreover, as demonstrated in the AVSTAT study, many cases undergoing AVS are bilateral, and even unilateral cases often subjected to targeted medication.[6] Although it is generally recognized that bilateral involvement is more common in milder cases, and lateralized involvement is more common in severe cases,[7] standardized severity classification has not yet been established. This is an important issue as the presence of severity classification might support recommendation with graded strength for AVS.

Through the current ES-PASC project of gathering opinions and achieving expert consensus, we propose a severity classification of PA, with the scope of refining and enhancing the quality of clinical practice for PA, supporting clinicians in their clinical decisions and standardize the approach to PA patients across multiple countries. The survey summarized the opinions of experts from referral centers in the European Network for the Study of Adrenal Tumors (ENS@T) and Japan as the Expert Consensus on the Primary Aldosteronism Severity Classification (EC-PASC).

Methods

Using the Delphi method, we conducted the EC-PASC study as a multinational, multicenter questionnaire-based survey. The project was proposed at the ENS@T meeting in October 2023, and a total of 40 centers from four continents (Europe, North America, South America, and Asia) affiliated with ENS@T were recruited. The steering and the rating groups were formed (Table S1). The steering group developed and delivered questionnaires to the rating group, collecting participants' answers and comments. The steering group aggregated the experts' opinions and, when opinions diverged, further questions were developed to include all different views and reach points of agreement in subsequent rounds. Through these repeated rounds, opinions gradually converged, and consensus was formed based on the majority vote. In October 2023, a Google Forms survey was conducted to establish a severity classification concept, assessing expert views on its importance, class count, taxonomy, and classification factors. The responses informed Round 2 (December 2023), where additional questions focused on timing, variable combinations, and grading methods for serum potassium, hypertension, and aldosterone status. Round 3 (January 2024) refined these grading details based on expert feedback. By March 2024, the steering group finalized the severity classification, integrating feedback on managing additional factors collected up to Round 4. The details of the questionnaires are described elsewhere (Table S2).

Application of EC-PASC to the cohort of PA patients

Among the participating centers, 26 centers from Europe, North and South America, Southeast Asia, and Japan provided data in response to our request. The data were collected within the prospective registries, with the information gathering period ranging from January 2004 to June 2024 and analyzed retrospectively in each center. PA was diagnosed in accordance with guidelines[1-4] in each center. A correlation between the PASC and the subtype diagnosis was investigated in PA patients with lateralized diagnosis, based on the protocol of individual center (Table S3). A commonly recommended parameter for lateralization is the AVS lateralization index, which is calculated as the ratio of aldosterone to cortisol concentrations in the dominant adrenal vein compared to the nondominant adrenal vein, measured with or without ACTH stimulation. Approval from local ethics committees was obtained to analyze patient data in all centers. The differences in lateralized proportions among the forms of PASC were analyzed using the Kruskal–Wallis test, followed by post hoc Bonferroni analysis to account for their skewed distribution. The study was conducted in accordance with the principles

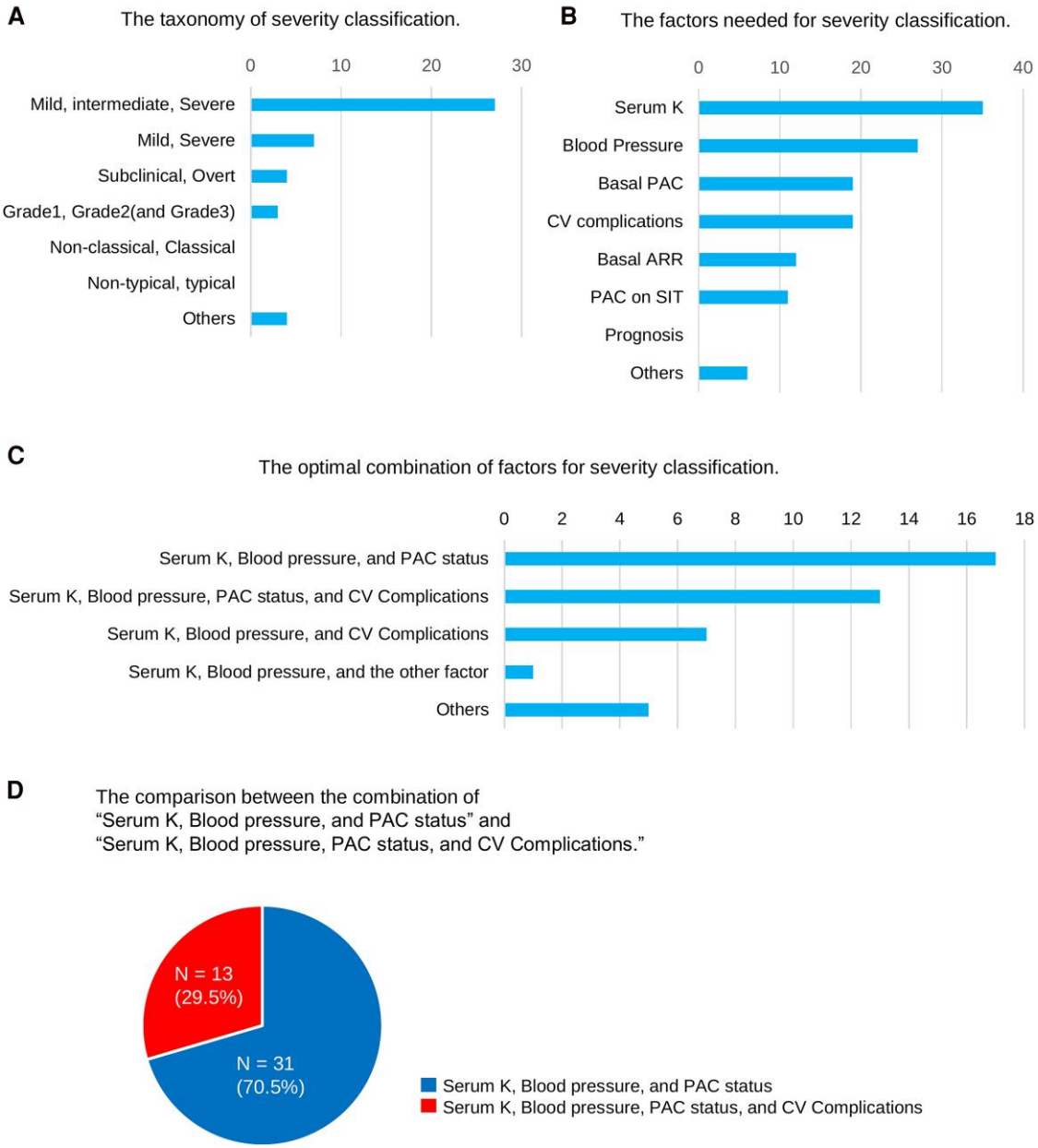


Figure 1. Questionnaires results: the taxonomy of severity classification (A), the factors needed for severity classification (B), the optimal combination of factors for severity classification (C), the comparison between the combination of "Serum K, Blood pressure, and PAC status" and "Serum K, Blood pressure, PAC status, and cardiovascular complications (D)".

of the Declaration of Helsinki. The overall coordination of the study was reviewed and approved by the ethics committee of Ijinkai Takeda General Hospital (Kyoto, Japan).

Results

The basic concept of severity classification

Initially, we inquired from the experts whether establishing severity criteria is beneficial for the clinical practice of PA. The majority of respondents supported the concept of developing PA severity criteria (95%, $n = 38$). Further questions concerned the appropriate number of severity classes, the timing of criteria use and its taxonomy. Half of the respondents ($n = 20$) selected one category of severity classification (Figure S1A). The majority supported applying it "after a positive confirmatory test" (79.1%, $n = 34$, Figure S1B) and dividing it into "mild, intermediate, severe" (60%, $n = 27$, Figure 1A). It was subsequently suggested to use "moderate" instead of "intermediate" severity. This terminology change was accepted.

Factors for classification

The factors selected as necessary for the severity classification were serum potassium (K) levels (87.5%, $n = 35$), blood pressure (BP) (67.5%, $n = 27$), basal plasma aldosterone concentration (PAC) (47.5%, $n = 19$), and history of cardiovascular complications (47.5%, $n = 19$) (Figure 1B). Other responses included cortisol co-secretion, renin suppression, CT findings, duration of hypertension, 24-hour urinary aldosterone excretion, and urinary albumin excretion. Subsequently, the optimal combination of

Table 1. Primary Aldosteronism Severity Classification (PASC).

Factors		Grade of each factor				
		Grade I (1 point)	Grade II (2 points)	Grade III (3 points)	Point for each factor	Total points
Serum K[a]		K > 3.5 mEq/L	3.0 ≤ K ≤3.5 mEq/L	K < 3.0 mEq/L	1-3	
Basal PAC[b]		60 ≤ PAC <100 pg/mL (166 ≤ PAC <277 pmol/L)	100 ≤ PAC <200 pg/mL (277 ≤ PAC <555 pmol/L)	PAC ≥200 pg/mL (PAC ≥555 pmol/L)	1-3	
Blood pressure	Untreated[c]	SBP: 140-159 mmHg and/or DBP: 90-99 mmHg	SBP: 160-179 mmHg and/or DBP: 100-109 mmHg	SBP ≥180 mmHg and/or DBP ≥110 mmHg		3-9
	Treated[d]	Controlled by 1-2 antihypertensive drug(s)	Controlled by 3 antihypertensive drugs or uncontrolled by 1-2 drug(s)	Controlled by more than 3 or uncontrolled by 3 or more antihypertensive drugs	1-3	

Total points (3-9)	PA severity classification (PASC)[e]
3, 4	Mild
5-7	Moderate
8, 9	Severe

Abbreviations: DBP, diastolic blood pressure; K, potassium; PAC, plasma aldosterone concentration; SBP, systolic blood pressure.
[a]Determined with the lowest value without potassium supplementation.
[b]PAC unit was converted from 60, 100, and 200 pg/mL to 166, 277, and 555 pmol/L, respectively (1000 pmol/L = 360.45 pg/mL, http://unitslab.com/). An average of 2-3 values is recommended if PAC shows significant variability.
[c]Untreated: untreated with antihypertensive drugs including diuretics and MR antagonists. If blood pressure is high normal, the patient is included as Grade I for convenience. If the patient is diagnosed as "normotensive PA", blood pressure is categorized as Grade I.
[d]Treated: treated with antihypertensive drugs including diuretics and MR antagonists. Controlled: SBP <140 mmHg and DBP <90 mmHg. Uncontrolled ≥140 mmHg and/or DBP ≥90 mmHg.
[e]If low-dose dexamethasone suppression test is performed and positive, consider it as a contributing indicator of severity.

factors for severity classification was determined based on the four most popular responses. The most supported combinations consisted of serum K, BP, and PAC status (39.5%, $n = 17$, Figure 1C). The second most voted was these three factors with the addition of cardiovascular complications (30.2%, $n = 13$). In the next round, these two options were compared and the majority selected the combination that did not include cardiovascular complications as a factor (70.5%, $n = 31$, Figure 1D).

Grading methods for serum potassium

When asked about grading hypokalemia, a three-tiered classification received majority support (53.5%, $n = 23$), followed by a two-tiered classification which obtained 30.2% support ($n = 13$, Figure S2A). Of these two approaches, when directly compared, the three-tiered classification received majority support (59.1%, $n = 26$, Figure S2B).

Grading methods for hypertension, with and without antihypertensive medication

In order to provide consistency with existing hypertension guidelines (ESH/ISH/ERA),[8] classification without antihypertensive agents was proposed as follows (SBP, systolic BP; DBP, diastolic BP): "Grade I: SBP 140-159 mmHg and/or DBP 90-99 mmHg, Grade II: SBP 160-179 mmHg and/or DBP 100-109 mmHg, Grade III: SBP ≥180 mmHg and/or DBP ≥110 mmHg (Table S4A)." Since some PA cases with normal BP exist, cases with BP below Grade I were classified as Grade I for convenience. A dedicated survey also considered the severity classification of blood pressure whilst on antihypertensive medication. The number of drugs used and whether BP was controlled or uncontrolled were considered. There was discussion about including MRAs, given they are directed treatments for PA. MRAs may influence the severity grading of hypertension, however, assessing their efficacy individually for each patient or categorizing them in detail within each grade was considered impractical. Therefore, despite their potential impact on grading, MRAs were considered as one of the medications for convenience. The final classification was determined as follows: Grade I: controlled by 1-2 antihypertensive drugs; Grade II: controlled by three antihypertensive drugs (including uncontrolled by 1-2 drugs); Grade III: controlled by more than three or uncontrolled by three or more antihypertensive drugs (Table S4B).

Grading methods for aldosterone

The most appropriate categories reflecting aldosterone status were requested, and basal PAC received the majority support at 53.5% ($n = 23$, Figure S3A) among basal PAC, basal aldosterone renin ratio, and PAC following a saline infusion test (SIT). The classification into three grades was favored (81.8%, $n = 36$) compared to the two grades. Regarding the cut-off settings for basal PAC, two methods were proposed: one using absolute numerical values and the other using the upper limit of normal (ULN). The classifications were as follows: "Grade I: 60 ≤ PAC <100 pg/mL (166 ≤ PAC <277 pmol/L), Grade II: 100 ≤ PAC <200 pg/mL (277 ≤ PAC <555 pmol/L), Grade III: PAC ≥ 200 pg/mL (PAC ≥ 555 pmol/L)," and "Grade I: from half the ULN to the ULN, Grade II: from the ULN to twice the ULN, Grade III: more than double the ULN." Despite comments about its susceptibility to fluctuations, the classification method using absolute numerical values was supported by 69.4% ($n = 25$) and was adopted (Figure S3B).

Additional factors

Whether the presence of cortisol co-secretion and/or an adrenal tumor on CT, if available at the time of PA diagnosis, could be used as supplemental reference findings for severity classification became a topic of discussion. Previous studies indicated that cortisol co-secretion is associated with poor

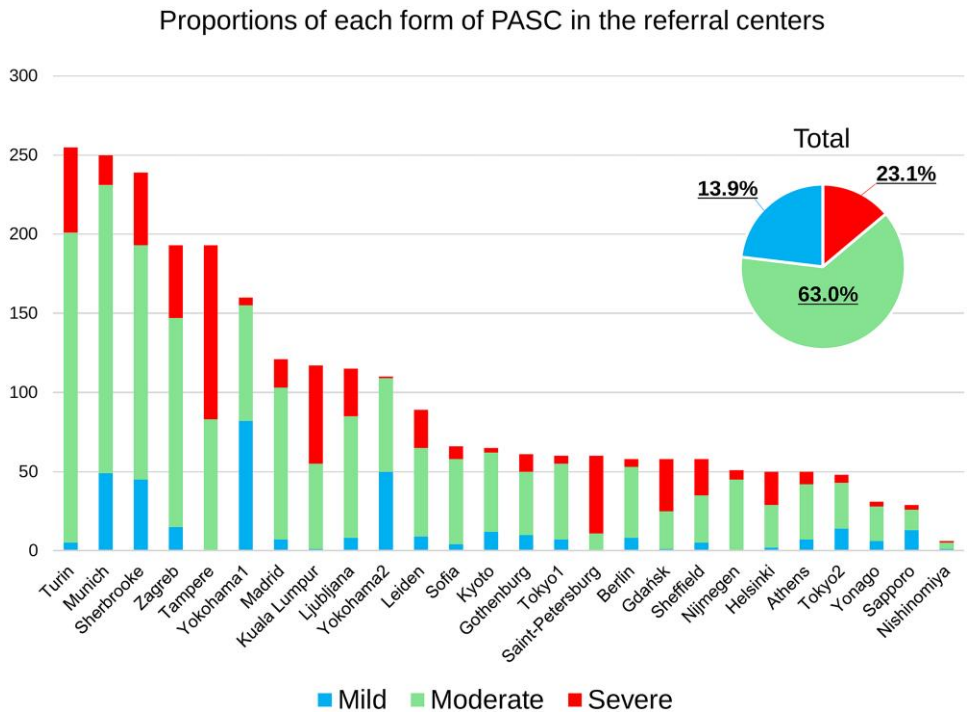


Figure 2. Proportions of each form of PASC in the referral centers. The results are sorted in order of the total number of cases.

postoperative clinical outcomes,[9-11] suggesting its relevance to severity. However, the low-dose dexamethasone suppression test evaluating cortisol co-secretion is not performed in routine clinical practice of PA and, therefore, is not included currently as a scoring factor. It should be considered as a significant feature contributing to severity, if it is conducted and results are positive. No experts explicitly advocated for the utilization of CT findings.

Generation of EC-PASC

Once each contributing factor was agreed upon, a scoring system was proposed that gave a total score between 3 and 9, scoring 1 to 3 points for each of the three constituents, serum potassium, blood pressure, and basal PAC (Table 1). This proposal received majority approval (85.7%, $n = 36$).

Validation of EC-PASC

To verify the clinical utility of the severity classification, we examined the distribution of severity categories and their correlation with PA subtypes in patients ($n = 2593$) across various centers. Overall, the distribution of PA severity was 13.9% for mild ($n = 361$), 63.0% for moderate ($n = 1633$), and 23.1% for severe ($n = 599$) PA classification, and combined mild and moderate cases accounted for 76.9% ($n = 1994$) of the total (Figure 2, Table S5A). Among the 361 cases of mild PA (13.9%), there was significant variability across the various facilities. Facilities such as Tampere, Saint-Petersburg, and Nijmegen reported no mild cases. In contrast, Japanese facilities, such as Yokohama1, Yokohama2, and Sapporo, reported that nearly half of their cases were classified as mild (51.3%, 45.5%, and 44.8%, respectively, Figure 2, Table S5A). Among the cases with subtype diagnosis ($n = 1910$) the proportion of lateralized cases increased with PA severity score; 14.7% in mild, 44.6% in moderate, and 72.6% in severe (Figure 3A–C, Table S5B). Significant differences were observed between the mild and moderate forms ($P = 3.20 \times 10^{-4}$), the moderate and severe forms ($P = 6.09 \times 10^{-5}$), and the mild and severe forms ($P = 2.10 \times 10^{-6}$, Figure 3D). Among the mild cases ($n = 245$), only 36 were classified as lateralized, accounting for 1.9% of the total cases with subtype diagnosis. In Japan, eight centers had a high number of mild case diagnoses with AVS ($n = 139$), constituting 56.7% of the mild cases of successful AVS. However, only two of these were diagnosed as lateralized. On the other hand, facilities with a high lateralized rate in mild cases might have focused on diagnosing and performing AVS on a limited number of cases suspected to be lateralized, potentially leading to overestimating its rate in mild cases.

Discussion

Assessing disease severity plays a crucial role in diagnosis and individualized decision-making. Primary aldosteronism is primarily categorized into lateralized subtype, mostly due to aldosterone-producing adenoma (APA) and bilateral subtype, characterized by bilateral aldosterone-producing lesions in both adrenal glands, such as bilateral aldosterone-producing adenomas, bilateral multiple aldosterone-producing micronodules, and, rarely, bilateral aldosterone-producing diffuse hyperplasia.[12] APA is associated with a higher frequency of hypokalemia and greater aldosterone secretion, suggesting that clinical severity is likely to be correlated with subtype. As recommended indicators for AVS, the presence of tumors and hypokalemia have been proposed.[13] These indicators are useful for predicting PA subtypes, but until now, there have been no reports on a method for grading the recommendation for further investigation, specifically AVS indications, according to the clinical severity of PA. In the present study, we have developed a novel PA severity classification (PASC)

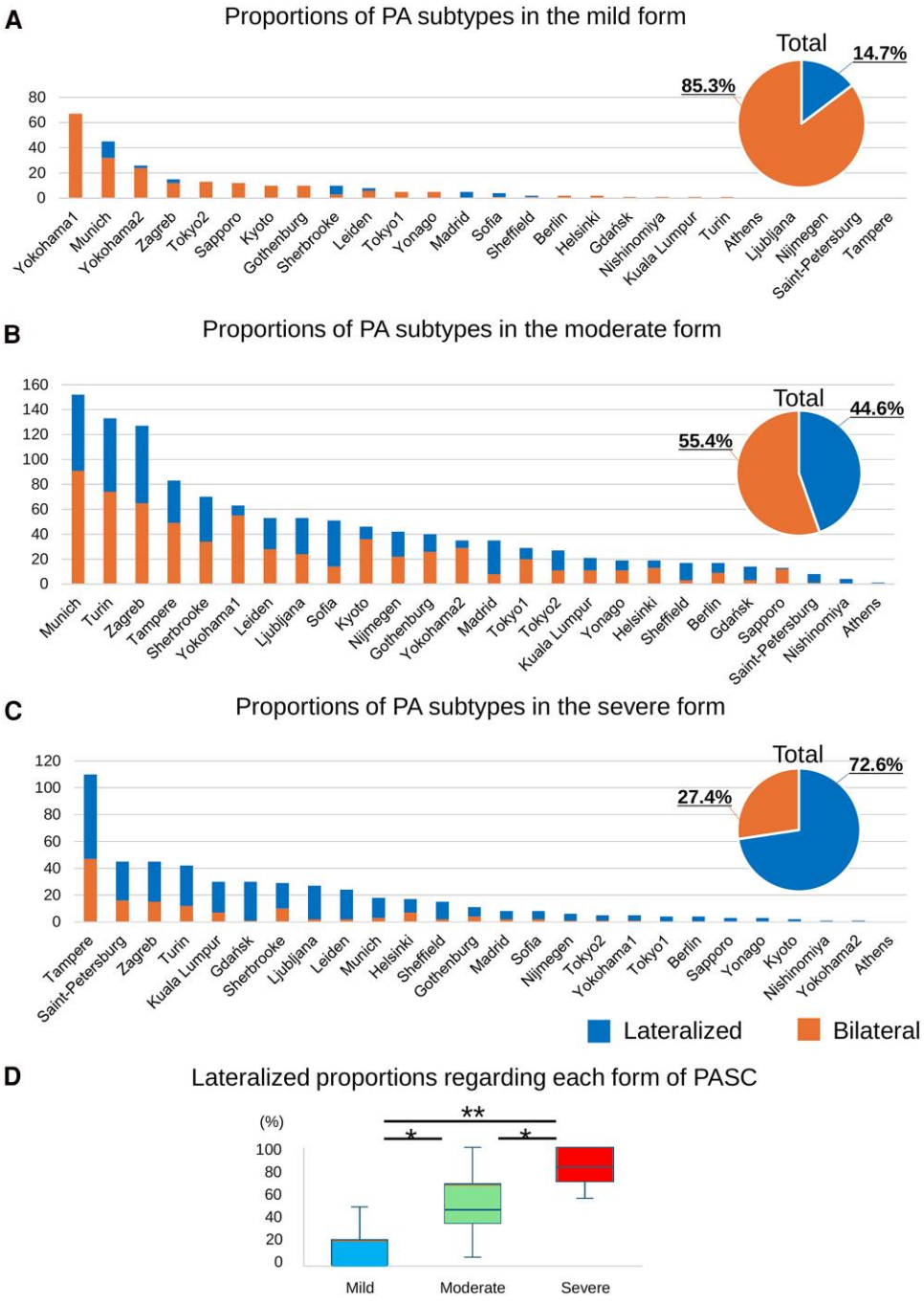


Figure 3. Proportions of PA subtypes in the mild (A), moderate (B), and severe (C) forms of PASC in the referral centers. The results are sorted in order of the total number of cases for each form. Comparison of lateralized proportions among each form of PASC (D). The Kruskal–Wallis test followed by *post hoc* Bonferroni analysis was used for statistical analysis. $*P < 5.0 \times 10^{-4}$; $**P < 5.0 \times 10^{-6}$.

through a Delphi Consensus of experts from multiple global centers. The priority was to make the classification easy to apply in daily clinical practice of hypertension, and the following two points were considered important: (1) Even with the same diagnosis of PA, it is necessary to further refine the selection of investigation and treatments according to severity, making establishing severity classification a crucial first step. (2) It can offer objective, severity-based evidence to guide whether to recommend AVS in preparation for surgical treatment or to prioritize medication avoiding invasive procedures.

The top three factors selected in the severity classification were serum K, BP, and PAC status. Hypokalemia is a characteristic feature of the more severe forms of PA, although its prevalence has been relatively low as less severe cases are detected; hypokalemia received the highest support as a factor in severity criteria. Existing evidence strongly supports its use in scoring systems to predict lateralized PA.[14-19]

BP grading without medication was based on existing guidelines. As the concept of "normotensive PA" has gained recognition,[20] it was categorized as Grade I. For grading BP under medication, the number of antihypertensive drugs used was considered. To avoid complexity in the clinical scoring system for general physicians, specifics regarding the types and quantities of antihypertensive drugs have not been detailed in

PASC. For the same reason, MRAs have been included as one of the antihypertensive agents.

The majority of experts favored basal PAC as the primary index for aldosterone status in severity classification, followed by PAC on SIT. While PAC on SIT is a more accurate indicator of aldosterone excess,[21] its not universally conducted as a confirmatory test,[22] limiting the utility of a classification system. Regarding aldosterone status, some experts pointed out concerns regarding the fluctuation of PAC.[23-25] We should be aware of this possible influence on the severity grading. The average of repeated determinations might improve the accuracy of PAC values. However, this is an issue also in the case detection and confirmatory testing, and there is no definite evidence for how many determinations of PAC are essential and recommended. Thus, PAC determined under generally recommended conditions is used to grade the severity. We will provide a footnote that an average of 2-3 values is recommended if PAC shows significant variability based on the physicians' discretion.

Opinions were divided on whether to include cardiovascular complications as a factor in the severity assessment. Establishing a direct cause-and-effect relationship between cardiovascular complications and PA poses challenges. Therefore, some experts strongly oppose including cardiovascular complications in the severity classification due to the risks of factual misinterpretation. Generally, severity assessments are often linked to predict prognosis and complications. Cardiovascular complications may be more appropriately evaluated as an outcome of severity rather than a component of severity itself. The three factors adopted in this classification reflect excess aldosterone at the time of diagnosis. Assessing the extent to which cardiovascular complications, which are also influenced by disease duration, correlate with PASC remains a future challenge.

Measurements of biochemical and clinical parameters should ideally adhere to established and standardized methods; however, a consensus-building process was not feasible due to the diversity among the centers and the design of the current study. In this respect, the measurement of BP is the same as that of biochemical and clinical parameters. However, it is strongly expected that BP measurements accord with the ESH/ISH/ERA Guidelines[8] for the management of arterial hypertension in all participating centers.

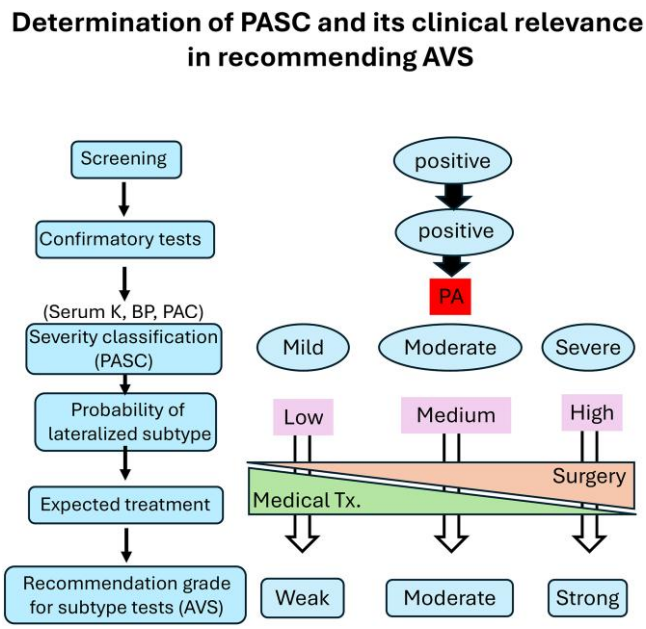


Figure 4. Proposal for the strategic application of PASC in the management of PA.

In recent years, as our understanding of PA has deepened, concepts like mild phenotype or subclinical PA—characterized by the absence of severe hypokalemia or hypertension—have emerged. Some studies suggest that even mild increases in aldosterone within physiological ranges could risk hypertension development.[26,27] A continuum of renin-independent aldosterone production linked to hypertension severity is now recognized.[28-31] However, definitions of mild PA vary, with terms like "early stage PA,"[32,33] "subclinical PA,"[28,34-36] and "autonomous aldosterone production"[37] being used. While some studies highlight its prevalence[38,39] and bilateral nature,[19] others note that mild PA may not increase the atherosclerotic burden or arterial stiffness beyond that observed essential hypertension.[40] The international inconsistency in diagnosing PA complicates the definition of a mild phenotype,[22] underscoring the need for further investigation and a standardized approach, such as we propose here with PASC.

In this study a severity classification for PA using three simple indicators, namely serum K, BP, and PAC was formulated. As a result of analyzing a total of 2593 cases with PA from 26 centers around the world, it was demonstrated that mild and moderate cases combined accounted for 76.9% of the total. Next, the subtyping (lateralized cases) cases by AVS at each center was investigated. In severe cases, the lateralized rate was the highest at 72.6%, followed by moderate form at 44.6% and mild form at 14.7%. The first choice of treatment for PA is adrenalectomy in unilateral or lateralized asymmetric severe cases, and drug therapy mainly uses MRAs in bilateral symmetric cases. Whilst AVS is central to determining lateralization, there are numerous issues with AVS, such as its invasiveness, so a rational basis is required for deciding whether to perform it. As this analysis showed a clear correlation between the severity classification score and the lateralized rate, we propose a graded recommendation based on PASC for the indication of AVS: weakly recommended for the mild form, moderately recommended for the moderate form, and strongly recommended for the severe form. When applying a test that is important for diagnosis but at the same time has drawbacks in terms of invasiveness and availability, adding a gradient based on severity by PASC to the recommendation level can have clinical significance in improving the quality of PA medical care and determining treatment policies (Figure 4). Hypertension is a common condition, especially in primary care settings. The increased use of screening tests often leads to more patients requiring further evaluation for PA. However, there are limited facilities and experts available to perform AVS, an invasive procedure despite its high success rate. Therefore, it would be beneficial to establish criteria that can help primary and secondary care physicians determine when to refer patients to specialized medical centers for AVS. This approach can help alleviate unnecessary burdens on patients with bilateral PA.

A limitation of our study is the significant variability between centers in the implementation rates for conducting confirmatory tests on screening positive cases, and in the rates for performing AVS in mild cases. These inter-institutional differences may have influenced the proportion of mild cases and the

lateralized ratio in AVS results. For example, in Japan, a nationwide PA registry (JPAS) facilitated the collection of evidence,[4] including subtype diagnosis, leading to proactive diagnosis and AVS implementation even for clinically mild cases. Consequently, the eight Japanese centers reported around half of all mild cases and almost two thirds of all mild cases who underwent AVS. In contrast, data from other centers showed lower rates of mild case diagnosis and AVS implementation, which may result in bias and an overestimation of the lateralized ratio in mild cases. Differences in the ethnicity and the details of the guidelines between countries could be other factors affecting the proportion of the PASC and subtype diagnosis. It is also true that variability exists among centers in the diagnostic criteria used for AVS. This variability is shaped by the experience, perspectives, and measurement methods of each center and expert, complicating efforts toward international standardization. Consequently, subtype diagnosis often relies on local criteria. Nevertheless, our multicenter analysis revealed a clear correlation between PASC and lateralized diagnosis, highlighting its clinical relevance. Additionally, severity assessment is generally used to predict disease prognosis and complications. While the PASC established in this study is meaningful as a grading system for AVS recommendations, it is essential to evaluate its association with cardiovascular complications, the internationally recognized postoperative remission criteria,[41] and the pathological classification system (HISTALDO)[42] in a prospective cohort study.

Conclusion

Primary Aldosteronism Severity Classification is a newly developed simplified, semi-quantitative classification of PA severity, PASC, based on universal biochemical and clinical parameters. As a clear correlation was found between the PASC and the probability of lateralized PA, this classification could be very beneficial for the primary physicians in considering whether to prioritize AVS with surgery in mind or the treatment with MRAs.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

Masanori Murakami (Conceptualization [lead], Data curation [lead], Formal analysis [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Visualization [lead], Writing—original draft [lead]), Mitsuhide Naruse (Conceptualization [lead], Data curation [equal], Formal analysis [equal], Funding acquisition [lead], Investigation [lead], Methodology [lead], Project administration [lead], Resources [lead], Supervision [lead], Validation [equal], Visualization [equal], Writing—original draft [lead]), Writing—review & editing [equal]), Hiroki Kobayashi (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Supervision [equal], Validation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Mirko Parasiliti-Caprino (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Fabio Bioletto (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Denise Brüdgam (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Validation [equal], Writing—review & editing [equal]), Isabel Stuefchen (Data curation [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Resources [equal], Validation [equal], Writing—review & editing [equal]), Martin Reincke (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Matthieu St-Jean (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Ivana Kraljevic (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—review & editing [equal]), Darko Kastelan (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Pasi Nevalainen (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Marta Araujo-Castro (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Norlela Sukor (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Michiel Nijhoff (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal],

Validation [equal], Writing—review & editing [equal]), Joanna Matrozova (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Oskar Ragnarsson (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Zulfiya Shafigullina (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Niina Matikainen (Data curation [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Athina Markou (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Georgios Piaditis (Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Shoichiro Izawa (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Takuyuki Katabami (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Takamasa Ichijo (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Akiyo Tanabe (Data curation [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Mika Tsuiki (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Miki Kakutani (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Norio Wada (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Seizaburo Masuda (Data curation [equal], Investigation [equal], Methodology [equal]), Alessandra Bacca (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Felix Beuschlein (Data curation [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Giuseppe Maiolino (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Henrik Falhammar (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Marianne Grytaas (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Kristian Løvås (Data curation [equal], Resources [equal], Supervision [equal], Writing—review & editing [equal]), Madson Almeida (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Raluca-Maria Furnica (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Troy Puar (Data curation [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Piotr Kmiec (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Stefano Masi (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Isabelle Bourdeau (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Laurence Amar (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Michael Dennedy (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Francesco Fallo (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Jaap Deinum (Data curation [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Samuel O'Toole (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Tetsuya Yamada (Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Marcus Quinkler (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), Andre Lacroix (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal]), and Tomaz Kocjan (Data curation [equal], Investigation [equal], Methodology [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal])

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Data availability

The data that support the findings of this study are available on request from the corresponding author.

References

1. Funder JW, Carey RM, Mantero F, *et al.* The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016;101(5):1889-1916. https://doi.org/10.1210/jc.2015-4061
2. Rossi GP, Bisogni V, Bacca AV, *et al.* The 2020 Italian Society of Arterial Hypertension (SIIA) practical guidelines for the management of primary aldosteronism. *Int J Cardiol Hypertens*. 2020;5:100029. https://doi.org/10.1016/j.ijchy.2020.100029
3. Mulatero P, Monticone S, Deinum J, *et al.* Genetics, prevalence, screening and confirmation of primary aldosteronism: a position

statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. *J Hypertens*. 2020;38(10):1919-1928. https://doi.org/10.1097/HJH.0000000000002510
4. Naruse M, Katabami T, Shibata H, *et al.* Japan Endocrine Society clinical practice guideline for the diagnosis and management of primary aldosteronism 2021. *Endocr J*. 2022;69(4):327-359. https://doi.org/10.1507/endocrj.EJ21-0508
5. Fassnacht M, Tsagarakis S, Terzolo M, *et al.* European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol*. 2023;189(1):G1-G42. https://doi.org/10.1093/ejendo/lvad066
6. Ohno Y, Naruse M, Beuschlein F, *et al.* Adrenal venous sampling-guided adrenalectomy rates in primary aldosteronism: results of an international cohort (AVSTAT). *J Clin Endocrinol Metab*. 2021;106(3):e1400-e1407. https://doi.org/10.1210/clinem/dgaa706
7. Naruse M, Tanabe A, Yamamoto K, *et al.* Adrenal venous sampling for subtype diagnosis of primary hyperaldosteronism. *Endocrinol Metab (Seoul)*. 2021;36(5):965-973. https://doi.org/10.3803/EnM.2021.1192
8. Mancia G, Kreutz R, Brunstrom M, *et al.* 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens*. 2023;41(12):1874-2071. https://doi.org/10.1097/HJH.0000000000003480
9. Murakami M, Rhayem Y, Kunzke T, *et al.* In situ metabolomics of aldosterone-producing adenomas. *JCI Insight*. 2019;4(17):e130356. https://doi.org/10.1172/jci.insight.130356
10. Peng KY, Liao HW, Chan CK, *et al.* Presence of subclinical hypercortisolism in clinical aldosterone-producing adenomas predicts lower clinical success. *Hypertension*. 2020;76(5):1537-1544. https://doi.org/10.1161/HYPERTENSIONAHA.120.15328
11. Jiang Y, Zhou L, Zhang C, *et al.* The influence of cortisol co-secretion on clinical characteristics and postoperative outcomes in unilateral primary aldosteronism. *Front Endocrinol (Lausanne)*. 2024;15:1369582. https://doi.org/10.3389/fendo.2024.1369582
12. Williams TA, Gong S, Tsurutani Y, *et al.* Adrenal surgery for bilateral primary aldosteronism: an international retrospective cohort study. *Lancet Diabetes Endocrinol*. 2022;10(11):769-771. https://doi.org/10.1016/S2213-8587(22)00253-4
13. Umakoshi H, Tsuiki M, Takeda Y, *et al.* Significance of computed tomography and serum potassium in predicting subtype diagnosis of primary aldosteronism. *J Clin Endocrinol Metab*. 2018;103(3):900-908. https://doi.org/10.1210/jc.2017-01774
14. Kobayashi H, Haketa A, Ueno T, *et al.* Scoring system for the diagnosis of bilateral primary aldosteronism in the outpatient setting before adrenal venous sampling. *Clin Endocrinol (Oxf)*. 2017;86(4):467-472. https://doi.org/10.1111/cen.13278
15. Kupers EM, Amar L, Raynaud A, Plouin PF, Steichen O. A clinical prediction score to diagnose unilateral primary aldosteronism. *J Clin Endocrinol Metab*. 2012;97(10):3530-3537. https://doi.org/10.1210/jc.2012-1917
16. Nanba K, Tsuiki M, Nakao K, *et al.* A subtype prediction score for primary aldosteronism. *J Hum Hypertens*. 2014;28(12):716-720. https://doi.org/10.1038/jhh.2014.20
17. Kocjan T, Janez A, Stankovic M, Vidmar G, Jensterle M. A new clinical prediction criterion accurately determines a subset of patients with bilateral primary aldosteronism before adrenal venous sampling. *Endocr Pract*. 2016;22(5):587-594. https://doi.org/10.4158/EP15982.OR
18. Kamemura K, Wada N, Ichijo T, *et al.* Significance of adrenal computed tomography in predicting laterality and indicating adrenal vein sampling in primary aldosteronism. *J Hum Hypertens*. 2017;31(3):195-199. https://doi.org/10.1038/jhh.2016.61
19. Kobayashi H, Abe M, Soma M, *et al.* Development and validation of subtype prediction scores for the workup of primary aldosteronism. *J Hypertens*. 2018;36(11):2269-2276. https://doi.org/10.1097/HJH.0000000000001855
20. Markou A, Pappa T, Kaltsas G, *et al.* Evidence of primary aldosteronism in a predominantly female cohort of normotensive individuals: a very high odds ratio for progression into arterial hypertension. *J Clin Endocrinol Metab*. 2013;98(4):1409-1416. https://doi.org/10.1210/jc.2012-3353
21. Thuzar M, Young K, Ahmed AH, *et al.* Diagnosis of primary aldosteronism by seated saline suppression test-variability between immunoassay and HPLC-MS/MS. *J Clin Endocrinol Metab*. 2020;105(3):e477-e483. https://doi.org/10.1210/clinem/dgz150
22. Naruse M, Murakami M, Katabami T, *et al.* International multicenter survey on screening and confirmatory testing in primary aldosteronism. *Eur J Endocrinol*. 2023;188(1):125-134. https://doi.org/10.1093/ejendo/lvac002
23. Tanabe A, Naruse M, Takagi S, Tsuchiya K, Imaki T, Takano K. Variability in the renin/aldosterone profile under random and standardized sampling conditions in primary aldosteronism. *J Clin Endocrinol Metab*. 2003;88(6):2489-2494. https://doi.org/10.1210/jc.2002-021476
24. Yozamp N, Hundemer GL, Moussa M, *et al.* Intraindividual variability of aldosterone concentrations in primary aldosteronism: implications for case detection. *Hypertension*. 2021;77(3):891-899. https://doi.org/10.1161/HYPERTENSIONAHA.120.16429
25. Eisenhofer G, Kurlbaum M, Peitzsch M, *et al.* The saline infusion test for primary aldosteronism: implications of immunoassay inaccuracy. *J Clin Endocrinol Metab*. 2022;107(5):e2027-e2036. https://doi.org/10.1210/clinem/dgab924
26. Vasan RS, Evans JC, Larson MG, *et al.* Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med*. 2004;351(1):33-41. https://doi.org/10.1056/NEJMoa033263
27. Baudrand R, Guarda FJ, Fardella C, *et al.* Continuum of renin-independent aldosteronism in normotension. *Hypertension*. 2017;69(5):950-956. https://doi.org/10.1161/HYPERTENSIONAHA.116.08952
28. Brown JM, Robinson-Cohen C, Luque-Fernandez MA, *et al.* The spectrum of subclinical primary aldosteronism and incident hypertension: a cohort study. *Ann Intern Med*. 2017;167(9):630-641. https://doi.org/10.7326/M17-0882
29. Brown JM, Siddiqui M, Calhoun DA, *et al.* The unrecognized prevalence of primary aldosteronism: a cross-sectional study. *Ann Intern Med*. 2020;173(1):10-20. https://doi.org/10.7326/M20-0065
30. Mehdi A, Rao P, Thomas G. Our evolving understanding of primary aldosteronism. *Cleve Clin J Med*. 2021;88(4):221-227. https://doi.org/10.3949/ccjm.88a.20166
31. Vaidya A, Hundemer GL, Nanba K, Parksook WW, Brown JM. Primary aldosteronism: state-of-the-art review. *Am J Hypertens*. 2022;35(12):967-988. https://doi.org/10.1093/ajh/hpac079
32. Vaidya A, Mulatero P, Baudrand R, Adler GK. The expanding spectrum of primary aldosteronism: implications for diagnosis, pathogenesis, and treatment. *Endocr Rev*. 2018;39(6):1057-1088. https://doi.org/10.1210/er.2018-00139
33. Turcu AF, Yang J, Vaidya A. Primary aldosteronism—a multidimensional syndrome. *Nat Rev Endocrinol*. 2022;18(11):665-682. https://doi.org/10.1038/s41574-022-00730-2
34. Ito Y, Takeda R, Takeda Y. Subclinical primary aldosteronism. *Best Pract Res Clin Endocrinol Metab*. 2012;26(4):485-495. https://doi.org/10.1016/j.beem.2011.11.006
35. Vecchiola A, Fuentes CA, Barros ER, *et al.* The aldosterone/renin ratio predicts cardiometabolic disorders in subjects without classic primary aldosteronism. *Am J Hypertens*. 2019;32(5):468-475. https://doi.org/10.1093/ajh/hpz023
36. Hundemer GL, Agharazii M, Madore F, *et al.* Subclinical primary aldosteronism and cardiovascular health: a population-based cohort study. *Circulation*. 2024;149(2):124-134. https://doi.org/10.1161/CIRCULATIONAHA.123.066389
37. Kmiec P, Sworczak K. Autonomous aldosterone secretion as a subclinical form of primary aldosteronism: pathogenesis and clinical

significance. *Exp Clin Endocrinol Diabetes*. 2022;130(1):7-16. https://doi.org/10.1055/a-1556-7784
38. Williams JS, Williams GH, Raji A, *et al*. Prevalence of primary hyperaldosteronism in mild to moderate hypertension without hypokalaemia. *J Hum Hypertens*. 2006;20(2):129-136. https://doi.org/10.1038/sj.jhh.1001948
39. Luo Q, Li N, Wang M, *et al*. Mild primary aldosteronism (PA) followed by overt PA are possibly the most common forms of low renin hypertension: a single-center retrospective study. *J Hum Hypertens*. 2020;34(9):633-640. https://doi.org/10.1038/s41371-019-0291-y
40. Lottspeich C, Kohler A, Czihal M, *et al*. Atherosclerotic burden and arterial stiffness are not increased in patients with milder forms of primary aldosteronism compared to patients with essential hypertension. *Horm Metab Res*. 2021;53(3):178-184. https://doi.org/10.1055/a-1326-2164
41. Williams TA, Lenders JWM, Mulatero P, *et al*. Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort. *Lancet Diabetes Endocrinol*. 2017;5(9):689-699. https://doi.org/10.1016/S2213-8587(17)30135-3
42. Williams TA, Gomez-Sanchez CE, Rainey WE, *et al*. International histopathology consensus for unilateral primary aldosteronism. *J Clin Endocrinol Metab*. 2021;106(1):42-54. https://doi.org/10.1210/clinem/dgaa484