Clinical characteristics and pre-surgery diagnostic criteria of aldosterone-producing adrenocortical carcinoma

Xinyi Zhang[1,2], Qingguo Lyu[1], Jinfang Ma[1,2], Xiaohui Pan[1,2], Qiang Wei[3], Jianwei Li[1], Yuchun Zhu[3], Sumin Shen[1,2], Jing Li[1], Yun Ou[4], Nanwei Tong[1,2]

[1]Department of Endocrinology and Metabolism, Sichuan University West China Hospital, Chengdu, Sichuan 610041, China;
[2]Center for Diabetes and Metabolism Research, Sichuan University West China Hospital, Chengdu, Sichuan 610041, China;
[3]Department of Urology, Sichuan University West China Hospital, Chengdu, Sichuan 610041, China;
[4]Department of Pathology, Sichuan University West China Hospital, Chengdu, Sichuan 610041, China.

To the Editor: Primary aldosteronism, characterized by hypertension, with or without hypokalemia, is the most frequent form of endocrine hypertension, which is mostly caused by bilateral adrenal hyperplasia or aldosterone-producing adrenocortical adenomas (APAA). However, it can also be induced by aldosterone-producing adrenocortical carcinoma (APAC), which is rare. Because of the rarity and malignancy, the clinical characteristics of APAC and the differences between APAC and APAA remain unclear, and the pre-surgical diagnosis of APAC is valuable. Therefore, we aimed to compare the clinical features of APAA and APAC by extracting data from APAC patient case reports and APAA clinical literature and developing pre-surgery diagnostic criteria for APAC.

To identify all APAC cases, we searched articles published from inception to June 2021 in PubMed, Embase, the Cochrane library, and three Chinese databases (China National Knowledge Infrastructure, Wanfang Database, and VIP Database) by using the terms "adrenocortical carcinoma", "primary aldosteronism", and "hyperaldosteronism". The inclusion criterion was an unequivocal APAC diagnosis. Available information was extracted, and the clinical features of APAC were analyzed. Additionally, literature that described APAA clinical characteristics (sample size of ≥100 participants) was systematically reviewed by searching the PubMed database. Clinical data from these publications were summarized using a one-arm meta-analysis. The results are expressed as mean ± standard deviation (SD) for normally distributed data and as median and range for non-normally distributed data, unless otherwise stated. Categorical variables were described as numbers and percentages. Methods for statistical analysis are shown in [Supplementary Methods, http://links.lww.com/CM9/B221]. This study was approved by the Ethics Committee of Sichuan University West China Hospital (No. 2021-169).

A total of 107 APAC cases [Supplementary Table 1, http://links.lww.com/CM9/B221] were identified, and we also included four APAC cases from our hospital [Supplementary Table 2, http://links.lww.com/CM9/B221] to establish the APAC database. For the APAA group, ten clinical studies were included [Supplementary Table 3, http://links.lww.com/CM9/B221]. The characteristics of APAC and APAA are summarized in [Table 1].

According to the available information, hypertension and hypokalemia were present in 94.5% (103/109) and 93.4% (99/106) of APAC cases, respectively. The mean systolic blood pressure in APAC patients was 185.1 mmHg (standard deviation [SD]: 3.5 mmHg), and the median diastolic blood pressure was 110.0 mmHg (range: 60.0–190.0 mmHg), and the median plasma potassium level was 2.4 mmol/L (IQR: 1.4–5.5 mmol/L), both of which reached statistical significance compared with APAA ($P < 0.01$). Additionally, compared with APAA, plasma aldosterone concentration (PAC) was higher in APAC (58.3 ng/dL [IQR: 7.2–4790.0 ng/dL] *vs.* 24.2 ng/dL [SD: 5.5 ng/dL], $P < 0.01$), plasma renin activity (PRA) was lower in APAC (0.2 [IQR: 0.1–0.5] *vs.* 0.4 [SD: 0.2] ng·mL^{-1}·h^{-1}, $P < 0.01$), and the elevated fold change of aldosterone to renin ratio (ARR) value was higher in APAC (13.0 [IQR: 0.9–798.3] *vs.* 2.5 [SD: 0.8] ng/dL per ng · mL^{-1} · h^{-1}, $P < 0.01$).

APAC tumor diameter and weight varied widely, from 2.0 cm to 35.0 cm (median value: 8.0 cm) and from 18.5 g to 2750.0 g (median value: 150.0 g), respectively. A significant difference in tumor size was noted between

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Correspondence to: Nanwei Tong, Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, No. 37, Guoxue Road, Chengdu, Sichuan 610041, China
E-Mail: tongnw@scu.edu.cn

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Table 1: Demographic and clinical features of PA induced by APAC and APAA.

Variable	APAC ($N = 111$)		APAA ($N = 2609$)		*P* value
	Results	*n*	Results	*n*	
Age (years)	46.1 ± 15.5	111	49.2 ± 2.5	1559	0.30
Gender (M/F)	51/59	110	684/748	1432	0.84
Duration of disease (months)	18.0 (0.3–300.0)	53	127.0 ± 38.9	1325	<0.01
Hypertension (present/absent)	103/6	109	–	–	–
Systolic blood pressure (mmHg)	185.1 ± 3.5	86	161.5 ± 6.0	2435	<0.01
Diastolic blood pressure (mmHg)	110.0 (60.0–190.0)	84	99.1 ± 3.3	2435	<0.01
Hypokalemia (present/absent)	99/7	106	509/57	566	0.20
Plasma potassium level (mmol/L)	2.4 (1.4–5.5)	99	3.2 ± 0.2	1432	<0.01
Hypernatremia (present/absent)	13/34	47	–	–	–
Plasma sodium level (mmol/L)	142.4 ± 7.1	46	141.7 ± 2.2	147	0.30
Side of tumor (L/R)	43/53	96	72/80	152	0.75
Maximum tumor diameter (cm)	8.0 (2.0–35.0)	95	1.7 ± 0.7	884	<0.01
Tumor mass weight (g)	150.0 (18.5–2750.0)	43	–	–	–
Metastasis (present/absent)	15/40	55	–	–	–
Relative value of PAC*	2.9 (0.9–532.2)	59	–	–	–
PAC (ng/dL)	58.3 (7.2–4790.0)	62	24.2 ± 5.5	1432	<0.01
Low renin (present/absent)	43/14	57	–	–	–
Relative value of PRA*	0.2 (0–0.8)	33	–	–	–
PRA (ng · mL^{-1} · h^{-1})	0.2 (0–3.0)	40	0.4 ± 0.2	1018	<0.01
ARR (ng/dL per ng · mL^{-1} · h^{-1})†	13.0 (0.9–798.3)	54	2.5 ± 0.8	1024	<0.01
Cortisol excess (present/absent)	20/50	70	–	–	–
Androgen excess (present/absent)	3/38	41	–	–	–

Results were expressed as *n*, mean ± SD in normally distributed data, and median plus range in the case of non-normally distributed data. Because the original data of APAA group is unavailable, the results were analyzed by using one-arm meta-analysis. * Because the serum aldosterone and renin test methods and the range of normal values varied remarkably, relative value of PAC was calculated as the multiple of the normal upper limit, relative value of plasma renin activity was calculated as the multiple of the normal lower limit. † ARR was calculated as the multiple of the cut-off point (30 ng/dL per ng · mL^{-1} · h^{-1}). APAA: Aldosterone-producing adrenocortical adenoma; APAC: Aldosterone-producing adrenocortical carcinoma; ARR: Aldosterone to renin ratio; F: Female; L: Left; M: Male; *N*: Number; PA: Primary aldosteronism; PAC: Plasma aldosterone concentration; PRA: Plasma renin activity; R: Right; SD: Standard deviation. –: Not applicable.

APAC and APAA because the mean APAA tumor diameter was only 1.7 cm (SD: 0.7 cm) ($P < 0.01$). Metastases were found in 15 patients at the initial diagnosis [Supplementary Table 4, http://links.lww.com/CM9/B221]. Detailed imaging and pathological information were lacking in most articles, and the available data are summarized in [Supplementary Tables 5 and 6, http://links.lww.com/CM9/B221].

In terms of treatments, anti-hypertensive medications, including spironolactone and adrenalectomy, were administered to 87 patients, while chemotherapy, radiotherapy, and mitotane were administered to 22, 3, and 26 patients, respectively. The available follow-up information indicated tumor recurrence in 42/82 (51.2%) patients, and 29/82 (35.4%) patients died during the follow-up period. The leading cause of death was tumor relapse or metastases, accounting for 69.0% (20/29) of all deaths.

The Kaplan–Meier survival analysis suggested a median survival time of 1460 days for APAC (standard error [SE], 425 days; 95% confidence interval [CI], 607–2293 days) [Supplementary Figure 1A, http://links.lww.com/CM9/B221] and a median time for both tumor recurrence and death of 365 days (SE, 97 days; 95% CI, 219–511 days) [Supplementary Figure 1B, http://links.lww.com/CM9/B221]. When APAC patients were divided into non-metastatic and metastatic groups at initial diagnosis, a significantly longer survival time (median value: 1550 days, 95% CI, 0–3687 days) was found in non-metastatic patients than in metastatic patients (median value, 146 days; 95% CI, 0–436 days) ($P \leq 0.01$) [Supplementary Figure 1C, http://links.lww.com/CM9/B221]. For time to either death or recurrence, age (≥45.4 years) and metastasis at diagnosis attained statistical significance in the Kaplan–Meier analysis. However, Cox regression did not find any significant prognostic predictive factors.

Although the diagnosis of APAC is mostly based on Weiss criteria,[1] our analysis showed that APAC had several unique clinical features compared with APAA, including larger tumor size, higher PAC, lower PRA, higher ARR, higher prevalence of cortisol cosecretion and possible androgen cosecretion, higher blood pressure, and lower potassium level. We found that tumor size was the most specific and sensitive marker for differentiating APAC and APAA. Therefore, we developed pre-surgery diagnostic criteria for APAC [Supplementary Tables 7 and 8, http://links.lww.com/CM9/B221]. If PA patients with adrenal glands are established, the following items might be useful in differentiating APAC and APAA: (1) tumor size: if the tumor size is >2.8 cm, there is a very high risk of APAC (sensitivity, 96.8%; specificity, 95.0%); if the tumor size is >3.5 cm, APAC is almost clinically definite (sensitivity, 88.4%;

specificity, 99.5%); (2) metastasis: if the patient has metastasis, APAC is almost clinically definite (specificity, 100.0%; sensitivity, 37.5%). (3) ARR: if the elevated fold change of ARR is >4.6 ng/dL per ng · mL^{-1} · h^{-1}, there is a very high risk of APAC (sensitivity, 70.4%; specificity, 99.5%). (4) PAC: if the PAC is >38.4 ng/dL, there is a very high risk of APAC (sensitivity, 62.5%; specificity, 99.5%). (5) Elevated androgen levels: if the patient has elevated androgen levels simultaneously, APAC is almost clinically definite (specificity, approximately 100.0%; sensitivity, 7.3%).

APAC is a rare disease with a poor prognosis that was first reported by Foye and Feichtmeir[2] in 1955. In 2005, Seccia *et al*[3] created a database of 58 published APAC cases. We updated this database by including APAC cases reported after 2005 and adding Chinese cases to obtain more accurate results for APAC clinical characteristics. Kaplan–Meier analysis in Seccia *et al*'s[3] study revealed that the median APAC patient survival was 546 days, and the time-lapse between surgery and either tumor recurrence or death was 212 days. However, the results from our updated APAC database suggested a median survival time of 1460 days, while the median time for either tumor recurrence or death was 365 days, which are both longer than Seccia's results. This increase in survival probably resulted from an earlier diagnosis and more advanced treatment of this disease. In addition, a higher 2-year survival rate was found in APAC patients diagnosed after 2005 (12/29, 41.4%) than in those diagnosed before 2005 (16/54, 30.2%). Current guidelines[4,5] suggest that surgical resection with the goal of a microscopically free margin (R0 resection) is the critical treatment in localized ACC patients. For metastatic or recurrent ACC, chemotherapy and mitotane are the most frequent treatments. However, a better prognosis and longer survival of APAC are still needed, and more tools are needed to achieve these improvements.

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Conflicts of interest

None.

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