ORIGINAL PAPER

Clinical cure vs a novel trifecta system for evaluating long-term outcomes of minimally-invasive partial or total adrenalectomy for unilateral primary aldosteronism: results of a multicentric series

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Introduction Several predictive scores to evaluate outcomes of adrenal surgery for unilateral primary aldosteronism (UPA), have been conceived. We compared a novel trifecta that summarizes outcomes of adrenal surgery for UPA with the clinical cure proposed by Vorselaars.

Material and methods Between March 2011 and January 2022, a multi-institutional dataset was queried for UPA. Baseline, perioperative and functional data were collected. Clinical and biochemical complete and partial success rates according to Primary Aldosteronism Surgical Outcome (PASO) criteria were assessed for the overall cohort. Clinical cure was defined either as normotension without antihypertensive medications or normotension with lower or equal use of antihypertensive medications. Trifecta was defined as the coexistence of ≥50% antihypertensive therapeutic intensity score (TIS) reduction (ΔTIS), no electrolyte impairment at 3-months and no Clavien-Dindo (2–5) complications. Cox regression analyses were used to identify predictors of long-term clinical and biochemical success. For all analyses, a two-sided p <0.05 was considered significant.

Results Baseline, perioperative and functional outcomes were analyzed. Out of 90 patients, at a median follow-up of 42 months (IQR 27–54) a complete and partial clinical success was observed in 60% and 17.7% of cases while a complete and partial biochemical success was achieved in 83.3% and 12.3% of cases, respectively. Overall trifecta and clinical cure rates were 21.1% and 58.9%, respectively. On multivariable Cox regression analysis, trifecta achievement (HR 2.87; 95% CI 1.45–5.58; p = 0.02) was the only independent predictor of complete clinical success at long-term follow-up.

Conclusions Despite its complex estimation and more restrictive criteria, trifecta but not clinical cure allows to independently predict composite PASO endpoints on the long run.

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INTRODUCTION

Primary hyperaldosteronism (PHA) or Conn's syndrome represents the most common cause of endocrine hypertension (HTN) [1, 2]. PHA is characterized by high plasma and urinary aldosterone and suppressed plasma renin [3]. According to endocrine society clinical guidelines, patients with bilateral adrenal hyperplasia are generally treated with mineralcorticoid receptor antagonists [4]. Conversely, unilateral PHA are recommended to undergo, either partial or total gland removal [5]. Minimally-invasive partial adrenalectomy (MIPA) or total adrenalectomy (MITA) represent the standard treatment of unilateral PHA [6, 7, 8].

The historical lack of homogenous and validated metrics for describing adrenalectomy outcomes for Conn' syndrome, has led to the introduction of PASO criteria for describing achievement of clinical and biochemical success [9]. However, the normalization of blood pressure without the need of antihypertensive medication is still reported with heterogeneity among adrenalectomy series, ranging from 20% to 80%, while the rate of persistent hypokalemia after surgery remains negligible or underestimated [10, 11].

In this scenario, several predictive scores to evaluate long-term functional outcomes of adrenalectomy for PHA, have been conceived. Notably, Vorselaars et al. proposed the definition of 'clinical cure' based on postoperative blood pressure and number of antihypertensive drugs [12]. More recently, Anceschi et al. introduced the concept of 'trifecta' to describe composite adrenalectomy outcomes for unilateral primary aldosteronism (UPA), regardless of the surgical approach considered [13].

The aim of the current study was to provide a head-to-head comparison between these two scoring systems for predicting both clinical and biochemical success according to PASO criteria on a multicentric adrenalectomy series at an extended follow-up.

MATERIAL AND METHODS

Study population

Between March 2011 and January 2022, a multi-institutional board-approved prospective adrenalectomy dataset was queried for 'unilateral primary aldosteronism' (UPA). Patients enrolled were divided into two groups according to surgical technique (MITA or MIPA). Indications for MIPA were limited to small tumors (<3 cm). Patients included were diagnosed with UPA identified by computed tomography (CT) and/or magnetic resonance (MR) and/or adrenal venous sampling, according to standard diagnostic work-up suggested by the endocrine society guidelines [5]. Patients with bilateral hyperplasia, malignant disease (primary or metastatic), other causes of adrenal-related endocrine HTN, incomplete preoperative/follow-up data regarding antihypertensive drug assumption or systolic/diastolic blood pressure were excluded.

Variables

Evaluated preoperative clinical and demographic characteristics included age, gender, American Society of Anesthesiologists (ASA) score, preoperative haemoglobin (Hb), therapeutic intensity score (TIS), clinical tumor size and side, serum potassium level. Intraoperative variables included mean operative time (MOT), % perioperative complications, % perioperative transfusions. Postoperative variables included length of hospital stay (LOS), postoperative Hb, median perioperative Hb drop (ΔHb). Complications within 30 days after surgery were recorded and graded according to the Clavien-Dindo classification. Significant complications were categorized as Clavien Grade III or higher. Functional results were reported and classified according to clinical PASO criteria. Information on preoperative antihypertensive therapy (number of drugs, class and dose) were retrieved from clinical charts and TIS metric was computed for each patient in order to estimate trifecta outcomes [13, 14]. TIS represents a proportional measure of prescribed to maximum US Food and Drug Administration (FDA) recommended dosage calculated for each antihypertensive medication preoperatively [15]. Follow-up consisted of an endocrinologic evaluation at 3, 6, 12 months after surgery. Trifecta and clinical cure achievement were calculated as previously described by Anceschi et al. and Vorselaars et al., respectively [12, 13].

Endpoints

The primary endpoint of the study was to compare trifecta and clinical cure rates among MIPA and MITA series. The secondary endpoint was to identify predictors of long-term complete and partial clinical/biochemical success according to PASO in the overall cohort.

Statistical analysis

Descriptive analyses were used. Frequencies and proportions were reported for categorical variables, while medians and interquartile ranges (IQRs) were reported for continuously coded variables. Differ-

ences between continuous variables were assessed with the Wilcoxon rank sum test, while Pearson's χ^2 test was used for categorical data. Univariable and multivariable Cox regression analyses were used to identify predictors of partial and absent clinical success.

For all analyses, a two-sided p <0.05 was considered significant. Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) software v.26.0 (IBM Corp, Armonk, NY, USA).

RESULTS

Baseline and perioperative characteristics

Overall, 90 eligible patients met inclusion criteria with a median follow-up of 42 months (IQR: 27–54). Of those, 61 underwent MITA and 29 MIPA, respectively (Table 1). No significant differences between groups were found at baseline for all variables considered (each p >0.2) except for median tumor size, which was significantly higher in MITA series (4.2 vs 2.7 cm; p = 0.001) and for tumor side, whereas the rate of left-sided adrenal masses in the MIPA cohort was significantly increased (37.7% vs 75.9%; p = 0.001). With regard to perioperative outcomes (Table 1), LOS was significantly higher in the MITA cohort (4 vs 3 days; p = 0.038). Overall complications rate and Clavien-Dindo grade distribution were homogeneous between groups (each p >0.4).

Functional outcomes

Median cumulative TIS score (range 0.25–1) was comparable between groups (0.5 vs 0.5; p = 0.989), with 34.5% patients requiring a combined drug regimen (p = 0.676). In the overall cohort, complete, partial, and absent clinical success rates were achieved in 54 (60%), 16 (17.7%), and 20 (22.3%) patients, respectively (Table 2). Complete, partial, and absent biochemical success was obtained in 75 (83.3%), 11 (12.3%), and 4 (4.4%) patients, respectively. The overall clinical cure rate was achieved in 58.9% patients, with no significant differences between the two groups (55% vs 66.7%; p = 0.433). Moreover, overall trifecta rate was 21.1% in the entire cohort with no difference between MITA and MIPA cohorts (16.3% vs 31%; p = 0.312).

Table 1. *Baseline data and perioperative outcomes*

Variable	Overall (n = 90)	Minimally-invasive total adrenalectomy (MITA n = 61)	Minimally-invasive partial adrenalectomy (MIPA = 29)	p value
Age at surgery (median, IQR)	54 (44–65)	54 (44.5–63)	57 (43.5–67.5)	0.408
Follow-up (months, median, range)	42 (27–54)	41 (24–50)	46 (32.7–57.5)	0.223
Gender (n, %)				0.519
Male	36 (40%)	23 (37.7%)	13 (44.8%)	
Female	54 (60%)	38 (62.3%)	16 (55.2%)	
ASA score (n, %)				0.763
1–2	73 (81.1%)	50 (82%)	23 (79.3%)	
3–4	17 (18.9%)	11 (18%)	6 (20.7%)	
Adrenal mass size (cm, n, IQR)	3 (2–5)	4.2 (2.35–6)	2.7 (1.8–2.85)	0.001
Side (n, %)				0.001
Left	45 (50%)	23 (37.7%)	22 (75.9%)	
Right	45 (50%)	38 (62.3%)	7 (24.1%)	
LOS (days, median, IQR)	4 (3–5)	4 (3–5)	3 (2.5–4)	0.038
Number of drugs (n, %)				0.676
No drugs	9 (10%)	7 (11.4%)	2 (6.8%)	
One class medication	50 (55.5%)	32 (52.4%)	18 (62%)	
Combined class medication (≥2)	31 (34.5%)	22 (36%)	9 (31.2%)	
TIS score (median, IQR)	0.5 (0.25–1)	0.5 (0.25–1.09)	0.5 (0.25–1)	0.989
Overall complications (n, %)	10 (11.1%)	7 (11.5%)	3 (10.3%)	0.873
Clavien grade (n, %)				
I	6	4	2	0.940
II	3	2	1	0.488
III	–	–	–	
IV	1	1	–	
V	–	–	–	

n – number of patients; IQR – interquartile range; ASA – American Society of Anesthesiologists; LOS – length of hospital stay; TIS – therapeutic intensity score

Table 2. *Functional outcomes*

Variable	Overall (n = 90)	Minimally-invasive total adrenalectomy (MITA n = 61)	Minimally-invasive partial adrenalectomy (MIPA = 29)	p value
Complete clinical success	54 (60%)	33 (54%)	21 (72.4%)	0.097
Partial clinical success	16 (17.7%)	14 (23%)	2 (6.8%)	0.136
Absent clinical success	20 (22.3%)	14 (23%)	6 (20.7%)	0.136
Complete biochemical success	75 (83.3%)	50 (81.9%)	25 (86.2%)	0.918
Partial biochemical success	11 (12.3%)	7 (11.4%)	4 (13.7%)	0.918
Absent biochemical success	4 (4.4%)	3 (4.91%)	1 (3.4%)	0.918
Trifecta	19 (21.1%)	10 (16.3%)	9 (31%)	0.312
ΔTIS ≥50 (3 months)	25 (27.8%)	13 (21.3%)	12 (41.3%)	0.067
No perioperative complications (any CD)	80 (88.9%)	53 (86.8%)	27 (93.1%)	0.813
No electrolyte imbalance (3 months)	76 (84.4%)	51 (83.6%)	25 (86.2%)	0.837
Clinical cure				
Normotension	53 (58.9%)	33 (55%)	20 (66.7%)	0.433
Clear improvement	11 (12.2%)	10 (15%)	1 (6.6%)	0.092
No clear success	26 (28.9%)	18 (30%)	8 (26.7%)	0.452

TIS – therapeutic intensity score; CD – Clavien-Dindo

Predictors of clinical success

On univariable Cox regression analysis, none of the included variables were predictive of partial clinical success, while adenoma size (HR 1.12; 95% CI 1.01–1.25; p = 0.03), clinical cure (HR 1.12; 95% CI 1.05–2.23; p = 0.04) and trifecta (HR 2.96; 95% CI 1.57–5.86; p = 0.02) were all predictors of complete clinical success (Tables 3, 4). On multivariable Cox regression addressing complete clinical success only trifecta (HR 2.87; 95% CI 1.45–5.58; p = 0.02) showed statistical significance.

Predictors of biochemical success

On univariable Cox regression addressing partial clinical success, only age (HR 0.94; 95% CI 0.88–0.99;

p = 0.04) achieved statistical significance (Table 5, 6). Conversely, adenoma size and trifecta were both predictors of complete biochemical success, on univariable (HR 2.72; 95% CI 1.46–5.06; p = 0.001 and HR 1.97; 95% CI 1.07–3.65; p = 0.03, respectively) and after multivariable adjustments (HR 2.87; 95% 1.53–5.36; p = 0.001 and HR 2.10; 95% CI 1.13–3.90; p = 0.018, respectively).

DISCUSSION

To date, PASO criteria represent the most comprehensive validated tool to assess composite functional outcomes after adrenal surgery for PHA [9]. However, the adoption of this metric did not obviate the historical heterogeneity among adrenalectomy outcomes, due to the stiff thresholds considered [10, 11].

Table 3. *Univariable and multivariable Cox regression analysis to identify predictors of partial clinical success according to PASO criteria*

Variable	Univariable analysis				Multivariable analysis			
	HR	95.0% CI		p value	HR	95.0% CI		p value
		Lower	Higher			Lower	Higher	
Age	0.98	0.92	1.04	0.619	–	–	–	–
Gender	0.53	0.14	1.99	0.352	–	–	–	–
ASA score 1–2 3–4	0.88	0.18	4.25	0.878	–	–	–	–
Adenoma size	1.84	0.37	9.05	0.451	–	–	–	–
Partial vs total adrenalectomy	0.04	0.15	2.8	0.580	–	–	–	–
Clinical cure	0.17	0.02	1.50	0.110	–	–	–	–
Trifecta	0.62	0.07	5.3	0.662	–	–	–	–

PASO – Primary Aldosteronism Surgical Outcome; ASA – American Society of Anesthesiologists; CI – confidence interval; HR – hazard ratio

Table 4. *Univariable and multivariable Cox regression analysis to identify predictors of complete clinical success according to PASO criteria*

Variable	Univariable analysis				Multivariable analysis			
	HR	95.0% CI			HR	95.0% CI		
		Lower	Higher	p value		Lower	Higher	p value
Age	0.98	0.95	1.08	0.169	–	–	–	–
Gender	1.18	0.62	2.26	0.596	–	–	–	–
ASA score 1–2 3–4	0.65	0.30	1.38	0.262	–	–	–	–
Adenoma size	1.12	1.01	1.25	0.031	1.11	0.99	1.25	0.062
Partial vs total adrenalectomy	1.63	0.67	3.95	0.276	–	–	–	–
Clinical cure	1.12	1.05	2.23	0.042	1.41	0.36	2.54	0.884
Trifecta	2.96	1.57	5.86	0.021	2.87	1.45	5.58	0.021

PASO – Primary Aldosteronism Surgical Outcome; Cl – confidence interval; HR – hazard ratio; ASA – American Society of Anesthesiologists

Table 5. *Univariable and multivariable Cox regression analysis to identify predictors of partial biochemical success according to PASO criteria*

Variable	Univariable analysis				Multivariable analysis			
	HR	95.0% CI			HR	95.0% CI		
		Lower	Higher	p value		Lower	Higher	p value
Age	0.94	0.88	0.99	0.041	–	–	–	–
Gender	0.99	0.27	3.60	0.989	–	–	–	–
ASA score 1–2 3–4	1.29	0.35	4.65	0.697	–	–	–	–
Adenoma size	0.04	0.01	16.5	0.553	–	–	–	–
Partial vs total adrenalectomy	1.42	0.40	4.87	0.597	–	–	–	–
Clinical cure	1.17	0.32	4.21	0.803				
Trifecta	0.03	0.01	21.3	0.460				

PASO – Primary Aldosteronism Surgical Outcome; Cl – confidence interval; HR – hazard ratio; ASA – American Society of Anesthesiologists

Table 6. *Univariable and multivariable Cox regression analysis to identify predictors of complete biochemical success according to PASO criteria*

Variable	Univariable analysis				Multivariable analysis			
	HR	95.0% CI			HR	95.0% CI		
		Lower	Higher	p value		Lower	Higher	p value
Age	1	0.98	1.02	0.738	–	–	–	–
Gender	1.30	0.75	2.26	0.336	–	–	–	–
ASA score 1–2 3–4	0.68	0.36	1.28	0.237	–	–	–	–
Adenoma size	2.72	1.46	5.06	0.001	2.87	1.53	5.36	0.001
Partial vs total adrenalectomy	1.27	0.74	2.18	0.370	–	–	–	–
Clinical cure	1.04	0.57	1.88	0.915				
Trifecta	1.97	1.07	3.65	0.032	2.10	1.13	3.90	0.018

PASO – Primary Aldosteronism Surgical Outcome; Cl – confidence interval; HR – hazard ratio; ASA – American Society of Anesthesiologists

Recently, Vorselaars et al. suggested the definition of clinical cure to evaluate the burden of blood pressure (BP) decrease in patients undergoing unilateral adrenalectomy [12]. Despite the user-friendly profile, major pitfalls of this score are represented by either the lack of information on anti-hypertensive drug dosage or biochemical functional assessment. To overcome these limitations, Anceschi et al. proposed the concept of trifecta in adrenal surgery for PHA. This scoring system is defined by the achievement of three main criteria: 1) absence of perioperative complications (Clavien-Dindo ≥2); 2) BP control evaluated by TIS score (ΔTIS ≥50%); 3) absence of post-operative electrolyte impairment [13].

In this scenario, we attempted the first head-to-head comparison between two major predictive tools of adrenalectomy outcomes for unilateral UPA. Our study has several noteworthy findings.

First, as a previous study shows, no significant differences were reported in terms of complete clinical success between MIPA and MITA cohorts [16]. Furthermore, according to our regression model, surgical technique was neither predictive of complete nor of partial clinical success (each p >0.2). This data further confirmed the feasibility of adrenal sparing surgery in patients affected by unilateral UPA [17].

Second, with regard to functional outcomes observed, at a median follow-up of 42 months (IQR: 27–54), the overall trifecta achievement rate was 21.1% while the normotension rate according to clinical cure was 58.9%. This wide discrepancy in identifying patients who achieved complete or partial clinical success potentially relied on the more restricted criteria for trifecta achievement.

Third, after adjusting our regression model for adenoma size, clinical cure and trifecta achievement, only trifecta was an independent predictor of either complete clinical or biochemical success (p = 0.02 and p = 0.018, respectively). Notably, the incidence of persistent of hypertension after adrenal surgery for UPA still remains a critical issue in contemporary clinical practice. Ideally, the best predictive tool in the UPA setting should identify which patients will benefit only with surgical treatment at an extended follow-up. Unfortunately, due to variables heterogeneity influencing blood pressure control, a clear discernment between refractory and newly onset of hypertension after surgery remains unclear. Additionally, the delayed timeframe evaluation between UPA diagnosis and treatment may negatively impact blood pressure recovery after adrenal surgery, jeopardizing the effective clinical success rates. Nevertheless, the multidisciplinary management of hypertension involving different clinical profiles, ranging from general practitioner to cardiologist advice may overestimate the clinical failure rates whereas multiple drug regimens aim to avoid cardiovascular complications rather than blood pressure control.

Fourth, in the overall cohort, the complete biochemical success rate was 83.3%. Our findings are comparable to previously published series [9, 18, 19] although electrolyte imbalance may not necessarily represent a biochemical failure rather than a potential underestimated bilateral PHA, a side-effect of multidrug antihypertensive therapy, or a consequence of long-standing untreated UPA [20]. Nonetheless, a larger adenoma size resulted in a higher probability of complete biochemical success (HR 2.87; p = 0.001). This data is in contrast with prior studies results [21]. A possible explanation may be represented by the lack of assessment of potential residual confounding variables such as aldosterone/renin ratios, cortisol values, histochemical (aldosterone synthase) and surgical factors not included in our dataset or simply a consequence of regression model overfitting.

In analogy to previously published data, we observed a consistent discrepancy between clinical and biochemical complete success rates [18, 22]. As aforementioned, the source of aldosterone excess removal could normalize the biochemical abnormalities. Conversely, blood pressure variability may be also influenced by vascular changes related to long-lasting, untreated UPA.

We acknowledge that the present study has several limitations. Firstly, in a multi-centric database, data are subject to selection, indication and performance bias. Moreover, since clinical and biochemical outcomes could be influenced by patients' comorbidities and UPA duration and severity, we were unable to include this information in our predictive models. Additionally, external validations of this scoring system are still lacking in contemporary literature. Notwithstanding these limitations, trifecta represents an alternative and comprehensive clinical tool for physicians in the prediction of all PASO endpoints compared to clinical cure at a long-term follow-up.

CONCLUSIONS

Clinical cure and trifecta system are both reliable and independent prognostic tool of standardized clinical success after either partial or total adrenalectomy. Despite its higher complexity estimation and more restrictive inclusion criteria, trifecta but not clinical cure allows to predict composite endpoints of PASO criteria in the long run.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

References

1. Rossi GP, Bernini G, Caliumi C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol. 2006; 48: 2293-2300.

2. Monticone S, Burrello J, Tizzani D, et al. Prevalence and Clinical Manifestations of Primary Aldosteronism Encountered in Primary Care Practice. J Am Coll Cardiol. 2017; 69: 1811-1820.

3. Young WF. Primary aldosteronism: renaissance of a syndrome. Clin Endocrinol (Oxf). 2007; 66: 607-618.

4. Simone G, Anceschi U, Tuderti G, et al. Robot-assisted Partial Adrenalectomy for the Treatment of Conn's Syndrome: Surgical Technique, and Perioperative and Functional Outcomes. Eur Urol. 2019; 75: 811-816.

5. 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: 1889-1916.

6. Milliez P, Girerd X, Plouin P-F, Blacher J, Safar ME, Mourad J-J. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol. 2005; 45: 1243-1248.

7. Savard S, Amar L, Plouin P-F, Steichen O. Cardiovascular complications associated with primary aldosteronism: a controlled cross-sectional study. Hypertension. 2013; 62: 331-336.

8. Mulatero P, Monticone S, Bertello C, et al. Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. J Clin Endocrinol Metab. 2013; 98: 4826-4833.

9. 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: 689-699.

10. Zhou Y, Zhang M, Ke S, Liu L. Hypertension outcomes of adrenalectomy in patients with primary aldosteronism: a systematic review and meta-analysis. BMC Endocr Disord. 2017; 17: 61.

11. Benham JL, Eldoma M, Khokhar B, Roberts DJ, Rabi DM, Kline GA. Proportion of Patients With Hypertension Resolution Following Adrenalectomy for Primary Aldosteronism: A Systematic Review and Meta-Analysis. J Clin Hypertens (Greenwich). 2016; 18: 1205-1212.

12. Vorselaars WMCM, Nell S, Postma EL, et al. Clinical Outcomes After Unilateral Adrenalectomy for Primary Aldosteronism. JAMA Surg. 2019; 154: e185842.

13. Anceschi U, Mormando M, Fiori C, et al. Surgical Quality, Antihypertensive Therapy, and Electrolyte Balance: A Novel Trifecta to Assess Long-Term Outcomes of Adrenal Surgery for Unilateral Primary Aldosteronism. J Clin Med. 2022; 11: 794.

14. Anceschi U, Mormando M, Fiori C, et al. The TIS score for the prediction of long-term clinical outcomes after minimally-invasive partial and total adrenalectomy for unilateral primary aldosteronism: Results of a multicentric series. Eur Urol. 2021; 79 (Suppl 1): S943-S944.

15. Levy PD, Willock RJ, Burla M, et al. Total antihypertensive therapeutic intensity score and its relationship to blood pressure reduction. J Am Soc Hypertens. 2016; 10: 906-916.

16. Anceschi U, Tuderti G, Fiori C, et al. Minimally Invasive Partial Versus Total Adrenalectomy for the Treatment of Primary Aldosteronism: Results of a Multicenter Series According to the PASO Criteria. Eur Urol Focus. 2021; 7: 1418-1423.

17. Flammia RS, Anceschi U, Tufano A, et al. Minimally Invasive Partial vs. Total Adrenalectomy for the Treatment of Unilateral Primary Aldosteronism: A Systematic Review and Meta-Analysis. J Clin Med. 2022; 11: 1263.

18. Vorselaars WMCM, van Beek D-J, Postma EL, et al. Clinical outcomes after surgery for primary aldosteronism: Evaluation of the PASO-investigators' consensus criteria within a worldwide cohort of patients. Surgery. 2019; 166: 61-68.

19. Swearingen AJ, Kahramangil B, Monteiro R, et al. Analysis of postoperative biochemical values and clinical outcomes after adrenalectomy for primary aldosteronism. Surgery. 2018; 163: 807-810.

20. Gruber S, Beuschlein F. Hypokalemia and the Prevalence of Primary Aldosteronism. Horm Metab Res. 2020; 52: 347-356.

21. Giacchetti G, Ronconi V, Rilli S, Guerrieri M, Turchi F, Boscaro M. Small tumor size as favorable prognostic factor after adrenalectomy in Conn's adenoma. Eur J Endocrinol. 2009; 160: 639-646.

22. Miller BS, Turcu AF, Nanba AT, et al. Refining the Definitions of Biochemical and Clinical Cure for Primary Aldosteronism Using the Primary Aldosteronism Surgical Outcome (PASO) Classification System. World J Surg. 2018; 42: 453-463. ■