

# The Relationship Between Baseline Cortisol Levels and Surgery Method of Primary Bilateral Macronodular Adrenal Hyperplasia

## Authors

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## ABSTRACT

Aim was to explore the associations between baseline cortisol levels and surgery method of primary bilateral macronodular adrenal hyperplasia (PBMAH). We retrospectively reviewed the clinical features and management of 30 patients (18 females and 12 males) who were diagnosed with PBMAH in our center between 2005 and 2019. Based on surgery method, we divided the patients into two groups: unilateral adrenalectomy (UA) group; and bilateral adrenalectomy (BA) group. Serum cortisol rhythm and 24-hour urinary free cortisol (UFC/24h) levels were assayed using chemiluminescence method. Associations between baseline cortisol levels and BA were assessed using logistic regression. The predictive value of baseline cortisol levels for BA was calculated using receiver operating characteristic (ROC) curves. Twenty patients (66.7%) underwent UAs and ten patients (33.3%) underwent BAs. After adjusting for age, sex, BMI, SBP, and adrenal volume, the concentrations of baseline serum cortisol (8 AM, 4 PM, and 0 AM) and UFC/24 h were associated with bilateral adrenalectomy (all  $p < 0.05$ ). The area under the ROC curve based on 8 AM serum cortisol level model was larger than that in models based on 4 PM, 0 AM serum cortisol levels and UFC/24 h, but the differences were non-significant (all  $p > 0.05$ ). According to maximum Youden index criteria, the optimal cutoffs of 8 AM serum cortisol level and UFC were 26.89  $\mu\text{g}/\text{dl}$  and 406.65  $\mu\text{g}/24\text{h}$ , respectively, for BA. The baseline cortisol levels are positively associated with BA. Increased levels of baseline cortisol levels may predict higher possibility of BA, which should be confirmed by prospective studies.

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## ABBREVIATIONS

PBMAH	Primary bilateral macronodular adrenal hyperplasia
CS	Cushing syndrome
UA	Unilateral adrenalectomy
BA	Bilateral adrenalectomy
UFC/24 h	24-hour urinary free cortisol
LDDST	Low-dose dexamethasone suppression test
HDDST	High-dose dexamethasone suppression test
ACTH	Adrenocorticotrophic hormone
PPNAD	Primary pigmented nodular adrenocortical disease
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
ROC	Receiver operating characteristic curve
AUCs	Areas under the curve
OR	Odds ratio
SD	Standard deviation

## Introduction

Primary bilateral macronodular adrenal hyperplasia (PBMAH), characterized by the presence of multiple nodules larger than 1 cm in both adrenal glands and overproduction of cortisol, is a rare cause of endogenous Cushing syndrome (CS) [1]. It was first described in 1964 by Kirschner et al. [2]. The actual incidence of PBMAH remains unclear because only some cases have clinical CS [3], and most are identified during radiological observations incidentally or the investigation of adrenal hypersecretion syndrome [4–6]. Its physical characteristics include central obesity, moon face, buffalo hump, purple abdominal striae, and multiple bruises of the extremities and its metabolic complications contain hypertension, diabetes, osteoporosis, and venous thrombo-embolism, etc. The clinical features of PBMAH are mainly associated with the levels of cortisol [4]. As our research center previously described [7], PBMAH could be divided into different subtypes (subclinical CS, clinical CS, and high risk PBMAH) based on the level of serum cortisol and clinical symptoms.

Adrenal surgery is an effective and safe selection for treatment of PBMAH with clinical CS, but there existed controversy on the concrete surgery methods [8–11]. Up to now, there are three surgery methods to treat PBMAH, including bilateral adrenalectomy (BA), unilateral adrenalectomy (UA), and simultaneous total unilateral adrenalectomy of the largest adrenal gland and partial adrenalectomy of the contralateral gland (adrenal-sparing surgery) [12–15]. BA has been taken for the treatment of choice to achieve cure of hypercortisolism [16], but it can result to adrenal insufficiency permanently, requiring lifelong corticosteroid replacement and causing health care burden, including under- and overreplacement associated with increased metabolic risk and adrenal crisis risk, respectively [4]. Considering these negative effects, UA and even adrenal-sparing surgery has been proposed as a promising and safe alternative to BA in patients with mild hypercortisolism or clear adrenal asymmetry [4, 17–19]. However, patients with UA or adrenal-sparing surgery may have the risk of recurrence and required a second surgery according to the CS-related manifestations such as uncontrolled hypertension, diabetes, obesity, and dyslipidemia [12], which correlate in part with the extent and duration of cortisol excess [20]. Due to small sample

size and limited available relative studies, especially in China, few studies are on the surgery method and baseline cortisol levels, which need further investigation.

In this study, we collected the clinical data from PBMAH patients with surgery in our center during the past 14 years and determined the predicative value of baseline cortisol levels for the surgery method of PBMAH.

## Subjects and Methods

### Subjects

This was a retrospective study, designed to collect hospital data on patients with PBMAH in detail. We performed this study in Shanghai Jiao Tong University Affiliated Ruijin Hospital between 2005 and 2019. PBMAH were screened for the reasons of CS or other complaints among 1025 patients. Patients were included as follows: 1) abdominal CT scanning revealed multiple nodules with a diameter  $\geq 1.0$  cm in the adrenal gland bilaterally; 2) overproduction of cortisol accompanied by a low or normal serum adrenocorticotrophic hormone (ACTH) concentration and no dexamethasone suppression; 3) normal pituitary gland; and 4) among patients who underwent surgery, the postoperative pathologic examination verified that the excised mass was adrenocortical hyperplasia. A total of 59 patients aged 40–68 years old were initially included in this study. Patients with hepatic and/or renal dysfunction (alanine transaminase  $\geq 97.5$  U/l and/or aspartate aminotransferase  $\geq 55.5$  U/l; serum creatinine  $\geq 115$   $\mu$ mol/l) and patients who refused surgical treatment were excluded. Finally, 30 patients were included in this study.

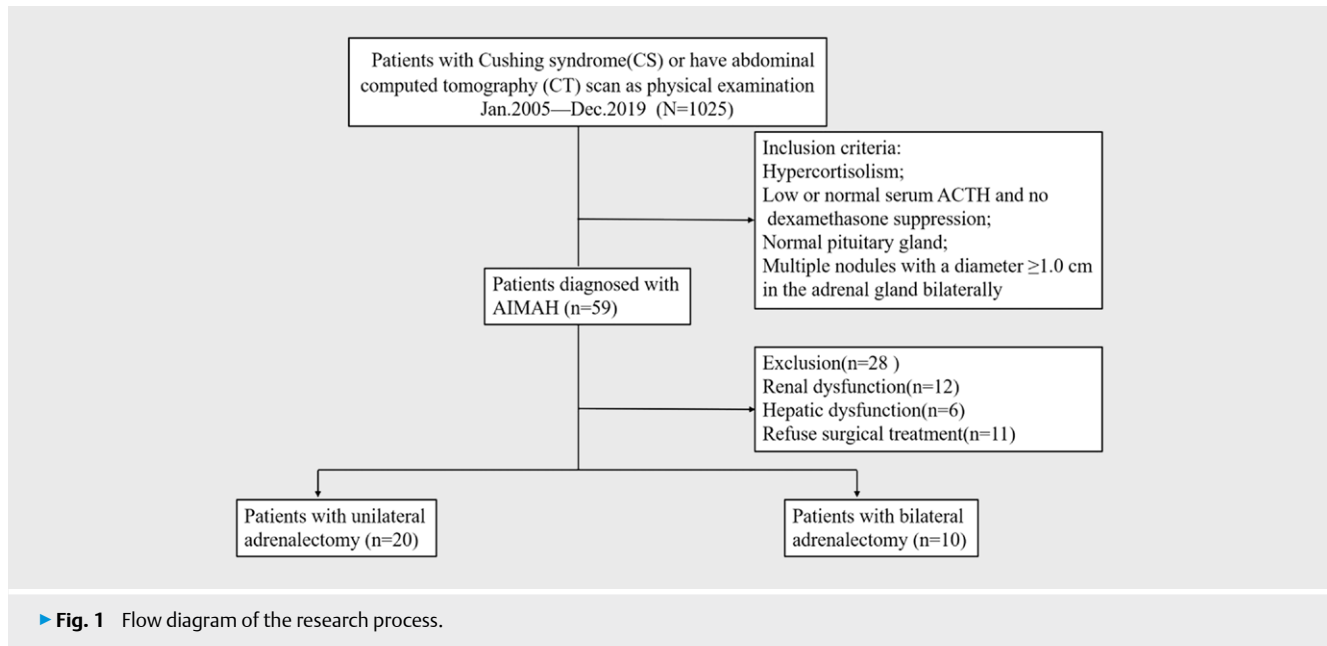
Patients were given the surgery based on clinical manifestations of CS including hypertension, hyperglycemia, obesity etc. According to the CT scan results, we first chose to completely remove the larger adrenal gland for asymmetric hyperplasia as reported [12]. After first surgery, all subjects in our study were followed up. If the hormone levels such as UFC elevated and/or the symptoms caused by hypercortisolemia recurred like hypertension, diabetes, obesity, dyslipidemia etc., a second operation was performed. Based on the surgery method, patients were divided into two groups: UA group (n = 20); and BA group (n = 10) (► Fig. 1).

### Ethics approval and consent to participate

This study was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Ruijin Hospital and conformed to the principles of the Helsinki Declaration II. Furthermore, written informed consent was received from each participant.

### Anthropometric and laboratory investigations

We measured the anthropometric and biochemical parameters at the time of admission. During height (m) and weight (kg) measurement, patients were barefoot and in light clothing. Body mass index (BMI) was calculated using weight divided by height squared ( $\text{kg}/\text{m}^2$ ). Overweight was defined as BMI greater than  $24.0$   $\text{kg}/\text{m}^2$ . Blood pressure was measured twice using a mercury sphygmomanometer with the subjects in a supine position and then averaged. We analyzed the serum cortisol concentration, 24-hour urinary free cortisol (UFC/24 h) level, and ACTH in all the patients with DPC Im-



mulite 2000 (Siemens Healthcare, Los Angeles, CA, USA). Patients were all subjected to low and high dose dexamethasone suppression tests (LDDST and HDDST). The patients had 3 blood test determinations (8 AM, 4 PM, and 0 AM) for serum cortisol levels on the same day.

Our reference ranges were as follows: UFC/24 h (Beckman; CA; USA): 21–111 µg; ACTH (mindray; Shenzhen; China): 7.0–65 pg/ml; 8 AM serum cortisol (Beckman; CA; USA): 6.7–22.6 µg/dl. If the cortisol level at 4 PM was less than the cortisol level at 8 AM and the cortisol level at 0 AM was less than the cortisol levels at 8 AM and 4 PM, and it was reduced at least 50% from night to morning, then the blood cortisol circadian rhythm was considered intact; if not, the circadian rhythm was lost. If morning plasma cortisol after 1 mg overnight dexamethasone suppression test (LDDST) or 8 mg overnight dexamethasone suppression test (HDDST) was below 50% of the baseline cortisol level, we considered it has no dexamethasone suppression. Hypertension was defined as systolic blood pressure (SBP), ≥ 140 mmHg and/or diastolic blood pressure (DBP), ≥ 90 mmHg [21] or self-reported history of hypertension, or have antihypertensive medication. Diabetes mellitus was defined as a fasting plasma glucose (FBG) of ≥ 7.0 mmol/l and/or 2-hour postprandial plasma glucose of ≥ 11.1 mmol/l and/or HbA1c of ≥ 48 mmol/mol according to the criteria proposed by the American Diabetes Association in the 2021 [22] or treatment with antidiabetic drugs. Hypokalemia was defined as serum potassium < 3.5 mmol/l; osteoporosis (OP) was defined as T-values for bone mineral density or bone mineral content that is more than 2.5 SD below the average value of the healthy adult [23].

### Imaging examination

All patients had plain and contrast CT scans of the adrenal gland bilaterally, all patients also had pituitary magnetic resonance (MR) scanning. Adrenal volume was measured by preoperative CT scan. An experienced technician analyzed the scan images. The adrenal gland was manually contoured on each image using a Siemens Vir-

tuoso workstation, generating an adrenal area for each slice. We calculated the adrenal volume by the sum of the segmental area multiplied by the interval between each slice (5 mm).

### Statistical analyses

Descriptive data are presented as mean ± SD for continuous parametric variables, and percentage for categorical variables. For comparison between groups, the independent samples *t*-test, and  $\chi^2$  test or the Fisher exact test were applied, respectively. We used binary logistic regression analysis to explore the associations of baseline serum cortisol levels (8 AM, 4 PM, and 0 AM), UFC/24 h with surgery method (UA or BA). A receiver operating characteristic (ROC) curve was used to graphically show the associations between baseline serum cortisol levels (8 AM, 4 PM, and 0 AM), UFC/24 h and BA as well as to evaluate the sensitivity and specificity of different thresholds of each indicator. We selected the optimal cut-offs from ROC curves according to the maximal Youden index criteria. Between comparisons of the areas under the curve (AUCs) based on baseline serum cortisol levels and UFC/24 h models were performed using MedCalc statistical software. A two-tailed *p*-value < 0.05 was considered statistically significant. All data were analyzed using SPSS20.0 Statistics software.

## Results

### Clinical characteristics of PBMAH patients

In the total of 30 patients, the average age was 50.8 ± 6.6 years (range 40–68 years), average BMI was 24.6 ± 2.9 kg/m<sup>2</sup> (range 19.5–30.4 kg/m<sup>2</sup>), twelve patients were male, accounting for 40% of all cases. Nineteen patients (63.3%) had weight gain. Twenty-five patients (83.3%) had typical clinical symptoms of CS. Serum cortisol circadian rhythm was lost in 27 patients (90.0%). Twenty-six patients (86.7%) had a high concentration of UFC/24 h. All patients had a neg-

ative response to LDDST and HDDST. Twenty-eight patients (93.3%) had hypertension, 15 (50.0%) had diabetes mellitus, 21 (70.0%) had hypokalemia, and 15 (50.0%) had osteoporosis.

There were no significant differences in the age, sex, SBP, DBP, ACTH and adrenal volume between the two groups (all  $p > 0.05$ ); however, the concentrations of baseline serum cortisol (8 AM, 4 PM, and 0 AM) in patients who have BAs were higher than those who have UAs (all  $p < 0.01$ ). UFC/24 h levels in patients with BAs were higher than patients with UAs ( $p = 0.005$ ) (► **Table 1**).

## Imaging examination

CT scans demonstrated that bilateral adrenal in PBMAH were enlarged and contained multiple nodules up to 5 cm in diameter without normal adrenal glands. The nodules are similar to adrenal adenomas: lipid rich, low attenuation value with no contrast administration on CT images, less than 10 Hounsfield Units (HU), and disappears quickly after intravenous injection of iodine contrast in consistent with the reported [24]. We compared the adrenal volume of larger side between the two groups and found no statistical difference ( $p = 0.588$ ) (► **Table 1**).

## The associations of baseline cortisol levels with surgery method

The concentration of baseline serum cortisol at 8 AM was positively associated with BA after adjusting for age, sex and BMI (OR 1.28,  $p = 0.010$ ), and additional adjustments for SBP (OR 1.28,  $p = 0.007$ ) and adrenal volume (OR 1.27,  $p = 0.018$ ). UFC/24 h was associated with BA (OR 1.01,  $p = 0.019$ ) after adjusting for age, sex and BMI, and additional adjustments for SBP (OR 1.01,  $p = 0.014$ ) and adrenal volume (OR 1.01,  $p = 0.019$ ). Baseline serum cortisol level at 4 PM and 0 AM were also positively associated with BA after adjusting for age, sex, BMI, SBP, and adrenal volume (► **Table 2**).

## The predicative value of baseline serum cortisol levels, UFC/24 h for surgery method of PBMAH

In descending order, the area under the ROC curves (AUC) was 0.85 and 0.83 for models based on 8 AM serum cortisol and UFC/24 h, respectively (all  $p < 0.05$ ). The AUC was largest in model based on 8 AM cortisol though non-significantly. ROC analysis showed that the threshold of 26.89  $\mu\text{g/dl}$  based on 8 AM serum cortisol model was the best cutoff to detect BA, with 66.7% sensitivity and 89.5% specificity. The threshold of 406.65  $\mu\text{g}$  based on UFC/24 h model was the best cutoff, with 77.8% sensitivity and 73.7% specificity (► **Fig. 2**).

## Discussion

The characteristic of PBMAH is bilateral macronodular hyperplasia of the adrenal glands and it can cause subclinical or overt CS [25, 26]. In most cases, we identified PBMAH by accident during computed tomography (CT) and magnetic resonance imaging (MRI) for unrelated conditions [4]. Among our surgical patients, 70% patients visited a doctor for hypertension. PBMAH predominantly affects women, but there is no difference in sex ratio in identified genetic cause [3]. In sporadic cases, the median age at diagnosis is about 55 [3, 27]. Our study included 18 females and 12 males with an average age of  $50.8 \pm 6.6$  years (range, 40–68 years)

► **Table 1** Clinical characteristics of PBMAH patients.

Clinical characteristics	Unilateral adrenalectomy (n = 20)	Bilateral adrenalectomy (n = 10)	p-Value
Age at diagnosis (years)	51.8 $\pm$ 6.7	48.7 $\pm$ 6.3	0.235
Male (%)	9 (45.0%)	3 (30.0%)	0.437
BMI (kg/m <sup>2</sup> )	21.6 $\pm$ 7.9	23.4 $\pm$ 8.5	0.557
BMI $\geq$ 24 kg/m <sup>2</sup>	10 (50.0%)	9 (90.0%)	<b>0.035</b>
Clinical symptoms of CS (%)	15 (75.0%)	10 (100.0%)	0.089
24 hour circadian rhythm			
8 AM serum cortisol ( $\mu\text{g/dl}$ )	18.5 $\pm$ 6.5	28.2 $\pm$ 6.7	<b>0.001</b>
4 PM serum cortisol ( $\mu\text{g/dl}$ )	15.7 $\pm$ 6.5	23.8 $\pm$ 7.1	<b>0.005</b>
0 AM serum cortisol ( $\mu\text{g/dl}$ )	13.5 $\pm$ 6.0	18.4 $\pm$ 4.2	<b>0.036</b>
Loss of circadian rhythm (%)	17 (85.0%)	10 (100.0%)	0.204
UFC/24 h ( $\mu\text{g}$ )	326.8 $\pm$ 257.4	692.9 $\pm$ 390.4	<b>0.005</b>
UFC > 111 $\mu\text{g}/24\text{ h}$ (%)	16 (80.0%)	10 (100.0%)	0.135
ACTH (pg/ml)	7.7 $\pm$ 4.4	15.4 $\pm$ 23.3	0.355
ACTH < 7.0 pg/ml (%)	11 (55.0%)	4 (40.0%)	0.446
Hypertension (%)	18 (90.0%)	10 (100.0%)	0.309
SBP (mmHg)	176.8 $\pm$ 28.7	174.5 $\pm$ 6.4	0.821
DBP (mmHg)	110.3 $\pm$ 24.3	112.5 $\pm$ 7.9	0.779
Adrenal volume (ml)	46.9 $\pm$ 4.9	51.2 $\pm$ 6.8	0.588
Negative response to LDDST (%)	20 (100.0%)	10 (100.0%)	1.000
Negative response to HDDST (%)	20 (100.0%)	10 (100.0%)	1.000
Diabetes mellitus (%)	10 (50.0%)	5 (50.0%)	1.000
Hypokalemia (%)	13 (65.0%)	8 (80.0%)	0.406
Osteoporosis (%)	8 (40.0%)	7 (70.0%)	0.128

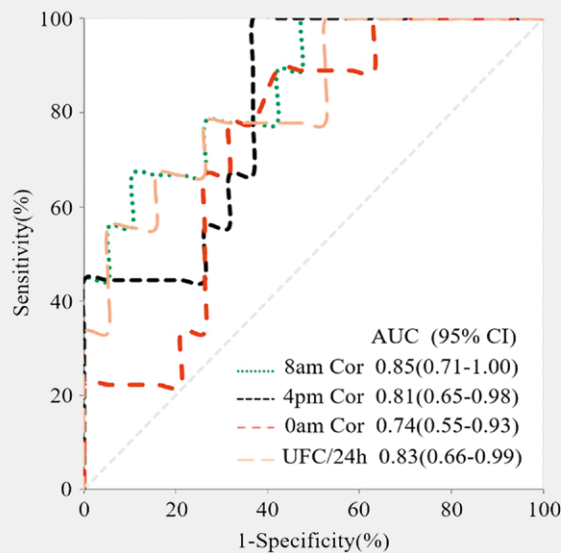
Data are mean  $\pm$  standard deviation or number (%). The independent samples *t*-test and  $\chi^2$  test or the Fisher exact test were used respectively for comparison between groups.; BMI: Body mass index; CS: Clinical syndrome; UFC/24 h: 24 hour urinary free cortisol; ACTH: Adrenocorticotropic hormone; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDDST: Low-dose dexamethasone suppression test; HDDST: High-dose dexamethasone suppression test.

at diagnosis, which were consistent with those reported [3, 27]. Clinical manifestations of PBMAH include weight gain, impaired glucose tolerance or diabetes mellitus, hypertension, osteoporosis and hypokalemia. Our research showed that 83.3% (25/30) patients have clinical symptoms of CS, similar to the research summarized by Duan (86.7%, 26/30) [28], but significantly higher than in the research by Libé (31.3%, 10/32) [29], this may be associated with the elevated UFC/24 h levels in most patients [28]. In these cases, hypertension was the most common clinical manifestation (93.3%), others include weight gain (63.3%), osteoporosis (50%), diabetes (50%) and hypokalemia (70%). Circadian rhythm of plasma cortisol was lost in 27 (90%) patients, and the level of UFC/24 h was normal only in 4 (13.3%) patients. Usually, ACTH is low in

► **Table 2** Associations of serum cortisol and UFC/24h levels with bilateral adrenalectomy.

	Model 1		Model 2		Model 3	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
8 AM Cor	1.28 (1.06–1.54)	0.010	1.28 (1.07–1.52)	0.007	1.27 (1.05–1.53)	0.013
4 PM Cor	1.33 (1.07–1.64)	0.010	1.37 (1.07–1.76)	0.013	1.38 (1.06–1.80)	0.016
0 AM Cor	1.31 (1.01–1.69)	0.038	1.34 (1.01–1.77)	0.040	1.33 (0.99–1.78)	0.056
UFC/24h	1.01 (1.00–1.01)	0.019	1.01 (1.00–1.02)	0.014	1.01 (1.00–1.02)	0.018

Data were calculated using a binary logistic regression model. Model 1 was adjusted for age, sex, BMI; Model 2 was adjusted ; for age, sex, BMI and SBP; and Model 3 was adjusted for age, sex, BMI, SBP and adrenal volume.; OR: Odds ratio; CI: Confidence interval; UFC/24h: 24-h urinary-free cortisol; Cor: Serum cortisol.



	Maximum Youden index		
	Cut-offs	Sensitivity(%)	Specificity(%)
<b>8 am Cor(ug/dl)</b>	26.89	66.7	89.5
<b>4 pm Cor(ug/dl)</b>	16.17	100.0	63.2
<b>0 am Cor(ug/dl)</b>	15.30	88.9	57.9
<b>UFC/24h(ug)</b>	406.65	77.8	73.7

► **Fig. 2** Receiver operating characteristic curves for predicting bilateral adrenalectomy.

PBMAH patients with subclinical or overt Cushing's syndrome, and sometimes not detectable. However, 15 (50%) patients in our research had non-suppressed ACTH level, this may be caused by the secretion of ACTH by the adrenocortical cells as demonstrated by Louiset et al. [30] in 2013. Both low and high dose dexamethasone suppression tests were not suppressed in 30 (100%) and 30 (100%) patients, respectively.

Historically, the mainstay treatment for PBMAH associated with CS was BA [9]. However, despite its undeniable efficiency in maximally decreasing cortisol in the blood and relieving symptoms, it leads to adrenal insufficiency permanently, with the need for corticosteroid replacement forever. Moreover, if replacement therapy is discontinued, life-threatening adrenal insufficiency (Addison's disease) can develop quickly [14, 31, 32]. Considering these adverse effects, an increasing number of patients, especially those with sub-

clinical CS or clear adrenal asymmetry, have undergone UA in recent years. As reported by some retrospective series [33–36], excessive cortisol secretion can be controlled satisfactorily and it is not common to have contralateral adrenalectomy or medical treatment due to recurrences. However, a recent retrospective study reported that despite the lower incidence of adrenal crisis and biochemical remission, the mortality rate in patients treated by UA was higher than that in patients treated by BA, potentially due to the inadequate control of hypercortisolism [37]. Recently, a more promising surgery method was proposed for the treatment of PBMAH, which was called adrenal-sparing surgery. In 2020, Tanno et al. [19] first reported this surgery method and demonstrated that most patients undertaken adrenal-sparing surgery had complete hypercortisolism control after 41 months follow-up without the disadvantages of lifetime corticosteroid replacement in a prospective cohort. However, as many patients in this study had mild hypercortisolism, the benefit of this surgery in PBMAH patients with overt CS is needed to be clarified. BA for the treatment of CS in PBMAH patients and selective UA of the larger adrenal in selected cases are advocated by Guidelines from the European Society of Endocrinology (ESE) and the Endocrine Society [10]. In our study, 10 patients with clinical symptoms of CS had BA and 15 patients had UA. Although having their recommendations and UA being an attractive surgical option, they agree that the gold standard has not yet been established and the treatment of the disease remains controversial. When selecting UA in PBMAH patients, the choice of adrenal to be removed must be considered. All patients with UA in our study chose to remove the larger adrenal as reported in the previous retrospective series [4, 33–35, 38], and can achieve an initial remission rate of more than 85%. It is hypothetically considered that the larger adrenal on imaging was the most active in cortisol production. As reported previously [7], we preferred to remove the right gland as the liver and vena cava were located on the right side, making it more difficult to perform a second surgery, in the condition that bilateral adrenal glands were symmetric.

Although UA is preferred by endocrinologists and urologists in patients with PBMAH, the procedure does not always relieve the symptoms because of recurrence. In such cases it is inevitable that patients need to undergo a contralateral adrenalectomy. According to the reports, a second adrenalectomy may be required as the cell mass increases in the contralateral adrenal gland [39, 40], and there may be a positive correlation between the size of the contralateral adrenal and the persistence of CS [34]. However, to date, there is no predictor of UA effectiveness in controlling hypercortisolism or avoiding recurrence from the residual adrenal tissue [20]. So, it is critical to identify those patients who need to have BA in the early stage. Early predication for surgery method is very difficult. The common judgement indicators may include the size and symmetry of bilateral nodules and cortisol levels. It fails to predict the surgery method just according to the size and symmetry of bilateral nodules, because some nodules are large but may have no functions. Some suggest BA for patients with overt hypercortisolism and CS, but no research reports that patients are more likely to have BA according to the baseline level of cortisol. As our study indicated, patients with a high cortisol level (8 am serum cortisol > 26.89 µg/dl or UFC/24 h > 406.65 µg) are more inclined to need

a contralateral adrenalectomy, the baseline serum and urinary cortisol levels are good markers to predict the surgery method.

However, our study does have some limitations. First, the sample size was limited, and further studies with a large sample size are needed to confirm the results. In addition, we chose to remove the larger adrenal gland first for patients on imaging, cortisol levels obtained by bilateral adrenal venous sampling (AVS) could also be used to select the resected adrenal gland. Finally, this was a single center retrospective observational study, and prospective and multicenter studies are required to confirm the associations between baseline cortisol levels and surgery method.

## Conclusions

In conclusion, the concentrations of baseline serum cortisol (8 AM, 4 PM, and 0 AM) and UFC/24 h in patients who had BA were significantly higher than those who had UA. PBMAH patients with higher concentrations of baseline serum cortisol and UFC/24 h should be more closely monitored and predisposed to undertake BA.

## Authors' Contributions

Jie Gao and Zhongwei Yu performed the statistical analysis and wrote the manuscript; Hongping Wang and Cuiping Zhang participated in the data collection and checked the data; Fukang Sun and Bilin Xu contributed to the discussion; Jun Lu and Tao Lei participated in the design of this study and edited the manuscript. All authors have read and approved the final manuscript.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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