Clinical Analysis of the Etiological Spectrum of Bilateral Adrenal Lesions: a Large Retrospective, Single-center Study

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Research Article

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Abstract

Purpose: To investigate the clinical characteristics, endocrinological function, and etiologies of patients with bilateral adrenal lesions.

Methods: A retrospective study of 777 patients with bilateral adrenal lesions was conducted at the Chinese General Hospital of the People's Liberation Army between January 2013 and January 2018. Patient demographic features, hormonal profiles, imaging findings, and histopathological findings were reviewed from the database records.

Results: Of the 777 patients with bilateral adrenal lesions, 495 were men, and the mean age at diagnosis was 52.0±13.0 years. A total of 511 (65.8%) cases were benign, followed by adrenal metastases (n=224, 28.8%), pheochromocytoma (n=26, 3.3%), adrenal lymphoma (n=9, 1.2%), and adrenal corticocarcinoma (ACC) (n=7, 0.9%). Hormonal evaluation revealed that 34.3% of bilateral adrenal lesions were functional. The primary etiologies of functional lesions were primary aldosteronism (16.6%, 129/777) , and PBMAH (8.8%, 68/777). Patients with lymphoma and metastases were significantly older than those with benign nonfunctional lesions (60.4±11.0 years vs. 54.5±10.4 years and 57.9±10.8 years vs. 54.5±10.4 years, respectively; P<0.001). Lesions in adrenal lymphoma, ACC, pheochromocytoma, metastases, CAH, tuberculosis, and Cushing's syndrome were significantly larger than benign nonfunctional lesions (all P<0.001).

Conclusion: Benign adrenal lesions and metastases to the lungs are the most common causes of bilateral adrenal lesions, and primary aldosteronism and BMAH are the most prevalent functional lesions. In addition, our findings suggest that patients with lymphoma or metastases are older and possess larger masses.

1 Introduction

Adrenal lesions are detected in approximately 1.0–5.1% of computed tomography (CT) scans taken to obtain different data [1]. Most of these lesions are unilateral and benign. Nevertheless, bilateral adrenal lesions are uncommon, with a prevalence of 7.8–15% [2]. The most common underlying pathology of bilateral adrenal lesions has been reported to be pheochromocytoma [3]. In 2017, Lele et al. reported a prevalence of bilateral adrenal lesions of 7.6% in the study population, and more hyperfunctional lesions were observed in these cases than unilateral adrenal lesions [4]. Hence, unilateral and bilateral adrenal lesions have different etiologies. Unfortunately, the few reports available on the incidence of bilateral adrenal lesions are insignificant and outdated. In the present study, a retrospective analysis based on a large population was conducted using hospital records to determine the prevalence, clinical presentation, size, and etiologies of adrenal lesions in the adrenal glands over a 5-year period.

2 Materials And Methods

2.1 Patients

Patient medical records from the Chinese People's Liberation Army General Hospital for the period 2013–2018 were reviewed, and the following discharge diagnoses were identified: "adrenal tumor," "adrenal adenoma," "adrenal lesion," "adrenal hyperplasia," "pheochromocytoma," "primary aldosteronism," "aldosterone-producing adenoma (APA)," "idiopathic hyperaldosteronism (IHA)," "Cushing's Syndrome (CS)," "primary bilateral macronodular adrenocortical hyperplasia (PBMAH)," "primary pigmented nodular adrenocortical disease (PPNAD)," "Cushing's disease," "ectopic adrenocorticotropic hormone (ACTH) syndrome," " tuberculosis," "adrenocortical adenoma," "adrenocortical carcinoma(ACC)," " adrenal lymphoma," and "congenital adrenal hyperplasia (CAH)." A total of 4,156 patients hospitalized in hematology, endocrinology, and other departments were screened for adrenal abnormalities using adrenal CT or magnetic resonance imaging (MRI), based on the above search results.

The inclusion criteria entailed radiological examinations of patients with the following conditions: 1) bilateral adrenal diffuse hyperplasia, 2) unilateral adrenal diffuse hyperplasia combined with contralateral adrenal nodular hyperplasia or adenomas, and 3) bilateral adrenal nodular hyperplasia or adenomas. All included patients underwent hormonal evaluation. The exclusion criteria were as follows: 1) radiological examinations of patients with unilateral adrenal diffuse or nodular hyperplasia or adenomas or atrophy and a contralateral, normal-looking adrenal gland; 2) bilateral adrenal atrophy; and 3) patients without hormonal evaluation or radiological examinations.

Finally, 777 patients hospitalized with bilateral adrenal lesions were included in the study. The baseline demographic and imaging characteristics of patients were extracted at initially radio-graphical diagnosis of bilateral adrenal lesions. This retrospective study was approved by the relevant Institutional Review Board (No. 2019 – 229), and informed consent was obtained from all participants. The information retrieved from the records at the onset of bilateral adrenal lesions included demographic data, clinical features, hormonal evaluation, imaging details of adrenals, and histopathological findings.

2.2 Endocrine investigation

Basic biochemical evaluations included plasma glucose, serum cortisol, plasma ACTH, 24-h urinary free cortisol (UFC), plasma free metanephrine (PFMN) normetanephrine (PFNMN), plasma active renin concentration, plasma aldosterone, and serum 17-hydroxyprogesterone (17-OHP) levels.

1) Subclinical Cushing's syndrome (SCS) was defined as a cortisol concentration ≥ 1.8 ug/dL after the dexamethasone suppression test (DST) in combination with at least one other abnormal test of the hypothalamic-pituitary-adrenal axis, not associated with typical signs and symptoms of hypercortisolism. 2) Cushing's syndrome was defined as at least two first-line biochemical tests (DST, UFC, and midnight serum cortisol) returning clearly abnormal results, included typical Cushing's syndrome and SCS [5].

3) A screening test for pheochromocytoma was considered positive if PFMN was ≥ 0.50 nmol/L and/or PFNMN ≥ 0.21 nmol/L, and a ^{131}I-metaiodobenzylguanidine (MIBG) scan was performed to confirm the diagnosis of pheochromocytoma [6]. 4) A screening test for primary aldosteronism (PA) was considered positive if plasma ARR was > 20 (plasma aldosterone concentration expressed in pg/mL and plasma active renin concentration in ng/mL/h), and saline infusion and/or captopril challenge testing were performed to confirm PA. The diagnoses of APA and IHA have been described in the literature [7]. 5) The subtypes of Cushing's syndrome with bilateral adrenal lesions, included Cushing's disease (CD), Ectopic ACTH dependent CS, PBMAH, PPNAD, bilateral adrenocortical carcinoma (ACC), and bilateral adrenocortical adenoma (BAA) secreting cortisol on both sides, Which is a rare cause of ACTH independent CS, were diagnosed according to the International Society of Endocrinology guidelines [5, 8]. 6) CAH was confirmed using clinical history, current clinical signs, hormonal levels (predominantly 17-OHP, ACTH, cortisol, plasma active renin concentration, plasma aldosterone, and androgens), and/or CYP21A2 gene mutational analysis [9]. 7) After excluding the above status, a diagnosis of nonfunctional adrenal lesions was established.

2.3 Histologically or image evaluation

Adrenal lymphoma was defined as a histologically proven lymphomatous lesion [10], and adrenal metastases were confirmed by biopsy or positron emissiontomography/ computed tomography (PET/CT). ACC was determined by histopathology according to the scoring system of Lin-Weiss-Bisceglia [11]. Adrenal tuberculosis was defined histologically or by imaging [12]. Benign, non-functional adrenal lesions were defined as characteristic images of masses with a baseline HU ≤ 10 [13], homogeneous internal texture, and benign washout patterns (for instance, absolute washout > 60% and relative washout > 40%) on CT scans [14, 15],signal dropout on opposed-phased imaging for chemical shift MRI [16], or benign-proven histopathology, which were non-functional diagnosed by endocrine examination. Dignosis of bilateral adrenal thickening was defined as radiologically diffuse thickening of bilateral adrenal glands. Size of adrenal tumors refered to the diameter of the largest adrenal tumor.

2.4 Statistical analysis

Normally distributed continuous variables are presented as means and standard deviations, and non-normally distributed variables are presented as medians and ranges. Categorical variables are expressed as frequencies and percentages. Continuous data were compared using a one-way analysis of variance. Categorical data were analyzed using the chi-squared test or Fisher's exact probability test. Statistical significance was set at $P < 0.05$. All data analyses were performed using SPSS (version 26.0; IBM, Armonk, NY, USA).

3 Results

3.1 Baseline demographic and imaging characteristics

The medical records of 777 patients (495 men, 282 women) with bilateral adrenal lesions who were admitted to hospital were reviewed. The mean age at onset of bilateral adrenal lesions was 52.0 ± 13.0 years, and the mean BMI was 25.6 ± 3.2kg/m^2. 636 (81.9%) patients were evaluated by imaging of unenhanced or washout CT. Bilateral tumors were detected by imaging in 492 (63.3%) cases and bilateral adrenal diffuse hyperplasia in 91 (11.7%) cases, the remaining 194 (25.0%) cases had unilateral adrenal diffuse hyperplasia combined contralateral adrenal tumors (Table 1). 474 (61.0%) cases with hypertension, 213 (27.4%) with diabetes, and 176 (22.7%) with hypokalemia were observed. The distribution of patients enrolled according to the departments is shown in Fig. 1. The highest proportion of patients with bilateral lesions was admitted to department of endocrinology.

Table 1
Baseline demographic and imaging characteristics of patients with bilateral adrenal lesions

Characteristic	Value
Gender, male/female (n)	495/282
Age (years)	52.0 ± 13.0
BMI (kg/m^2)	25.6 ± 3.2
Hypertension (n, %)	474 (61.0%)
Diabetes mellitus (n, %)	213 (27.4%)
Hypokalemia (n, %)	176 (22.7%)
Technique used for imaging	
Unenhanced or washout CT	636 (81.9%)
Unenhanced/washout CT and Chemical shift MRI	45 (5.8%)
Unenhanced/washout CT and FDG-PET/CT	68 (8.8%)
Unenhanced/washout CT and ^{68}Ga-DOTATATE-PET/CT or ^{131}I-MIBG	28 (3.6%)
Imaging features	
Bilateral adrenal diffuse hyperplasia (n, %)	91 (11.7%)
Unilateral adrenal diffuse hyperplasia combined contralateral adrenal tumors (n, %)	194 (25.0%)
Bilateral adrenal adrenal tumors (n, %)	492 (63.3%)
Adrenal vein sampling (n, %)	42 (5.4%)
Surgery (n, %)	130 (16.7%)
FDG-PET/CT:18-fluorodeoxyglucose positron emission tomography/computed tomography; ^{68}Ga-DOTATATE-PET/CT:^{68}Ga-labeled1,4,7,10-tetraazacyclododecane–1,4,7,10-tetraacetic acid–octreotate positron emission tomography/computed tomography;	
MIBG:^{131}I-metaiodobenzylguanidine	

3.2 Etiology of bilateral adrenal lesions

Based on histopathology and hormonal function, bilateral adrenal lesions in our study were classified as benign or malignant. Among the 511 (65.8%) patients with benign bilateral adrenal lesions, 222 (28.6%) had nonfunctional lesions, 38 (4.9%) CAH, 10 (1.3%) adrenal tuberculosis, 129 (16.6%) primary aldosteronism, and 112 (14.4%) Cushing's syndrome (Table 2).

Table 2
The etiologies of bilateral adrenal lesions

Etiologies of bilateral adrenal lesions	N (%)
Non-functional adrenal lesions	222 (28.6%)
Tuberculosis	10 (1.3%)
CAH	38 (4.9%)
Primary aldosteronism	129 (16.6%)
Cushing's syndrome	112 (14.4%)
Pheochromocytoma	26 (3.3%)
ACC	7 (0.9%)
Lymphoma	9 (1.2%)
Adrenal metastases	224 (28.8%)
Lung carcinoma	148 (19.1%)
Gastric carcinoma	15 (1.9%)
Colorectal carcinoma	14 (1.8%)
Hepatocelluar carcinoma	15 (1.9%)
Ensophageal carcinoma	3 (0.4%)
Genitourinary carcinoma	4 (0.5%)
Ovarial carcinoma	3 (0.4%)
Pancreatic carcinoma	3 (0.4%)
Gallbladder carcinoma	3 (0.4%)
Breast carcinoma	5 (0.6%)
others	6 (0.8%)
CAH: Congenital adrenal hyperplasia;ACC: Adrenocortical carcinoma	

Among the 266 (34.2%) cases of malignant bilateral adrenal lesions, the most common etiology was adrenal metastases (n = 224, 28.8%), followed by pheochromocytoma (n = 26, 3.3%), adrenal lymphoma (n = 9, 1.2%), and adrenal corticocarcinoma (n = 7, 0.9%). The primary-tumor sites of the bilateral adrenal metastases in our study, in decreasing order of frequency, were the lungs (19.1%), stomach (1.9%), hepatocellular tissues (1.9%), intestines (1.8%), kidney (1.2%), breast (0.6%), and pancreas (0.4%) (Table 2).

3.3 Clinical characteristics and bilateral adrenal lesions

The highest body mass index (BMI) at onset of bilateral adrenal lesions was found in patients with primary aldosteronism (27.1 ± 3.6 kg/m^2), followed by that in patients with Cushing's syndrome (26.4 ± 3.6 kg/m^2), tuberculosis (25.4 ± 5.0 kg/m^2), adrenal benign nonfunctional lesions (25.4 ± 1.8 kg/m^2), metastases (23.8 ± 3.9 kg/m^2), lymphoma (23.6 ± 4.4 kg/m^2), ACC (23.6 ± 4.4 kg/m^2), CAH (23.0 ± 5.0 kg/m^2), and pheochromocytoma (22.9 ± 5.5 kg/m^2). Thus, the BMIs at onset of bilateral adrenal lesions of patients with pheochromocytoma, CAH, ACC, and adrenal metastases were significantly less than those in patients with benign nonfunctional lesions (22.9 ± 45.5 kg/m^2 vs. 25.4 ± 1.8 kg/m^2; 23.0 ± 5.0 kg/m^2 vs. 25.4 ± 1.8 kg/m^2; 23.6 ± 4.4 kg/m^2 vs. 25.4 ± 1.8 kg/m^2; and 23.8 ± 3.9 kg/m^2 vs. 25.4 ± 1.8 kg/m^2, respectively; all $P < 0.001$) (Table 3).

Table 3
Characteristics of patients with bilateral adrenal lesions

	Benign					Malignant			
	Non-functional adrenal lesions	Tuberculosis	CAH	Primary aldosteronism	Cushing's syndrome	Pheochromocytoma	Adrenal metastases	ACC	Lymphoma
Total(n,%)	222(28.6%)	10 (1.3%)	38 (4.9%)	129(16.6%)	112(14.4%)	26(3.3%)	224(28.8%)	7(0.9%)	9(1.2%)
Male/Female	158/64	4/6	13/25	81/48	43/69	19/7	168/56	4/3	5/4
Age(years)	54.5 ± 10.4	53.2 ± 13.0	28.9 ± 16.7***	53.6 ± 8.6	50.1 ± 11.8	32.9 ± 13.8***	57.9 ± 10.8***	49.7 ± 9.2	60.4 ± 11.0***
BMI(kg/m^2)	25.4 ± 1.8	25.4 ± 5.0	23.0 ± 5.0***	27.1 ± 3.6	26.4 ± 3.6	22.9 ± 5.5***	23.8 ± 3.9***	23.6 ± 4.4***	23.6 ± 4.4*
Left-sided size(cm)	2.0 ± 1.3	3.5 ± 1.5***	3.6 ± 1.1***	1.5 ± 0.6	3.5 ± 2.4***	3.5 ± 2.1***	3.1 ± 2.0***	3.5 ± 1.9***	7.8 ± 2.1***
Right-sided size(cm)	1.8 ± 1.2	2.2 ± 0.2	3.7 ± 1.1***	1.4 ± 0.6	3.1 ± 1.9***	4.4 ± 1.9***	3.2 ± 1.9***	6.1 ± 3.4***	7.5 ± 3.4***
Compared with benign nonfunctional adrenal lesions, *presents P value < 0.05, **0.01 presents P value < 0.01;***presents P value < 0.001									
CAH: Congenital adrenal hyperplasia;ACC: Adrenocortical carcinoma									

The mean ages at onset of bilateral adrenal lesions of patients with pheochromocytoma, CAH, lymphoma, ACC, adrenal metastases, benign nonfunctional lesions, tuberculosis, Cushing's syndrome and primary aldosteronism were 32.9 ± 13.8, 28.9 ± 16.7, 60.4 ± 11.0, 49.7 ± 9.2, 57.9 ± 10.8, 54.5 ± 10.4, 53.2 ± 13.0, 50.1 ± 11.8, and 53.6 ± 8.6 years, respectively. Thus, patients with pheochromocytoma and CAH were significantly younger than those with benign nonfunctional lesions (32.9 ± 13.8 years vs. 54.5 ± 10.4 years and 28.9 ± 16.7 years vs. 54.5 ± 10.4 years, respectively; all $P < 0.001$). Patients with lymphoma and adrenal metastases were significantly older (60.4 ± 11.0 years vs. 54.5 ± 10.4 years and 57.9 ± 10.8 years vs. 54.5 ± 10.4 years, all $P < 0.001$) (Table 3).

The etiologies of bilateral adrenal lesions, in decreasing order of diameter, were lymphoma (right: 7.5 ± 3.4 cm, left: 7.8 ± 2.1 cm), followed by ACC (right: 6.1 ± 3.4 cm, left:3.5 ± 1.9 cm), pheochromocytoma (right: 4.4 ± 1.9 cm, left: 3.5 ± 2.1 cm), CAH (right: 3.7 ± 1.1 cm, left: 3.6 ± 1.1 cm), Cushing's syndrome (right: 3.1 ± 1.9 cm, left: 3.5 ± 2.4 cm), tuberculosis (right: 2.2 ± 0.2 cm, left: 3.5 ± 1.5 cm), adrenal metastases (right: 3.2 ± 1.9 cm, left: 3.1 ± 2.0 cm), benign nonfunctional lesions (right: 1.8 ± 1.2 cm, left: 2.0 ± 1.3 cm), and primary aldosteronism (right: 1.4 ± 0.6 cm, left: 1.5 ± 0.6 cm). Thus, all bilateral adrenal lesions, except those in primary aldosteronism, were significantly larger than benign nonfunctional adrenal lesions (all $P < 0.001$) (Table 3).

3.4 Functional status and bilateral adrenal lesions

Endocrinological evaluation revealed that 267 patients (34.3%) exhibited hyperfunction. The primary etiologies of functional lesions were primary aldosteronism (16.6%, 129/777) and PBMAH (8.8%, 68/777). Cushing's disease accounted for 3.6% (28/777), followed by pheochromocytoma (3.3%, 26/777), BAA (1.5%, 12/777), PPNAD (0.4%, 3/777), and ectopic ACTH syndrome (0.1%, 1/777). Male patients were more common, the incidence of typical Cushing's syndrome was lower, and the size of adrenal lesions was larger in the PBMAH group than in the PPNAD group (all $p < 0.01$). In addition, patients with PPNAD were significantly younger than those with BMAH ($p < 0.01$) (Table 4). Of this total, 120 patients had bilateral adrenal incidentalomas. 3 of 120 patients were ACC. Endocrinological evaluation showed that 96 (80.0%) of these patients had nonfunctional tumors, 14 (11.6%) had SCS, 6 (5.0%) had primary hyperaldosteronism, and 4(3.3%) had pheochromocytomas.

Table 4
Clinical characteristics of patients with hypersecretion glucocorticoid in bilateral adrenal lesions

	PBMAH	PPNAD	Bilateral adrenal adenoma	Cushing's disease	Ectopic ACTH syndrome
N(male/female)	68(38/30)	3(1/2)	12(2/10)	28(1/27)	1(1/0)
Age(year)	52.4 ± 10.8**	35.7 ± 10.1	42.5 ± 10.7	44.7 ± 10.0	30
BMI(kg/m^2)	26.7 ± 3.4	25.3 ± 3.0	26.7 ± 2.7	27.6 ± 4.0	18.9
Hypertension(n)	54(83%)	3(100%)	8(67%)	26(93%)	0(0%)
Diabetes(n)	29(45%)	1(33%)	2(17%)	18(64%)	0(0%)
Hypokalemia(n)	14(22%)	0(0%)	1(8%)	14(50%)	0(0%)
Left size(cm)	4.0 ± 2.6**	1.0 ± 0.4	2.1 ± 0.9	2.0 ± 1.1	hyperplasia
Right size(cm)	3.0 ± 1.4**	0.7 ± 0.1	2.2 ± 1.0	2.0 ± 0.5	hyperpalsia
*presents P value < 0.05, **presents P value < 0.01, *** presents P value < 0.001, all of them compared with PPNAD.					
PPNAD: primary pigmented adrenocortical disease; PBMAH:Primary bilateral macronodular adrenocortical hyperplasia; ACTH: adrenocorticotropic hormone					

4 Discussion

In a large study of 777 patients with bilateral adrenal lesions, we demonstrated that the vast majority of bilateral adrenal lesions were benign nonfunctional lesions and adrenal metastases, followed by primary aldosteronism, Cushing's syndrome, CAH, and pheochromocytoma. Consistent with our findings, benign nonfunctional adenomas and metastases were also the most common causes of bilateral adrenal lesions according to the Peking University Third Hospital [17]. However, a tertiary care endocrine center in western India reported that the predominant cause of bilateral adrenal lesions was pheochromocytoma (40%), followed by tuberculosis (27.1%), primary adrenal lymphoma (10%), metastases (5.7%), nonfunctional adenomas (4.3%), and primary bilateral macronodular adrenal hyperplasia (4.3%) [3]. This contradiction may be due to varying patient inclusion criteria, patient-admission departments, and availability of and accessibility to imaging evaluation. In contrast, a higher proportion of functional lesions in patients with bilateral adrenal lesions than in those with unilateral adrenal lesions has been reported in the recent literature [4, 18]. This is consistent with our finding in which a prevalence of 34.3% was observed in these cases. Bilateral lesions have been reported to be more commonly associated with genetic alterations favoring tumor growth than with cortisol overproduction [19]. In addition, a lower prevalence of tuberculosis has been reported in recent literature, and it may be potentially associated with the improvement in public health education.

Among the 266 patients with malignant adrenal lesions, 224 were confirmed to have adrenal metastases, which occurred in patients with lung, gastrointestinal, and renal carcinomas. Nonetheless, we also found a high prevalence of adrenal metastases arising from liver and breast cancers. This result is consistent with that reported by Lam et al. [20]. Furthermore, bilateral adrenal lesions arising from disseminated cancers occurred late in the course of the disease and increased rapidly in size, a phenomenon possibly related to the rich sinusoidal blood supply to the adrenal glands. Therefore, adrenal metastases were the most common cause of bilateral malignant adrenal lesions, and it is possible that the size of bilateral adrenal lesions increased over a short period in older adults. Thus, thorough imaging evaluation is necessary to detect primary tumors, especially those in lung cancer. Additionally, our results showed the prevalence of 5.8% patients with bilateral incidentalomas were malignant in low-risk patients without known malignancy, which concurs with the published literature [21].

Furthermore, our study demonstrated a higher prevalence of hormonal activity among patients with bilateral adrenal lesions. The possibility of varying prevalence of functional lesions between patients with bilateral and unilateral lesions is reportedly related to genetic alterations. Primary aldosteronism was the most common cause of hyperhormonal lesions, followed by BMAH. However, Cushing's disease and cortisol-producing adrenocortical adenoma have been reported to account for 70% and 20% of cases, respectively, whereas BMAH has only accounted for 3% of cases [19].The prevalence of BMAH varies in clinical series due to the high prevalence of SCS, despite massive adrenal enlargement. In our study, we also demonstrated a higher prevalence of SCS among patients with bilateral incidentalomas. Other small series found similar results [18]. A larger size of adrenal nodules was observed in patients with PBMAH in our study, and this is potentially associated with the inactivating germline mutations in the ARMC5 putative tumor suppressor gene, which has been shown to cause altered cell survival and decreased steroidogenesis in order to increase the prevalence of SCS while enlarging the adrenal glands [22–25]. This potentially excludes the reason why patients with PBMAH have frequently been diagnosed with massive adrenal enlargement at an older age before the widespread use of radiological evaluation, indicating that the measurement of post-1 mg DST high morning cortisol concentrations should be suggested in all cases of bilateral adrenal enlargement, especially those ranging from 1 to 5 cm, to rule out SCS.

The mean age of patients with PPNAD in our study was 35.7 years, which concurs with that reported by Stratakis et al. [26]. This may be explained by the pathogenesis of PPNAD, which is predominantly attributed (up to 73%) to an inactivating germline mutation in the PRKAR1A gene [27]. Interestingly, we also found that PPNAD had a slight female predominance and presented more florid Cushing features than BMAH. This is consistent with the existing literature, which asserts that harboring mutations in the cyclic adenosine monophosphate pathway (PRKACA and GNAS) are generally smaller in size and present with more overt hypercortisolism [28]. Most patients with PPNAD have been shown to also exhibit the Carney complex, which comprises skin

lentigines, myxomas, and other endocrine and non-endocrine tumors. Thus, PPNAD should be suspected in patients with primary bilateral adrenal micronodules at a younger age, and timely screening for other components of CNCs should be considered.

Our study has certain limitations that should be discussed. First, this was a retrospective review of inpatients from a single center, thus potentially resulting in an overestimation of the proportion of functional and malignant lesions. Second, some data, such as that on adrenal vein sampling or biopsies, were unavailable to demonstrate whether bilateral adrenal lesions had the same function or pathology. Third, we didn't retrieve the image features, including the shape, pattern of growth, the detail of non-contrast HUs and washout indices for the bilateral adrenal lesions. Fourth, most of the benign adrenal lesions were diagnosed by imaging feature, without histology results.

5 Conclusion

The most common etiology of bilateral adrenal lesions in hospitalized patients in our study was benign adrenal lesions, followed by metastases, pheochromocytoma, lymphoma, and ACC. Primary hyperaldosteronism and BMAH were the most common functional lesions. In addition, patients with lymphoma are generally older and present with larger masses. Therefore, clinical characteristics, hormonal profiles, and lesion size are helpful in distinguishing the etiologies of bilateral adrenal lesions.

Declarations

Conflict of Interest

The authors declare that no competing financial interests exist.

Author Contributions

Fangfang Yan and Jinyang Zeng: collected data and wrote the manuscript draft. Yulong Chen, Yu Cheng, Yu Pei, Li Zang, Kang Chen, Weijun Gu, Jin Du, Qinghua Guo, Xianling Wang, Jianming Ba, Zhaohui Lv, Jingtao Dou: contributed to discussion and revision. Guoqing Yang and Yiming Mu: designed the study and revised the submission. All authors contributed to the discussion and approved the final manuscript for the version to be submitted.

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Ethical Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and was approved by the Ethics Committee(No. 2019-229).

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Figures

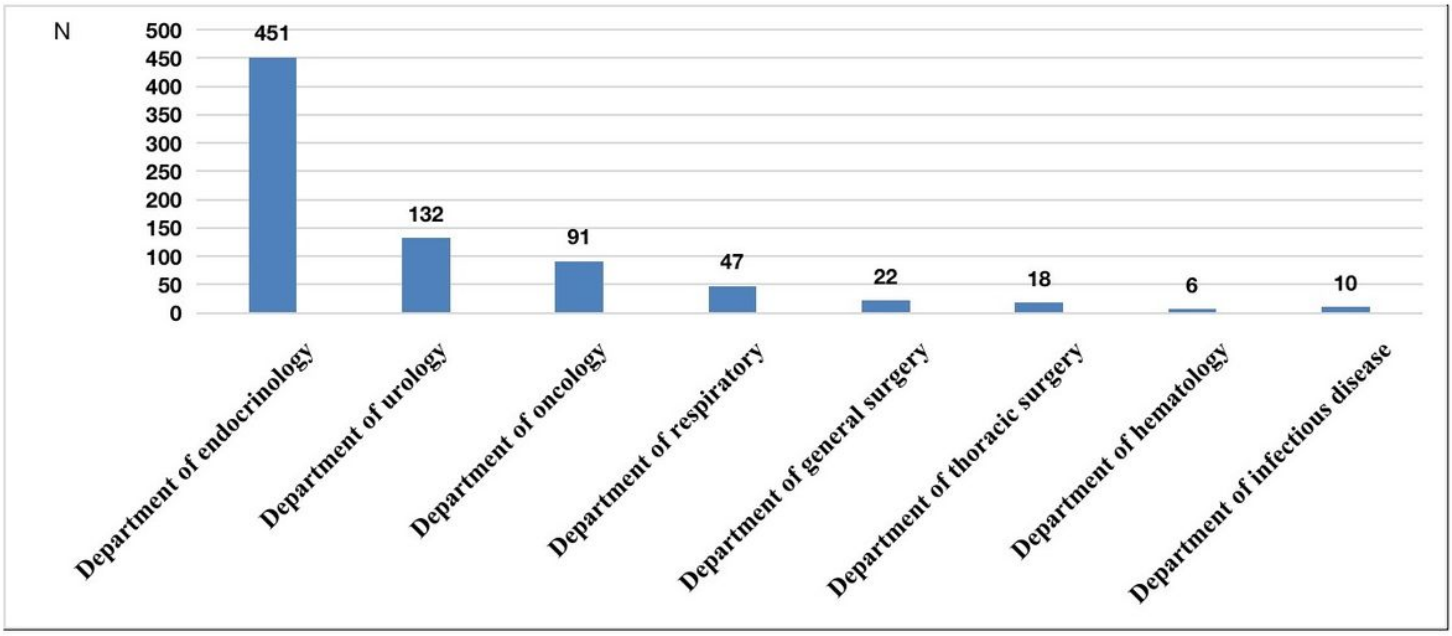

Figure 1

The distribution of patients according to the departments