

## Original Article

# Clinical features of 99 patients with huge (size $\geq 6$ cm) adrenal incidentaloma

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**Abstract:** Objective: With the development of radiological techniques, the diagnostic yield of adrenal incidentaloma reveals a significant rising trend. However, within the established diagnosed cases, the incident of huge adrenal incidentaloma (HAI) still remains to be rare. Here, we reported a large sample size of HAI with the analysis of clinical features. Methods and materials: 99 patients with an adrenal mass who were discovered incidentally by computed tomography (CT) or ultrasound (US) and were undertaken for further general examination or nonadrenal disease from January 2005 to December 2014 were studied retrospectively. The age, sex, location and size of masses, blood pressure, fasting glucose, concomitant symptoms, functionality, reasons for detection, imaging, histological findings and the follow-up for all patients were described. Results: Target patients consist of 54 males (54.54%) and 45 females (45.45%), aged between 18 and 77, and the average age was 45.75 years old. Adrenal masses were mostly found in patients in their sixth decade (31.31%). 49.49% of masses were found in right adrenal gland, 47.47% were found in left, and 3.03% were found bilaterally. The sizes of the masses range from 6 to 15 cm with an average size of 8.09 cm. All patients underwent surgical resections. Pheochromocytoma (35.35%) was the largest part of the final postoperative histopathologic diagnosis, followed by malignant masses (21.21%). Conclusion: The features of benign, malignant, non-functional and functional adrenal masses in our huge adrenal incidentaloma that were incidentally found and diagnosed at our hospital were presented in this paper. Most of the features were similar to those from previous reports about CAI.

**Keywords:** Huge adrenal incidentaloma (HAI), Common adrenal incidentaloma (CAI)

## Introduction

The incidence rate of Common adrenal incidentaloma (CAI) increases with the development of imaging diagnostic methods including ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) [1]. The term adrenal incidentaloma (AI) is usually defined as an adrenal mass unexpectedly detected through imaging diagnostic procedures performed for reasons including a prior unrelated to adrenal dysfunction, a suspected dysfunction and the physical examination and firstly described over three decades ago [2-4]. Especially along with recent advancements in imaging technology, positive detection rate of adrenal incidentalomas has remarkably increased [5, 6]. According to recent studies, most CAIs are benign,

nonfunctional tumors, only 10% of these masses are related to abnormal hormone secretion [7], and they are rarely found to be malignant [8]. To date, the size of mass has been recognized to be the strongest prognostic predictor of malignancy for AIs [4, 9]. Thus, it is of much importance to confirm whether a HAI is functional or nonfunctional, and possibly malignant than a CAI. There are varies of imaging techniques and biochemical tests utilized to formulate the differential diagnosis for AI [10], among which the most frequently used method is non-enhanced CT [11, 12]. There have been numerous studies about CAIs since they were firstly described [2, 3]. However, most of the studies concerned about CAI and conducted in Western patients [13, 14]. Few studies with small scale of patients have reported the clinical findings of

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**Table 1.** Baseline features of 99 patients with HAI

Feature	Value
Age, year (18-77)	
<30	15 (15.15)
≥30, <40	15 (15.15)
≥40, <50	27 (27.27)
≥50, <60	31 (31.31)
≥60, <70	8 (8.08)
≥70	3 (3.03)
Sex	
Males	54 (54.54)
Females	45 (45.45)
SBP (mmHg)	147.15 ± 38.31
DBP (mmHg)	96.35 ± 21.17
Fasting glucose (mg/dL)	6.31 ± 2.68
Site	
Right	49 (49.49)
Left	47 (47.47)
Bilateral	3 (3.03)
Concomitant disease	
Hypertension	35 (35.35)
Diabetes mellitus	21 (21.21)
Others	8 (8.08)
Reasons of detected	
Nonadrenal symptoms*	50 (50.50)
General examination	49 (49.49)

Values are presented as number (%) or mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure.

\*Nonadrenal symptoms, abdominal pain, fever, hematuria, back pain, etc.

Als in Asians [15] and studies on the Chinese population are more fewer, let alone such a large sample of patients with HAIs (length ≥6 cm) in our study. Accordingly, the objective of this study was to describe the clinical features of the 99 patients with HAI diagnosed by CT or US in Urology department of The First Hospital affiliated to China Medical University. To our knowledge, such a large sample of patients with HAI like our cohort has not been reported so far.

### Materials and methods

#### Study population

We retrospectively analyzed the medical records of 99 patients with HAI (length ≥6 cm) from Urology Department, First Affiliated Hospital of China Medical University from 2005.01 to

2014.12. None of the patients exhibited clinical symptoms of adrenal disease. The patients had adrenal masses detected on CT or US that were indicated for nonadrenal concerns, and patients who were discovered due to recurrent attacks of headache, debilitation, sweating, and palpitation did not belong to the object to be studied. The basic information, including age, gender, as well as the anatomic features such as size and location of the mass, histopathologic findings, and endocrine functionality of the mass, were recorded.

#### Checks

About imaging, which is considered as a useful diagnostic method in differentiating the benign and the malignant masses on nonenhanced CT, the HU values were measured. The nature of the masses was determined based on histopathologic findings for surgically resected specimens. Taking functionality into account, the baseline hormonal tests of patients who were checked were recorded including: (1) the levels of free metanephrine in plasma; (2) the levels of up-right and decubitus plasma aldosterone; (3) upright and decubitus plasma rennin activity; (4) plasma cortisol (at 8:00 am and 3:00 pm). All the survival patients were followed up for a period of 3 months to 10 years after they were discharged from the hospital.

#### Statistics

The SPSS19.0 software was performed for statistical analysis. All results are expressed as mean ± SD for continuous variables. *P* values <0.05 were taken as statistically significant.

#### Ethics statement

The study was performed according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of the First hospital of China Medical University. All patients in our hospital were given the following statement: "You may participate in an anonymous study of the knowledge of clinical research in our department. The purpose is to gain understanding of public awareness and knowledge of clinical research so that educational programs can be prepared to adequately inform the public about clinical research. Each study has been approved by the ethics committee of the First hospital of China Medical University". All data in our study were collected only from those who

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**Table 2.** Functionality and histopathologic diagnosis of 99 patients with HAI

	No. of patients (%)
Functional diagnosis	27 (27.27)
Hyperaldosteronism	14 (14.14)
Hypercatecholaminism	8 (8.08)
Hypercortisolism	5 (5.05)
Histopathologic diagnosis	99 (100.00)
Pheochromocytoma	35 (35.35)
Malignancy*	21 (21.21)
Adenoma	18 (18.18)
Myelolipoma	10 (10.10)
Cyst	9 (9.09)
Ganglioneuroma	5 (5.05)
Teratoma	1 (1.01)

\*Malignancy, including metastatic carcinoma (8), malignant pheochromocytoma (5), cortical carcinoma (4), sarcomatoid carcinoma (3).

**Table 3.** The HU of 99 HAI with a Histopathologic Diagnosis

HD (n)*	HU (mean $\pm$ standard)
Pheochromocytoma (32)	34.79 $\pm$ 10.51
Malignancy (19)	32.59 $\pm$ 7.41
Adenoma (15)	36.67 $\pm$ 8.40
Myelolipoma (8)	-48.88 $\pm$ 35.99
Cyst (6)	25.23 $\pm$ 15.23
Ganglioneuroma (5)	29.40 $\pm$ 3.13
Teratoma (1)	28

\*n, the number of patients detected by CT.

provided verbal informed consent. Written consent was not obtained because of the study was anonymous and de-identified prior to analysis. So the identifying information was not collected in this study. All the methods were approved by the ethics committee.

### Results

#### Baseline features

99 patients with HAI (length  $\geq$ 6 cm) were selected from 1654 patients who received operation for adrenal tumor between 2005 and 2014, which occupied 5.99% of the total 1654 patients. The 99 patients were divided into different groups by age: ages under 30 hold 15.15% (15/99), between 30 and 40 hold 15.15% (15/99), between 40 and 50 hold 27.27% (27/99), between 50 and 60 hold

31.31% (31/99), between 60 and 70 hold 8.08% (8/99), and older than 70 years old hold 3.03% (3/99). The average age of the 99 patients was 45.75 (range, 18-77 years old). Patients consist of 54 males (54.54%) and 45 females (45.45%), Maximum diameter of the masses is 15 cm and with an average size of 8.09 cm. We found that there were 49 subjects (49.49%) and 47 subjects (47.47%) discovered with a mass in the right and left adrenal gland respectively, and 3 subjects (3.03%) with bilateral adrenal neoplasms. The most common reason for abdominal imaging was nonadrenal symptoms (50.74%), including abdominal pain, fever and hematuria, etc. Other reasons were general examination (36.03%) and back pain (13.23%). The clinical features of the 99 patients with HAI are described in detail in **Table 1**, specifically.

#### Functionality and histopathologic diagnosis

Of the entire patient cohort, 27 patients (27.27%) had functional tumors based on the biochemical and baseline hormonal evaluation, which were composed of hypercatecholaminism (8.08%), hyperaldosteronism (14.14%) and hypercortisolism (5.05%) respectively. Without concerning the functionality of the tumor, all of the patients in this cohort had received surgical resection because of the huge size ( $\geq$ 6 cm) of the tumors. According to the pathological diagnosis, pheochromocytoma (35.35%) was the most common tumor observed. Followed by 21 subjects (21.21%) with malignancy, 18 subjects (18.18%) with cortical adenoma, 10 subjects (10.10%) with myelolipoma, 9 subjects (9.09%) with cyst, 5 subjects (4.04%) with ganglioneuroma and 1 subject (1.01%) with teratoma (**Table 2**).

#### The values of HU

86 (86.86%) of the 99 patients with HAI were detected by CT. And the others (13.13%) were detected by US. The mean  $\pm$  standard error of the HU density was measured by nonenhanced CT in the 86 patients. The specially lowest values of the HU density were myelolipoma with -48.88  $\pm$  35.99 and the values range from 114 to -20. The HU density of cortical adenoma and pheochromocytoma were 36.67  $\pm$  8.40 and 34.79  $\pm$  10.51, respectively (**Table 3**).

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### *The follow-up*

53 subjects missed follow-up after surgery. The other 46 patients were successfully followed up for, including 34 subjects with benign masses and 12 subjects with malignant masses. One of the 34 benign subjects who suffered distant metastasis 3 months after her surgery died of tumor recurrence, and she was also diagnosed as cortical adenoma after the first surgery. The other 33 patients with benign tumor are still alive. Seven of the 12 subjects with malignant masses died of distant metastasis, and two of the seven presented a survival time more than 36 months (70 and 47 months). The remaining 5 subjects with malignant masses are still alive, and the longest survival time was 104 months till now.

### **Discussion**

In this retrospective study of 99 patients with HAI that were found by CT or US, the high peak age is in their sixth decade (33.09%). Incidence decreased in people older than 60 (11.11%) and younger than 30 (15.15%). This may be due to the increased opportunities for general examinations, and people also bear a high incidence of other diseases in their 50's and 60's. Also, general examination is required to avoid adrenal incidentalomas growing too large (length  $\geq 6$  cm) in China as was demonstrated in our cohort. Many previous studies have reported that adrenal incidentalomas are more common in females for they may receive CT or US scanning in a higher frequency than men [16-19]. In our cohort, however, masses were more commonly found in males (54.54%) rather than females (45.45%). Some studies about CAI, have reported the similar incidences of masses in males and females, based on autopsy findings [4, 20].

49 masses were found in right (49.49%), 47 were in left (47.47%), and the other 3 occurred bilaterally (3.03%). Studies about the incidence of masses on either side have not reached consistent conclusion previous. However, our result was a little different from that approximately 10% of adrenal masses are detected bilaterally in most other literature reports [4, 19, 21]. Hypertension (35.35%) constitutes the largest part of the concomitant disease. Therefore, it is necessary to do an adrenal check when the patient suffered a refractory hypertension.

Regarding the functionality of masses, our results showed that 27 (27.27%) patients of the entire cohort with 99 cases, had masses that were functional. The incidence of functional tumors in our cohort is almost consistent with previous studies [14, 19, 22], the incidence of functional tumors in those literatures ranges from 5% to 25%. Such a low percentage of functional tumors could be one of the reasons why tumors can grow so large ( $\geq 6$  cm). In our cohort of patients with HAI, all tumors sizes were greater than or equal to 6 cm, the malignant tumors occupied 24.24% based on histopathologic diagnosis. It is confirmed that the risk of malignancy increases along with the size of the lesion according to the results from other reports. For tumors  $\geq 6$  cm, the incidence of malignant tumors is 25%, whereas it is only about 6% for tumors smaller than 6 cm [23]. Of the benign subjects, pheochromocytoma (35.35%) is the most common diagnosis, the malignant (24.24%) holds the second place, and the cortical adenoma (16.16%) is the third frequent type. However, this diagnosis result is obviously different from the one that cortical adenoma accounted for the largest part of CAI in other reports [24]. There is a high incidence (39%) of PCC in patients with HAI (length  $\geq 6$  cm) based on some previous studies [25, 26].

In addition to the nature and the functionality of tumors, HU value of nonenhanced CT is also an important feature of HAI. HU is a unit that represents the dilution values of basic pixel in CT images via arbitrary numbers. The high specificity and sensitivity have been reported, however, the value greater than 20 HU implying malignancy required to be confirmed yet [27]. In our study of HAI, the benign and malignant tumors revealed no significant difference. This phenomenon was mostly consistent with the results from previous reports [28]. They proposed that the contrast enhancement of wash-out may be helpful to do it. In all of the subjects from our cohort, the values of HU were measured in 85 patients. Myelolipoma showed the lowest level whose average value was -48.88. Some studies have reported that high concentrations of intracellular lipid can lower the CT attenuation [29]. In our cohort, the huge myelolipoma can be called the lipid-rich AI. Considering this data, it was possible to differentiate adrenal myelolipoma. Of course, a lot of limitations to distinguish different diagnoses based on unenhanced CT densitometry, because dif-

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ferent tumors may present as a similar lipid content. Some literatures reported that the identification of negative HU can provide some tips to differentiate different types of AIs, including myelolipoma, adenomas, metastases, pheochromocytomas and malignancy [30].

About postoperative follow-up, one patient, who was diagnosed as cortical adenoma, died of systemic metastases 3 months after surgery. And two patients with malignant masses present a survival time more than three years. But it is difficult to draw a definitive conclusion since some patients were failed to follow up and the sample size was too small.

There are still restrictions and limitations with this study because all diagnosis were made by a single medical department. Therefore, the data from our cohort may not be representative for the entire Chinese population. In our study, only a few cases were used to compare with the results of previous literatures. However, our study offers the advantage of being the largest samples of HAI data in our hospital, and we hope that these can be on behalf of the patients with HAI in China and Asia more or less. Regarding the difference from other reports, further researches still need to be done.

### Conclusions

In conclusion, the clinical features of 99 patients with HAI from our hospital, such as baseline features, evaluation of serum plasma, non-functionality and functionality, benign and malignant, values of HU, follow-up etc., were described in this study. Most of our results were similar to previous studies of CAI. While the HU value shows some differences from other previous reports. All of the differences need further research in patients from large sample size and multicenter.

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### Disclosure of conflict of interest

None.

### Authors' contribution

Conceived and designed the experiments: CK ZG. Performed the experiments: ZG XM. Analyz-

ed the data: ZG XM. Contributed reagents/materials/analysis tools: ZG ZZ. Wrote the paper: ZG ZZ. Wrote the first draft of the manuscript: ZG.

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