Original Article

Reliability of Adrenal Computed Tomography in Predicting the Functionality of Adrenal Incidentaloma

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Abstract

Background: Adrenal incidentaloma (AI) is an adrenal mass discovered accidentally during abdominal or chest imaging techniques not aimed to adrenal gland assessment. Guidelines suggested confirming the benignity of AI radiologically and excluding hormonal dysfunctions. This study evaluated the reliability of computed tomography (CT) scan radiological parameters in predicting the functionality of AI. **Patients and Methods:** A cross-sectional study performed in Faiha Specialized Diabetes, Endocrine and Metabolism Centre from July 2017 to July 2018, involving 38 patients (23 females [60.5%]) harbouring 43 AI referred for evaluation. For all patients, we assessed history, physical examination, radiological parameters of AI by CT scan (native Hounsfield unit [HU]), maximum diameter and absolute percentage washout [APW] and blood investigations (glycated haemoglobin, adrenocorticotropic hormone, aldosterone, renin, aldosterone/renin ratio, normetanephrine, metanephrine, dehydroepiandrosterone sulphate, cortisol and 1 mg overnight dexamethasone suppression test). **Results:** Native CT adrenal HU ≥ 18.5 was statistically significant seen in most functional AI (FAI) ($P = 0.006$), especially in patients with mild autonomous cortisol excess (MACE) and pheochromocytoma (PCC) with $P = 0.02$ in both. Maximum diameter was significantly high (≥ 40 mm) in PCC and congenital adrenal hyperplasia (CAH) ($P = 0.018$ and 0.008, respectively). APW was significantly $< 60\%$ only in PCC ($P = 0.02$). **Conclusions:** Native HU was the most significant radiological parameter in predicting the functionality of FAI, MACE and PCC, but not in CAH and aldosterone-producing adenoma. The maximum diameter was significant in predicting the PCC and CAH, whereas the APW was significant in predicting PCC only.

Keywords: Adrenal adenomas, adrenal computed tomography, adrenal incidentaloma

INTRODUCTION

Adrenal incidentaloma (AI) is a mass or lesion of ≥ 10 mm discovered accidentally in the adrenal gland during an imaging procedure for the chest or abdomen not aimed to assess the adrenal gland.[1] The AI is a common problem for referral to endocrine centres for assessment.[2] Most of AIs are benign and hormonally inactive, but about 20%–40% of them show subtler forms of hormonal overproduction such as cortisol hypersecretion, hyperaldosteronism, sex steroid or pheochromocytoma [PCC]).[3,4]

Those lesions of <10 mm require no further assessment unless there is clinical evidence of hormonal dysfunction.[1,5]

The prevalence of AI in autopsy studies is about 2% and 4% in radiological studies; it is increasing in elderly and rare in children,[2] whereas it is bilateral in 15% of cases and about 0.3%–0.6% in general population.[6] The detection of AI is a growing problem due to increasing incidence which is most likely attributed to significant developments in radiological procedures.[7]

Most guidelines advised to ensure the benign nature of AI radiologically and to exclude hormonal dysfunction such

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as PCC, aldosterone-producing adenoma (APA), mild autonomous cortisol excess (MACE) and androgen-producing tumours in the presence of high clinical suspicion. Adrenal computed tomography (CT) can assess the benignity of AI through different parameters such as native attenuation value in Hounsfield units (HU), maximum diameter, absolute percentage washout (APW) (which refers to the characteristics of enhancement and de-enhancement of contrast media), heterogeneity, regular margins and presence or absence of necrosis or haemorrhage.[1,8,9] Hormonal assessment is costly, needs special preparation during assays and large false-negative and false-positive results are reported; for these reasons, in our study, we tried to assess the radiological CT parameters at different cut-off values in the prediction of different hormonal dysfunctions. Native HU of ≤10% and APW ≥60% go with the diagnosis of benign AI, especially adrenal adenoma. These two parameters are affected by intracellular lipid contents of AI.[1,8] Triphasic CT adrenal protocol is indicated for AI >10 HU to differentiate between lipid-poor adenoma and malignancy; it consists of native study 1 min and 15 min after giving contrast and application of the following formula to find APW:[9]

$$APW = ([\text{1-min HU} - \text{15-min HU}]/[\text{1-min HU} - \text{native HU}]) \times 100$$

PATIENTS AND METHODS

Study design
A cross-sectional study was performed in Faiha Specialized Diabetes, Endocrine and Metabolism Centre (FDEMC) from July 2017 to July 2018 involving patients with AI referred for endocrine evaluation.

Inclusion criteria
All patients referred to FDEMC with AI for endocrine assessment regardless of their ages.

Exclusion criteria
We excluded patients with the following conditions:

- Concomitant use of drugs that affect dexamethasone metabolism increase (phenobarbital, phenytoin, carbamazepine, primidone, rifampin, rifapentine, ethosuximide and pioglitazone); reduce dexamethasone metabolism (fluoxetine, diltiazem, cimetidine, itraconazole, ritonavir, fosaprepitant and aprepitant). Others are drugs that cause an increase in cortisol-binding globulin such as oestrogens, mitotane[10] and those causing overproduction of catecholamines such as tricyclic antidepressants[11]
- Major psychiatric illnesses[12,13]
- Excessive alcohol intake[14,15]
- Overt clinical features of hypercortisolism
- History of pituitary or adrenal surgery
- Cancers elsewhere in the body and send for CT of the abdomen for the staging and accidentally discovered that he has adrenal mass.

Ethical approval
The ethical committee of FDEMC approved the study under reference number 56/35/22, with written informed consent obtained from each patient.

History and physical examination
We took a full detailed history from all patients including identity, rapid weight gain, easy bruising, abdominal obesity, fatigue, proximal muscle weakness, rapid hair growth or rapid masculinisation, sudden severe headache, palpitation, anxiety attacks, sweating and attacks of rapid rising of blood pressure. Family history, past medical and surgical history, drug history and new onset or worsening of both diabetes and hypertension, all had been taken.

Then proper clinical examination was done by a single person for cushingoid features (rounded or moon face, buffalo hump, supraclavicular fat pads, thin skin, striae [wide and violaceous] and proximal myopathy). Body weight and height were measured in standing position with bare feet and light clothes using Stadiometer SECA-763. Body mass index (BMI) had been calculated by dividing weight in kg by the square of height in m^2 (as well established method).

Blood pressure was measured in a sitting position after 5 min of rest on two sides with two readings 5 min apart, and we took the average, using semi-automated oscillometric method (Omron HEM-780). Hypertension was diagnosed in patients already on antihypertensive drugs or blood pressure equal or more than 140 mmHg in systole or 90 mmHg in diastole.[16]

Laboratory investigations
Samples collection
We collected early morning fasting blood samples for serum cortisol, dehydroepiandrosterone sulphate (DHEA-S) and routine chemistry analysis. Plasma samples were collected for aldosterone, renin, metanephrine, normetanephrine, adrenocorticotropic hormone (ACTH) and glycated haemoglobin (HbA1C).

Hormonal assessment
Serum DHEA-S, cortisol and plasma ACTH were analysed using principles of electrochemiluminescence immunoassay by Cobas e411 (Roche Diagnostics, Germany). Serum was assessed for routine chemistry through the fully automated chemical analyser (Cobas c311 [Roche Diagnostics, Germany]). Plasma aldosterone, renin, normetanephrine, metanephrine and serum 17-hydroxyprogesterone (17-OHP) for those with elevated DHEA-S for the diagnosis of congenital adrenal hyperplasia (CAH) were analysed using enzyme-linked immunosorbent assay (ELISA) by the (DRG)R ELISA kit system (Germany). The diagnosis of primary aldosteronism was considered by measuring the aldosterone/renin ratio (ARR) >5.7.[17] The elevation of plasma metanephrine and/or normetanephrine four times above the normal value was used to establish the diagnosis of PCC.[18]

HbA1c was measured by fully automated high-performance

liquid chromatography system (Bio-Rad D-10 analyser). The diagnosis of diabetes mellitus was made according to the American Diabetic Association diagnostic criteria[19] or the patient is known to have diabetes and on treatment.

Dynamic tests

ACTH stimulation test for those patients with borderline 17-OHP (200–1000 ng/dL) and the diagnosis of CAH was considered if the level of 17-OHP exceeded 1000 ng/dL.[20]

One milligram overnight dexamethasone suppression test (1-mg ONDST) for all patients with usual protocol to exclude MACE and abnormal results was considered if the morning cortisol is ≥1.8 µg/dL (50 nmol/L).[21]

Adrenal imaging

We reassessed the CT films of all patients and reviewed the suspicious films with a second expert radiologist not oriented to the functionality status of these lesions. For those patients who did not have proper films, we tried to send them new adrenal CT scan and advised the radiologist to do proper triphasic protocol study if indicated (for those patients with native HU >10). The HU of an AI in native film was measured with an ellipsoid or circular region of interest (ROI), which was drawn to include more than 50% of the adrenal lesions at selected CT section and in a region away from calcification, cystic, necrotic, haemorrhagic foci, blood vessels and peripheries of the lesions.[22]

Protocol of adrenal computed tomography-scan

First, we did native density HU for adrenal incidentaloma. When the HU ≤10, we stop at this point, and the patient was assorted as having Lipid-rich adenoma.[1] If the native HU was more than 10, we measured APW by triphasic CT adrenal protocol. If the APW ≥60%, we classified the patient as a case of Lipid-poor adenoma; for those with APW <60% or suspicious radiological features, surgery was considered.[1,8]

The diagnosis of adrenal cyst and myelolipoma depended on the characteristic CT appearance.[23]

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) of Chicago, Illinois (version 23.0) was used for computerisation and analysis of data.

Continuous variables including general patient's data such as age, BMI, systolic blood pressure and diastolic blood pressure, CT data (HU, diameter and APW) and hormonal data (DHEA-S, cortisol, ACTH, ONDST, aldosterone, renin, ARR, metanephrine and normetanephrine) were summarised as mean ± standard deviation.

Age of the patients was categorised into ≥40 years and <40 years and BMI into ≥30 kg/m^2 and <30 kg/m^2. The receiver operating characteristic (ROC) curve was used to find the cut-off with best sensitivity and specificity for adrenal CT characteristics in the form of HU, diameter and APW in correlation with the functionality of AI. Categorical variables such as age and BMI groups, AI diagnosis and categories of adrenal CT

findings (HU, diameter and APW) were summarised as numbers and frequencies *n* (%). Correlations between categorical and continuous variables were done using independent Student's *t*-test, whereas Chi-square test was used for correlation between the categorical variables. For all the comparative tests, *P* < 0.05 was considered statistically significant.

RESULTS

A total of 38 patients were enrolled in this study with a mean age of 47.6 ± 18.3 years, 23 (60.5%) were females, and 69.8% of patients were 40 years and above. The mean BMI was 27.7 ± 7.2 kg/m^2, and 17 patients (44.7%) were obese. Twelve patients (31.5%) had type 2 diabetes, and 25 patients (65.7%) had hypertension with mean systolic blood pressure was 133.2 ± 17.8 mmHg and mean diastolic blood pressure was 81.5 ± 13.7 mmHg.

As shown in Table 1, we have 38 patients harbouring 43 AI, 12 of them had non-functioning adenomas (NFA), seven adrenal cysts and five MACE (with cortisol levels after 1-mg ONDST at 26.4, 18.4, 2.9, 2.3 and 2.1 µg/dL (normal value <1.8 µg/dL). Four patients had PCC (levels of normetanephrine were 1967, 1860, 1515 and 955 Pg/mL [normal value <180 pg/mL] [one of them co-secreted cortisol causing MACE (cortisol was 26.3 µg/dL (normal value 5–25) and after 1-mg ONDST cortisol level was 2.1 µg/dL; two patients had APA (ARR was 16 and 12 respectively), two had myelolipomas and only one had extramedullary hematopoiesis (EMH). Five patients had bilateral AIs (two CAH, one non-Hodgkin lymphoma [NHL], one ACTH-secreting PCC and one NFA). The NFA and adrenal cysts showed right-sided predilection, left side in PCC and equal in the rest of the lesions. One PCC showed highest HU of 100, followed by a NFA which showed an HU of 75.

The myelolipoma showed the maximum diameter by 110 mm, followed by MACE with 105 mm and then PCC with 80 mm. The minimum diameter was noticed in NFA with 13 mm, followed by APA by 16 mm.

The highest APW was noticed in NFA by 100%, followed by PCC with 91% and MACE by 75%.

Ten (26%) of our patients underwent surgery, two of them due to suspicious radiological features, but histopathology confirmed adenomatous nature of lesions, four with PCC, one patient with bilateral ACTH-secreting PCC (normetanephrine was 4634 Pg/mL), one patient due to enlarging cyst, one patient with bilateral NHL and one patient with thalassemia presented with large, suspicious AI, which proved by histopathological examination to be EMH.

Table 2 shows significant statistical association between age <40 years with MACE and CAH (*P* = 0.01 and 0.02, respectively), but non-significant in functioning AI (FAI [as a whole]), PCC and APA (*P* = 0.5, 0.09 and 0.7, respectively).

The majority of patients with adrenal cysts (5 [71.4%]) were significantly below the age of 40 years as compared to 1 (6.3%)

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Table 1: General characteristics of adrenal incidentaloma

AI	n=38; 100%			Mean±SD (43 AI)			Surgery	
	RT (55%)	LT (32%)	Bilateral (13%)	HU	Diameter (mm)	APW** (100%)	Yes	No
Total 43 AI	21	12	5				10	28
NFA (32%)	7	5	1	17.5±18.1	29.3±10.3	63±28	2£	11
Cyst (16%)	7			21.2±6.2	54.4±21.4	NA	1~	6
MACE* (14%)	3	3*		31±12.1	47.4±33.4	51.2±28.0	2	3
PCC* (9%)	1	3*		46.5±35.8	59.5±17.9	44.5±20.5	2	2¥
CAH (9%)			2	26±7.7	50.5±7	62.5±0.7		2
APA (5%)	1	1		10.5±0.7	23±9.8	56		2
Myelolipoma (5%)	1	1		-5±2.8	65±63.6			2
ACTH Secreting PCC (5%)			1	33±8.4	42±17.6	51.5±9.1	1	
EMH (2%)	1			50	72		1£	
NHL (5%)			1	34±4.2	37±12.7		1	

*One incidentaloma co-secrete normetanephrine and cortisol, **Unfortunately APW were not present in 22 AI, ¥Unfortunately lost from follow-up, £The indication of surgery was high suspicious radiological features. ~Rapid enlarging in size. AI=Adrenal incidentalomas, NFA=Non-functioning adenoma, MACE=Mild autonomous cortisol excess, CAH=Congenital adrenal hyperplasia, APA=Aldosterone-producing adenoma, ACTH=Adrenocorticotropic hormone, PCC=Pheochromocytoma, EMH=Extra medullary haematopoiesis, NHL=Non-Hodgkin lymphoma, SD=Standard deviation, HU=Hounsfield unit, APW=Absolute percentage washout, NA=Not applicable

Table 2: Association of adrenal incidentaloma with patient's characteristics

Diagnosis	Age (years)			Gender		BMI$^{€€}$ (kg/m^2)			HTN		DM	
	<40, n (%)	≥40, n (%)	Mean±SD	Male, n (%)	Female, n (%)	<30, n (%)	≥30, n (%)	Mean±SD	Yes, n (%)	No, n (%)	Yes, n (%)	No, n (%)
AI												
FAI	6 (35.3)	11 (64.7)	49.8±22.1	4 (23.5)	13 (76.5)	13 (76.5)	4 (23.5)	24.3±5.5	11 (64.7)	6 (35.3)	6 (35.3)	11 (64.7)
NFAI	7 (26.9)	19 (73.1)	46.1±15.7	11 (42.3)	15 (57.7)	10 (43.5)	13 (56.5)	30.2±7.4	14 (53.8)	12 (46.2)	6 (23.1)	20 (76.9)
P	0.5	0.5		0.2		0.03	0.009		0.4		0.3	
MACE	3 (50.0)	3 (50.0)	43.6±20.5	2 (33.3)	4 (66.7)	5 (83.3)	1 (16.7)	23.6±5.7	5 (83.3)	1 (16.7)	2 (33.3)	4 (66.7)
NFAI*	1 (6.2)	15 (93.7)	50.4±15.5	5 (31.2)	11 (68.8)	5 (38.5)	8 (61.5)	31.6±7.5	9 (56.3)	7 (43.7)	4 (25.0)	12 (75.0)
P	0.01	0.4		0.9		0.07	0.03		0.2		0.7	
PCC$^{\$}$	2 (33.3)	4 (66.7)	46.±25.6	2 (33.3)	4 (66.7)	6 (100.0)	0 (0.0)	20.8±3.9	5 (83.3)	1 (16.7)	3 (50.0)	3 (50.0)
NFAI*	1 (6.2)	15 (93.8)	50.4±15.5	5 (31.2)	11 (68.8)	5 (38.5)	8 (61.5)	31.6±7.5	9 (56.2)	7 (43.8)	4 (25.0)	12 (75.0)
P	0.09	0.2		0.9		0.01	0.005		0.2		0.2	
APA	0 (0.0)	2 (100.0)	76±22.6	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	30.6±4.1	2 (100.0)	0 (0.0)	1 (50.0)	1 (50.0)
NFAI*	1 (6.2)	15 (93.8)	50.4±15.5	5 (31.2)	11 (68.8)	5 (38.5)	8 (61.5)	31.6±7.5	9 (56.2)	7 (43.8)	4 (25.0)	12 (75.0)
P	0.7	0.051		0.5		0.7	0.8		0.2		0.4	
CAH	2 (50.0)	2 (50.0)	43±20.7	0 (0.0)	4 (100.0)	2 (50.0)	2 (50.0)	26.6±31.6	0 (0.0)	4 (100.0)	0 (0.0)	4 (100.0)
NFAI*	1 (6.2)	15 (93.8)	50.4±15.5	5 (31.2)	11 (68.8)	5 (38.5)	8 (61.5)	31.6±7.5	9 (56.2)	7 (43.8)	4 (25.0)	12 (75.0)
P	0.02	0.4		0.1		0.6	0.2		0.04		0.2	
Cyst	5 (71.4)	2 (28.6)	36.1±5.9	5 (71.4)	2 (28.6)	4 (57.1)	3 (42.9)	29.6±7.6	3 (42.9)	4 (57.1)	0 (0.0)	7 (100.0)
NFAI*	1 (6.2)	15 (93.8)	50.4±15.5	5 (31.2)	11 (68.8)	5 (38.5)	8 (61.5)	31.6±7.5	9 (56.2)	7 (43.8)	4 (25.0)	12 (75.0)
P	0.001	0.03		0.07		0.4	0.5		0.5		0.1	

$^{€€}$BMI was calculated for 35 patients only (40 AIs) because three patients are on wheel chare and BMI cannot be calculated, *NFAI after omission of 7 adrenal cysts, 2 NHL and one EMH, $^{\$}$PCC including ACTH-secreting PCC which was bilateral (2 incidentalomas). AI=Adrenal incidentaloma, FAI=Functioning adrenal incidentaloma, NFAI=Non-functioning adrenal incidentaloma, BMI=Body mass index, DM=Diabetes mellitus; HTN, hypertension, MACE=Mild autonomous cortisol excess, PCC=Pheochromocytoma, APA=Aldosterone-producing adenoma, CAH=Congenital adrenal hyperplasia, SD=Standard deviation, ACTH=Adrenocorticotropic hormone

in non-functioning AI (NFAI) ($P = 0.001$). Regarding gender, hypertension and diabetes mellitus, these showed no significant association with functionality, except in CAH patients where none of them had hypertension ($P = 0.04$). Patients with FAIs and PCC were significantly none - obese in comparison with NFAIs.

After excluding the lesions of non-adrenal origin from AI (EMH and NHL, but including the cysts), HU and AI functionality showed a ROC curve with good accuracy [Figure 1] (area under the curve [AUC] = 0.742, $P = 0.01$, confidence interval: 0.58–0.89). A cut-off HU of 18.5 and above had shown the best sensitivity and specificity for functionality (82.4% and 68.2%, respectively). On the other hand, AI diameter did not show a significant ROC curve with an AUC = 0.626 and $P = 0.18$.
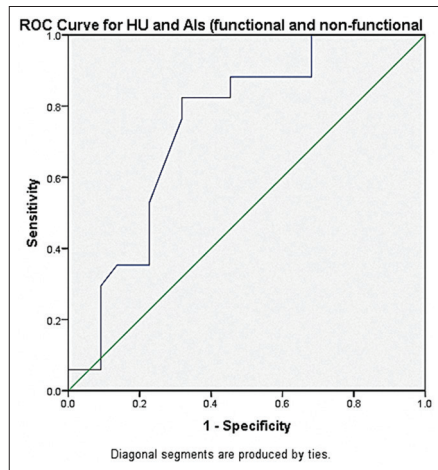
AI diameter of 40 mm and above had the best sensitivity and specificity for functionality (64.7% and 60%, respectively). We did not plot ROC curve for APW due to large missing of values 22 (52.4%).

When we omitted adrenal cyst, NHL and EMH from the final analysis of NFAI because they turn to be a different pathology [Table 3], apart from APA and CAH, most of

Figure 1: Receiver operating characteristic curve for Hounsfield unit and Adrenal incidentaloma (functional and non-functional)

FAI had an HU significantly ≥18.5 ($P = 0.006$ for FAI and 0.002 for both MACE and PCC) despite that the mean HU was significantly high only in FAI and PCC ($P = 0.04$, 0.01), respectively. Regarding maximum diameter, this was significantly high (≥40 mm) only in those patients with PCC and CAH ($P = 0.018$ and 0.008, respectively). Although adrenal cyst was non-functioning, it had significantly high (≥40 mm) maximum diameter ($P = 0.04$).

The APW was significantly <60% only in patients with PCC (100%).

DISCUSSION

As previous studies reported,[3,24] the majority of our patients were >40 years with female/male ratio 1.5:1. An Italian review explained the female predominance in many medical radiological reports rather than autopsy studies (where no significant gender differences) being a consequence of more frequent abdominal imaging in females than males.[25] A suggested explanation for the increasing prevalence of AI with age maybe due to localised atherosclerotic, ischemic damages leading to compensatory overgrowth.[7]

Coinciding with results of a French study performed in Cochin Hospital, Paris, our patients with MACE were significantly younger than those with NFAIs.[26]

Table 3: Comparison of radiological parameters by computerised tomography - scan between different types of adrenal incidentaloma

Diagnosis	HU				Maximum diameter (mm)				APW**			
	n	<18.5, *n* (%)	≥18.5, *n* (%)	Mean±SD	*n*	<40, *n* (%)	≥40, *n* (%)	Mean±SD	*n*	<60, *n* (%)	≥60, *n* (%)	Mean±SD
AI[ee]												
FAI	42	3 (17.6)	14 (82.4)	31.3±20.3	42	6 (35.3)	11 (64.7)	47.5±22.1	20	8 (66.7)	4 (33.3)	52.4±19.0
NFAI		15 (60.0)	10 (40.0)	19.4±16.8		14 (56.0)	11 (44.0)	41.5±23.6		2 (25.0)	6 (75.0)	67.6±29.3
P		0.006		0.04		0.1		0.41		0.06		0.1
MACE	21	0 (0.0)	6 (100.0)	30.5±10.9	21	3 (50.0)	3 (50.0)	47.8±29.9	12	3 (60.0)	2 (40.0)	51.2±28.0
NFAI*		11 (73.3)	4 (26.7)	14.5±18.5		11 (73.3)	4 (26.7)	34.1±23.2		2 (28.6)	5 (71.4)	63±28.3
P		0.002		0.06		0.3		0.27		0.2		0.4
PCC	21	0 (0.0)	6 (100.0)	42±28.8	21	1 (16.7)	5 (83.3)	53.8±18.2	11	4 (100.0)	0 (0.0)	48±13.0
NFAI*		11 (73.3)	4 (26.7)	14.5±18.5		11 (73.3)	4 (26.7)	34.1±23.2		2 (28.6)	5 (71.4)	63±28.3
P		0.002		0.01		0.018		0.07		0.02		0.3
APA	17	2 (100.0)	0 (0.0)	10.5±0.7	17	2 (100.0)	0 (0.0)	23±9.8	8	1 (100.0)	0 (0.0)	56.0
NFAI*		11 (73.3)	4 (26.7)	14.5±18.5		11 (73.3)	4 (26.7)	34.1±23.2		2 (28.6)	5 (71.4)	63±28.3
P		0.4		0.7		0.4		0.5		0.1		0.8
CAH	19	1 (25.0)	3 (75.0)	26.0±7.7	19	0 (0.0)	4 (100.0)	50±7.0	9	0 (0.0)	2 (100.0)	62.5±0.7
NFAI*		11 (73.3)	4 (26.7)	14.5±18.5		11 (73.3)	4 (26.7)	34.1±23.2		2 (28.6)	5 (71.4)	63±28.3
P		0.07		0.2		0.008		0.18		0.4		0.9
Cyst	22	4 (57.1)	3 (42.9)	21.2±6.2	22	2 (28.6)	5 (71.4)	54.4±21.4	7	0 (0.0)	0 (0.0)	0.0
NFAI*		11 (73.3)	4 (26.7)	14.5±18.5		11 (73.3)	4 (26.7)	34.1±23.2		2 (28.6)	5 (71.4)	63±28.0
P		0.4		0.3		0.04		0.06		0.5		0.2

[ee]The total number of AIs in this table was 42 because we cannot obtain full detailed radiological parameters of one patient, *We omit NHL, EMH and cyst from NFAI analysis, because they were proven by typical CT finding and/or biopsy finding to be something different diagnosis, **Unfortunately we calculated the APW accurately only in 20 AIs due to improper imaging protocol. CT=Computerised tomography, NFAI=Non-functioning adrenal incidentaloma, FAI=Functional adrenal incidentaloma, HU=Hounsfield unit in non-enhanced CT scan (native), APW=Absolute percentage washout, MACE=Mild autonomous cortisol excess, PCC=Pheochromocytoma, APA=Aldosterone-producing adenoma, CAH=Congenital adrenal hyperplasia, *n*=Number of the patients, SD=Standard deviation

Majority of patients in this study were none obese, similar to an Italian study.[27] Strikingly, more than half of patients with NFAIs in our study were significantly obese suggesting a tendency of these patients (with NFAIs) to develop obesity and the metabolic syndrome that needs to be studied thoroughly in the future as also alluded by a Brazilian study from Rio de Janeiro.[28]

In parallel with many large studies, we reported right-sided predilection in all types of AI (except the PCC) and approximate prevalence of bilateral AI.[3,24] Our patients with PCC showed left-sided predilection as also reported by a study from Cleveland, Ohio, USA.[29] The accuracy of ultrasound in detecting the right-sided AI may explain the right-sided predominance.[30]

In the present study, neither hypertension nor diabetes mellitus was useful in predicting the functionality of AI as also concluded in a recent Japanese study.[31] Our study data showed a higher percentage of FAI than many previous studies.[3,32] This could be explained by study design, different community nature, referral bias, increased awareness towards MACE in patients with AI and the cut-off point of 1-mg ONDST used in our study. The most common type of FAI in our study was MACE, followed by PCC, CAH and APA with one ACTH-secreting PCC, an arrangement which was concordant with many studies.[2]

Some studies tried to correlate between the radiological features of AI and the functionality; Italian multicentric retrospective study suggested an increased risk to develop MACE for those AI ≥24 mm[33] while our data reported all patients with CAH and the majority of patients with PCC significantly had a maximum diameter of more than 40 mm.

A French study from Paris reported that majority (79%) of cortisol-producing AI had an HU >10.[26] Coinciding with the results of this French study, we found that all our patients with MACE had an HU >18.5. An explanation for this increasing HU is the change in the structure of cortisol-producing cells from lipid-rich cells (clear cells) to lipid-poor cells (compact cells) because of the reduction in the intracytoplasmic fat.[26] In the present study, all patients with PCC showed native HU of more than 18.5 HU and an APW <60% coinciding with many studies which reported that 87%–100% of those patients with PCC showed an HU >10.[34] At variance with our data, some studies mentioned that PCC may present with HU of <10 and with APW >60% due to fatty degeneration within the PCC.[35]

We referred two patients with NFAI of 41 mm and 42 mm diameter to surgery because of suspicious radiological finding where their HU were 34 and 25, and their APW were 6% and 58%, respectively. Histopathological examination confirmed the diagnosis of adrenocortical adenoma in both patients; this phenomenon was well studied in a retrospective study from Seoul, Korea, where they evaluated the sensitivity of CT scan in the diagnosis of adrenal adenoma in relation to the size of the lesion.[22] This Korean study concluded that

there was a decline in the sensitivity of CT scan imaging protocol of the adrenal gland in differentiating adenomatous from non-adenomatous AI when the lesion size ≥30 mm. Consequently, a considerable number of patients wrongly diagnosed as having non-adenomatous AI and exposed to unnecessary invasive procedures such as biopsy or surgery. From a pathological point of view, the tumour with increasing size become more liable for ischemia which may be complicated by fibrotic, liquefactive, degenerative changes and reduction in the amount of lipid-rich cells, making the tumour more heterogeneously enhanced. These pathological changes increase the HU value and decrease the APW.[22] In contrast to large adrenal adenoma, the smaller one shows low HU in the native study and high APW due to rich lipid contents.[36]

Consequently, a precise and careful determination of the site and size of ROI should be undertaken, especially in large AI to cover more than 50% of its size as this will lead to decrease in the loss of CT scan sensitivity for the diagnosis of adrenal adenoma and improving the recognition of carcinoma.[37]

Limitations

These include small study size, single-centre study and short duration. Added to this fact, a lot of radiological departments in many hospitals do not follow the recommendations and guidelines suggested by most radiologic societies in performing triphasic adrenal CT scan, resulting in poor and undependable images to measure the APW.

Conclusions

More than half of our AI were non-functioning, whereas the most frequent type of FAI is MACE. High HU is the most significant radiological parameter in predicting the functionality of AI.

There was a bias among surgeons and physicians in Southern Iraq in the referral of patients with AI to assess functionality. Improving awareness of radiologists to follow proper sequences of triphasic adrenal CT protocol plus increasing awareness among doctors for early referral of AI for assessment of function should be encouraged.

Conflicts of interest
There are no conflicts of interest.

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