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Retrospective Study of Clinical Characteristics, Natural History and Predictive Factors for Mild Autonomous Cortisol Secretion (MACS) in Patients with Adrenal Incidentalomas in Malaysia

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Abstract

Introduction. Adrenal incidentalomas (AIs) are frequently discovered during imaging performed for unrelated conditions. While most are benign and non-functional, a subset demonstrates hormonal activity or malignant potential. This study aimed to describe the clinical and radiological characteristics, natural history and predictors of mild autonomous cortisol secretion (MACS) in a Malaysian cohort.

Methodology. This retrospective multicentre study reviewed medical records of 251 patients with AIs from three tertiary hospitals in Malaysia. Data on demographics, imaging findings, hormonal evaluations, histopathological diagnoses and longitudinal follow-up, including serial imaging and hormonal assessments, were collected and analysed.

Results. The median age of the cohort was 58 years (IQR 19), with a slight female predominance (53%). The population was predominantly Malay (n = 126, 50.2%), followed by Chinese (36.3%) and Indian (12.7%). The median follow-up duration was 39 months.

Most AIs were non-malignant (92%) and non-functioning (72%). Bilateral lesions were present in 9.6% of patients. Among non-malignant AIs, 27% were functioning, with higher rates of hypertension and osteoporosis, larger tumour size and greater tumour density. Adrenalectomy was more commonly performed in the functioning group, mainly for MACS and pheochromocytoma. In contrast, 94% of benign non-functioning AIs were managed conservatively, with no cases of malignant transformation and only one case developing hormonal activity over a median follow-up of 30 months. Among the 20 malignant AIs, 12 were primary adrenal carcinomas. Malignant AIs were associated with larger size, overt Cushing's syndrome, higher Hounsfield units, lower contrast washout and increased mortality.

MACS was identified in 12.7% of the cohort. It was associated with bilateral lesions, larger tumour size, and higher prevalence of diabetes, dyslipidaemia, obesity and osteoporosis. On multivariate analysis, only bilaterality and osteoporosis remained significant predictors of MACS.

Conclusion. This study reinforces that most benign non-functioning AIs carry minimal risk of progression, supporting less intensive follow-up in stable cases. Bilaterality and osteoporosis were identified as independent predictors of MACS, emphasizing the importance of targeted hormonal and bone health monitoring in these patients.

Key words: adrenal incidentalomas, mild autonomous cortisol secretion (MACS), metabolic disorders, osteoporosis, bilateral adrenal incidentalomas

INTRODUCTION

Adrenal incidentaloma (AI) refers to a clinically silent adrenal lesion that is incidentally discovered during imaging for non-adrenal-related conditions. The prevalence of AI in the general population is estimated to be 2-4%, based on radiological series.[1,2] The incidence of adrenal nodules at autopsy is as high as 32% among patients who had no evidence of adrenal disease prior to their deaths.[3] While most of these lesions are benign and non-functional, the natural history of these tumors remains incompletely understood. One of the critical challenges in managing AI is differentiating between benign and malignant lesions. Additionally, it is crucial to determine whether these

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typically asymptomatic tumors may be hormonally active, potentially leading to autonomous cortisol secretion, catecholamine excess, hyperaldosteronism, or hyperandrogenism.

Currently, most guidelines for the management of AIs recommend that all patients with AI must be screened for cortisol excess, whereas the evaluation for pheochromocytoma or primary aldosteronism (PA) is recommended for those with Hounsfield Unit (HU) more than 10 on pre-contrast computed tomography (CT) imaging or arterial hypertension, respectively.[4-6] While there is general agreement on the initial evaluation of AIs, significant differences exist among these guidelines regarding re-imaging, repeat hormonal testing, and the management of AIs that cannot be easily characterized as benign or malignant based on CT scans. The recommendations range from advising against repeated imaging and hormonal screening to follow-up imaging within 3 to 6 months and annual hormone testing for several years. The discordance between these guidelines complicates coordinated management, which often requires input from a multidisciplinary team.

Mild autonomous cortisol secretion (MACS), the most common functional form of AI characterized by biochemical abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis without overt clinical signs of Cushing's Syndrome, has been reported in 5-20% of AI patients.[7,8] A well-established concept is that cortisol secretion in the adrenal gland follows a continuum from physiological to pathologically increased levels.[9] Detecting MACS is vital as it has been associated with several cardiometabolic risk factors, including obesity, arterial hypertension, dyslipidaemia and osteoporosis.[9,10] Some studies have shown that these complications may improve after adrenalectomy, while others suggest worsening in untreated patients.[11,12] Consequently, the optimal management and long-term follow-up of AI patients remain subjects of debate. While numerous studies on AIs have been conducted in Western countries, there is a lack of data from this region. The primary objective of this study was to describe the natural history, clinical and radiological characteristics of patients with AI. The secondary objective was to identify clinical predictors associated with MACS.

METHODOLOGY

Study design

This was a retrospective observational study conducted in three urban tertiary hospitals under the Ministry of Health, Malaysia. Medical records of patients with adrenal incidentaloma referred to the endocrine units of participating centers between January 2010 and June 2020 were reviewed and analyzed. This study was approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health of Malaysia.

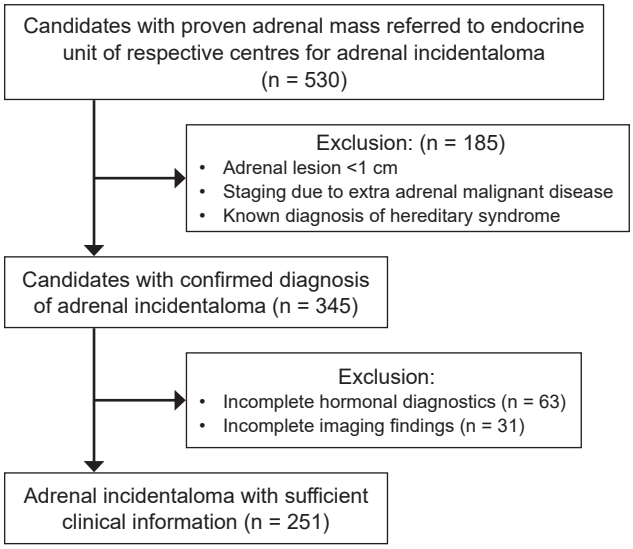

Figure 1. Flow diagram of patient selection for inclusion in the study and Consort diagram.

Patient selection

Adult patients aged 18 years and above diagnosed with AI between January 2010 and December 2020, who were referred to the endocrine units at the respective centers mentioned above were recruited. We excluded patients with AIs measuring less than one centimeter, pregnant individuals, those who did not undergo biochemical and radiological evaluation to assess for functioning adrenal lesions, individuals with a history of extra-adrenal malignancies or hereditary syndromes of endocrine neoplasia and patients taking medications such as glucocorticoids, estrogens, or antipsychotics that interfere with hormonal assessments.

Study Procedure

Medical records of patients with AI referred to the endocrine units of participating centers between January 2010 and June 2020 were reviewed. A data collection form was used to obtain relevant information. Baseline demographics, including age, gender, ethnicity, relevant comorbidities such as hypertension, diabetes mellitus, dyslipidaemia, obesity (body mass index >27.5 kg/m^2), osteoporosis or a history of fragility fracture, were obtained. Indications for the initial CT imaging resulting in the detection of adrenal incidentalomas were obtained from medical records when available and most frequently included evaluation for abdominal pain, sepsis of unknown origin, renal calculi and gynaecological conditions. Patients were classified as having diabetes if they were receiving antidiabetic treatment, hypertension if they were on antihypertensive medication and dyslipidaemia if they were taking lipid-lowering drugs. Osteoporosis was diagnosed if the individual had a T-score of less than -2.5 on dual-energy X-ray absorptiometry (DEXA), if performed, or was on osteoporosis medications. Not all patients underwent routine bone mineral density (BMD) testing.

The clinical symptoms or signs suggestive of a functional tumour: uncontrolled hypertension, hypokalaemia, easy bruising, thinning of skin, weight gain, proximal muscle weakness, uncontrolled blood glucose level, paroxysms of palpitations, headache, diaphoresis or indicators of malignancy like significant weight loss, were documented.

Results of biochemical evaluation, including morning serum cortisol after 1 mg dexamethasone suppression test (1 mg-DST), 24-hour urine catecholamine or metanephrine, plasma aldosterone renin ratio (ARR), serum dehydroepiandrostenedione-sulfate (DHEA-S), serum testosterone and 17-hydroxy progesterone levels were recorded, if performed. MACS was diagnosed if there was a lack of suppression in the 1 mg-DST and low dose DST (cut-off cortisol value less than 50 nmol/L), with suppressed DHEA-S (if performed), without any symptoms or signs of overt Cushing's syndrome. Potential causes of false positive DST (e.g., poor dexamethasone absorption, concurrent illness, or interfering medications) were considered at the time of interpretation. In most cases, a single DST was performed; repeat testing was not routinely undertaken across participating centers. Pheochromocytoma was diagnosed by an elevated 24-hour urine catecholamine or metanephrine level and confirmed based on histological findings post-adrenalectomy. PA was diagnosed based on an elevated ARR and confirmed by the lack of suppression in plasma aldosterone levels after saline infusion or fludrocortisone suppression test.

All AIs were further characterized by a three-phase CT adrenal protocol. The laterality, size (largest transverse diameter in centimeters), HU and absolute contrast washout (in percentage) of the adrenal lesion were captured. The histopathological findings of the resected adrenal tumours of individuals who underwent adrenalectomy or adrenal biopsy were recorded.

The treatment modality (observation or surgical intervention), repeated biochemical evaluations and imaging findings (if conducted), including changes in tumor size, HU, functioning status or malignant transformation, follow-up duration and outcome at the last follow-up, were captured for all patients.

Sample size calculation

Sample size was estimated a priori using Epi Info™ StatCalc (version 5.5.9, Cohort module) with a two-sided confidence level of 95%, power of 80%, and a 1:1 unexposed-to-exposed ratio. Assuming an outcome rate of 6.4% in the unexposed group[4,8] and a relative risk of 3.0 (19.2% in the exposed group), the minimum required sample size was 212 patients (106 per group). Of 530 patients screened, 251 were eligible and included, exceeding the required number.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) for normally distributed variables, or as median (interquartile range, IQR) for non-normally distributed variables. All data were analyzed using the IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Data completeness exceeded 95% for all key variables. The highest missingness was observed for body mass index (32%), which was excluded from relevant analyses.

The normality of data was determined by the Kolmogorov–Smirnov test (if sample size>50) or the Shapiro-Wilk test (if sample size is ≤50). Student's T-test or Mann-Whitney U test (if the data were not normally distributed) was used to assess the difference in variables between two groups. The Chi-square test or Fisher's exact test (when expected cell counts were <5) was used to assess associations between categorical variables in independent groups, while McNemar's test was applied for paired before-and-after data within the same group. The Wilcoxon ranked test was used to compare variables for paired subjects for data that was not normally distributed. Univariate and multivariate logistic regression analyses were performed to assess the association between patient characteristics and MACS, with the binary dependent variable defined as the presence of MACS. The p-value <0.05 was considered statistically significant.

RESULTS

Of the 530 patients screened during their follow-up at the endocrine clinics of the three Ministry of Health hospitals, 251 were included. Data completeness exceeded 95% for all key variables. The highest missingness was observed for body mass index (32%), which was excluded from relevant analyses.

The baseline clinical and radiological characteristics of the study population are summarized in Table 1.

The median age of the cohort was 58 years (IQR 19), and was mostly women (53%), with the majority being Malay (n = 126, 50.2%), followed by Chinese (36.3%) and Indian (12.7%). The median follow-up duration was 39 months.

Most (83.6%) of the AIs were unilateral. The median tumour diameter was 2.0cm (IQR 1.6). Examination of tumour density on CT scans indicated that 34% of the lesions had a HU of 10 or less, while 36.8% had a HU of 20 or less. Majority (83.6%) of the lesions had an absolute contrast washout of more than 60%. Bilateral AIs were identified in 24 (9.6%) patients. All were non-malignant. Ten were functioning, with MACS being the most common subtype (80%) (Figure 2). All bilateral MACS lesions were macronodular, whereas 2 of the 14 non-functioning bilateral AIs were disseminated tuberculosis.

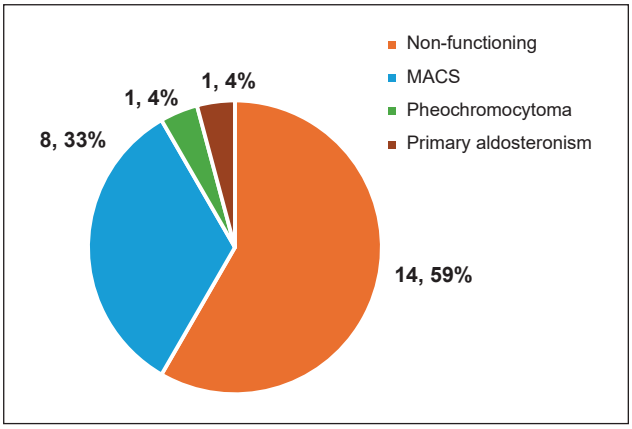

Figure 2. Pie chart describing diagnostic distribution among patients with bilateral adrenal incidentalomas (n = 24).

Table 1. Baseline clinical and radiological characteristics of all individuals with adrenal incidentaloma (N = 251)

Characteristics	Value
Age (years)	58 (19)
Male	118 (47.0%)
Ethnicity	
Malay	126 (50.2%)
Chinese	91 (36.3%)
Indian	32 (12.7%)
Others	2 (0.8%)
Comorbidities	
Diabetes	112 (44.6%)
Hypertension	175 (69.7%)
Dyslipidaemia	141 (56.2%)
Obesity	89 (35.4%)
Osteoporosis / Fragility Fracture	29 (11.5%)
Radiological features	
Size (cm)	2 (1.6)
Density, HU	15 (28.3)
Number of patients with:	
HU <10	85 (34.0)
HU 11-20	73 (29.2)
HU >20	92 (36.8)
Characteristic (N, %)	
Homogenous	177 (70.8)
Heterogenous	56 (22.4)
Uncharacterized	17 (6.8)

Values are presented as number (%) or median (interquartile range). Percentages were calculated using available data. One case had missing characterization data

Non-malignant functioning and non-functioning adrenal incidentalomas

A total of 231 (92.0%) patients were diagnosed with non-malignant AI, of whom 27% were characterized as functioning. The comparison of clinical and radiological characteristics of patients with non-malignant functioning AI with non-functioning AIs was summarized in Table 2. Functioning AI was associated with a higher prevalence of hypertension (88.8% vs. 63.1%, p <0.001) and osteoporosis (20.6% vs. 8.3%, p = 0.012). They were larger in size (2.5 cm vs. 1.7 cm, p <0.001), had higher density (16 HU vs. 12 HU, p <0.001) and a lower rate of absolute contrast washout greater than 60% (84.1% vs. 97.0%, p <0.001) compared to patients with non-functioning AIs. The surgical intervention rate was much higher among patients with functioning Ais, with 63.5% undergoing adrenalectomy mainly due to MACS (41.5%) and pheochromocytoma (41.5%). There were 10 patients with non-malignant, non-functioning AI subjected to adrenalectomy due to tumour size more than 4 cm. Five of them had HU less than 10, while almost all (90%) had absolute contrast washout of 60% or more. Histopathologically, all the tumours were benign, with myelolipoma accounting for 5 cases, followed by 4 cases of lipid-poor adenomas and a single case of extramedullary haematopoiesis.

Of the 63 (25%) individuals with benign functional tumors, 32 (50.8%) were diagnosed with MACS, 17 (27.0%) with pheochromocytoma, 13 (20.6%) with primary aldosteronism and one person (1.6%) with overt Cushing's syndrome.

Malignant adrenal incidentalomas

Twenty patients (8.0%) were diagnosed with malignant adrenal lesions. Primary adrenal cancer was discovered in twelve patients, out of which eleven were adrenocortical carcinomas and one was leiomyosarcoma. The remaining eight patients had adrenal metastasis. Primary sites of malignancy were the lungs (n = 4), kidneys (n = 2), ovaries (n = 1) and pancreas (n = 1).

In comparison with benign AIs, malignant AIs were associated with significantly higher incidence of weight loss and overt Cushing, larger tumour size (5.8 cm vs.1.9 cm, p <0.001), higher HU (51 vs. 14, p <0.001) and higher proportion of absolute contrast washout less than 60% (80.0% vs. 8.7%, p <0.001) on imaging. A significantly higher proportion of malignant AIs exhibited androgen secretion (15% vs. 0%, p <0.001), with no significant difference in the secretion of other hormones. Only 50% of the malignant AIs underwent surgical intervention, with a 70% mortality rate. A total of six patients (2.4%) had functioning malignant adrenal incidentalomas, with the majority (n = 4) being females. All were cortisol-secreting adrenocortical carcinoma (ACC) except one, which was a cortisol-secreting metastatic ovarian teratoma. Three out of the five cases of cortisol-secreting ACC also secrete androgen. Overt Cushing's syndrome was the most common presentation in this specific cohort (n=4, 66.6%).

Natural history of non-functioning benign adrenal incidentalomas

A total of 168 patients (66.9%) had benign non-functioning AIs, of whom 158 (94%) were treated conservatively. We included 108 patients with at least 2 follow-up CT imaging with a median follow-up of 30 months to examine the natural history of non-functioning benign AIs. There was no clinically significant change in the median tumor size over follow-up (1.7 cm to 1.8 cm, p = 0.699), and the proportion with contrast washout >60% remained stable (97.5% vs. 96.3%, p = 1.000. Despite the median HU remaining constant

at 12, the change in HU from baseline to final follow-up was significant (p = 0.001), likely due to variations in the distribution and spread of the data. Only one patient (0.6%) progressed to become functional after a year, associated with an increase in nodule size by 0.3 cm and worsening glycemia with underlying diabetes. None of the patients in this sub-cohort developed malignant transformation over time.

MACS: Clinical predictors and natural history

MACS was present in 12.7% (n=32) of our study population. Compared with the rest of AIs, patients with MACS exhibited larger tumor size, were more likely to be bilateral with higher rates of diabetes, dyslipidemia, obesity, osteoporosis and spinal fractures (Table 3). A representative CT image of the right adrenal adenoma in one of the patients with MACS from our cohort is shown in Figure 3.

Table 2. Comparison of clinical and radiological characteristics of patients with non-malignant functioning vs. non-functioning adrenal incidentalomas (n = 231)

Characteristic	Functioning AIs (n = 63)	Non-functioning AIs (n = 168)	*P* value[c]
Age	59 (24.5)	58 (0.9)	0.519
Male	31 (49.2%)	79 (47.0%)	0.814
Comorbidities			
Diabetes Mellitus	36 (57.1%)	70 (41.6%)	**0.050**
Hypertension	56 (88.8%)	106 (63.1 %)	**<0.001**
Dyslipidemia	42 (66.7%)	91 (54.1%)	0.125
Obesity	25 (39.7%)	51 (30.4%)	0.455
Osteoporosis /Fragility Fractures	13 (20.6)	14 (8.3%)	**0.012**
Symptoms			
Overt Cushing	1 (1.6%)	NA	NA
Uncontrolled hypertension[a]	12 (19.0%)	NA	NA
Hypokalemia[b]	3 (4.7%)	NA	NA
Paroxysms of headache, palpitations, diaphoresis	9 (14.3%)	NA	NA
Radiological characteristics			
Size (cm)	2.5 (2.0)	1.7 (0.9)	**<0.001**
Density/ HU	16 (20.0)	12 (31.0)	**<0.001**
Absolute contrast washout >60%	53 (84.1%)	163 (97.0 %)	**<0.001**
Bilateral	10 (15.8%)	14 (8.3%)	0.106
Outcome			
Adrenalectomy	40 (63.5%)	10 (6.0%)	**<0.001**
Duration of follow up (months)	24 (4.0)	36 (1.0)	**0.004**
Mortality	0	3 (1.8%)	0.903

Values are presented as number (%) or median (interquartile range)

[a] defined as high blood pressure on either 3 or more antihypertensives or controlled on 4 antihypertensives

[b] defined as serum potassium less than 3.5 mmol/L

[c] chi squared test for categorical data and Mann-Whitney U Test for continuous data set

P value ≤0.05 is considered statistically significant

NA, not applicable.

Table 3. Baseline characteristics of MAC vs. Non-MACS

	MACS (n = 32)	Non-MACS (n = 219)	*P* value*
Demographic			
Age, years	59 (24)	58 (19)	0.649
Male	13 (40.6%)	105 (47.9%)	0.438
Metabolic comorbidities			
Diabetes Mellitus	21 (65.6%)	91 (41.6%)	**0.011**
Hypertension	27 (84.4%)	148 (67.6%)	0.053
Dyslipidemia	25 (78.1%)	116 (53.0%)	**0.007**
Obesity	18 (56.3%)	71 (32.4%)	**0.008**
Osteoporosis	12 (37.5%)	17 (7.8%)	**<0.001**
Spinal Fracture	6 (18.8%)	5 (2.3%)	**<0.001**
Outcome (Alive)	32 (100%)	202 (91.8%)	0.103
Radiological characteristics			
Size, cm	2.4 (1.1)	1.9 (1.5)	**0.019**
HU	13 (0.6)	15 (25.7)	0.931
Contrast Washout >60%	31 (97%)	192 (87.7%)	0.122
Bilateral	8 (25%)	16 (7.3%)	**0.001**

*Chi-squared test for categorical variables and Mann Whitney U test for continuous variables.

P value<0.05 was considered statistically significant.

Values are expressed as number (%) or median (interquartile range).

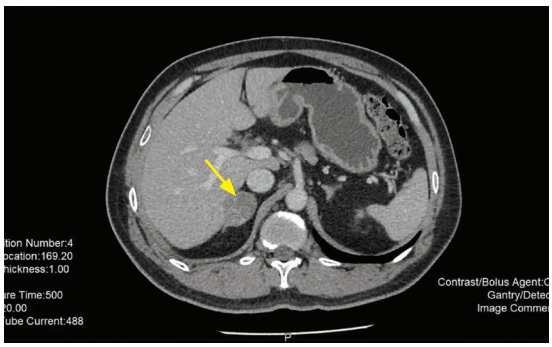

Figure 3. Representative CT image from our cohort: right adrenal adenoma in a patient with mild autonomous cortisol secretion (MACS). Axial CT showing a well-circumscribed right adrenal mass (3.3 × 3.4 × 3.2 cm) in a patient with MACS, predominantly hypodense with scattered hyperdense areas, no calcification, and >60% washout. Clear fat planes are seen with adjacent structures, with mild abutment of the liver margin.

MACS was associated with diabetes mellitus, dyslipidaemia, obesity and osteoporosis in the univariate analysis. After adjustment for potential confounders in the multivariate analysis, bilateral lesions and osteoporosis remained independently associated with MACS, conferring 4.5-fold and 10.9-fold increased odds, respectively (Table 4, Figure 4).

A total of 17 patients (53%) with MACS underwent adrenalectomy. Surgical intervention was associated with significant improvement in glycemic control and a reduction in the number of antihypertensives, with no tumor recurrence. For the 15 patients (47%) with MACS who were managed conservatively, there was a significant increase in median tumor size from 2.1 cm to 2.5 cm

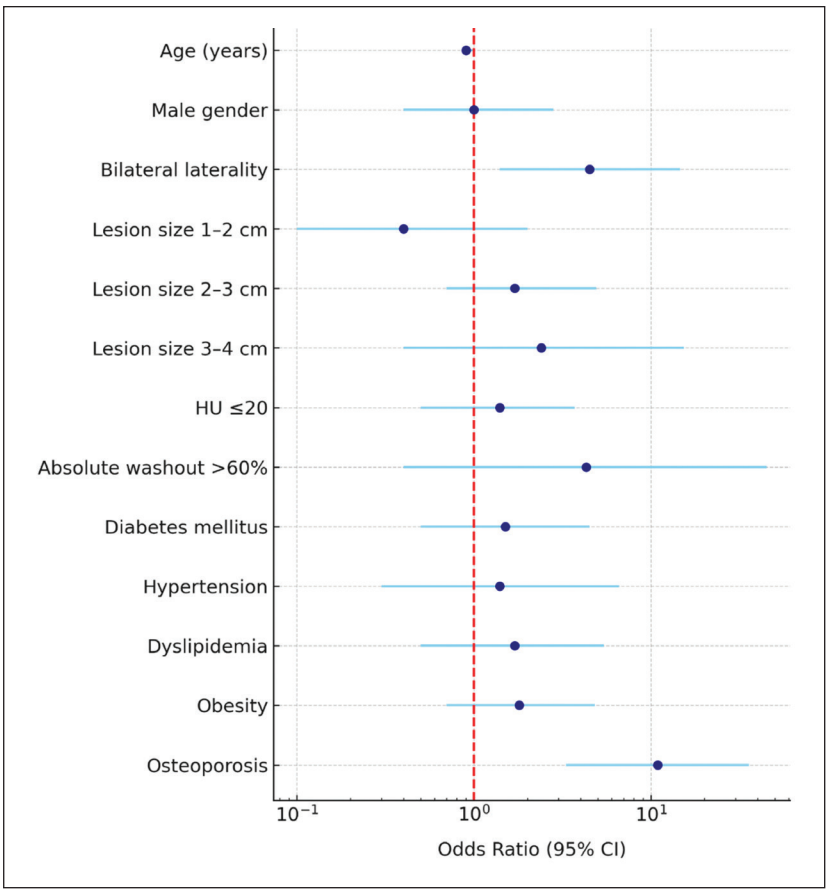

Figure 4. Multivariate predictors of mild autonomous cortisol secretion (MACS). Forest plot illustrates the odds ratios (OR) and 95% confidence intervals (CI) for predictors of MACS from multivariate logistic regression analysis. The vertical dashed line represents the null value (OR = 1.0).

Table 4. Clinical parameters associated with the development of MACS (N = 32)

	Univariate analysis*		Multivariate analysis*,#	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, years	4.8 (0.7 – 29.9)	0.656	0.9 (0.9 – 1.0)	**0.123**
Gender				
Male	1.3 (0.6 – 2.9)	0.439	1.0 (0.4- 2.8)	0.928
Laterality				
Bilateral	0.2 (0.9- 0.6)	**0.003**	4.5 (1.4–14.6)	**0.012**
Size of lesion at diagnosis, cm				
1–2 cm (vs >4 cm)	0.6 (0.2–2.3)	0.500	0.4 (0.1–2.0)	0.271
2–3 cm (vs >4 cm)	2.8 (0.9–9.2)	0.085	1.7 (0.4–7.9)	0.500
3–4 cm (vs >4 cm)	2.4 (0.6–10.1)	0.222	2.4 (0.4–15.3)	0.341
HU				
≤20	1.3 (0.6–2.9)	0.498	1.4 (0.5- 3.7)	0.560
Absolute Contrast Washout				
>60	4.4 (0.6–33.3)	0.156	4.3 (0.4–45.0)	0.222
Comorbidities				
Diabetes mellitus	2.7 (1.2–5.8)	**0.013**	1.5 (0.5–4.5)	0.466
Hypertension	2.6 (0.9 – 7.0)	0.061	1.4 (0.3–6.6)	0.667
Dyslipidemia	3.2 (1.3 – 7.6)	**0.010**	1.7 (0.5–6.4)	0.428
Obesity	2.7 (1.2 – 5.7)	**0.010**	1.8 (0.4–7.5)	0.431
Osteoporosis	5.4 (2.3 – 12.5)	**<0.001**	10.9 (3.3–35.5)	**<0.001**

* Based on logistic regression analysis, the statistical significance level was 0.05.

Variables with an association of p <0.20 were selected for a multivariable analysis; OR: Odd ratio; CI: Confidence interval.

[a] Race was analyzed using Chi-square test (overall association with MACS).

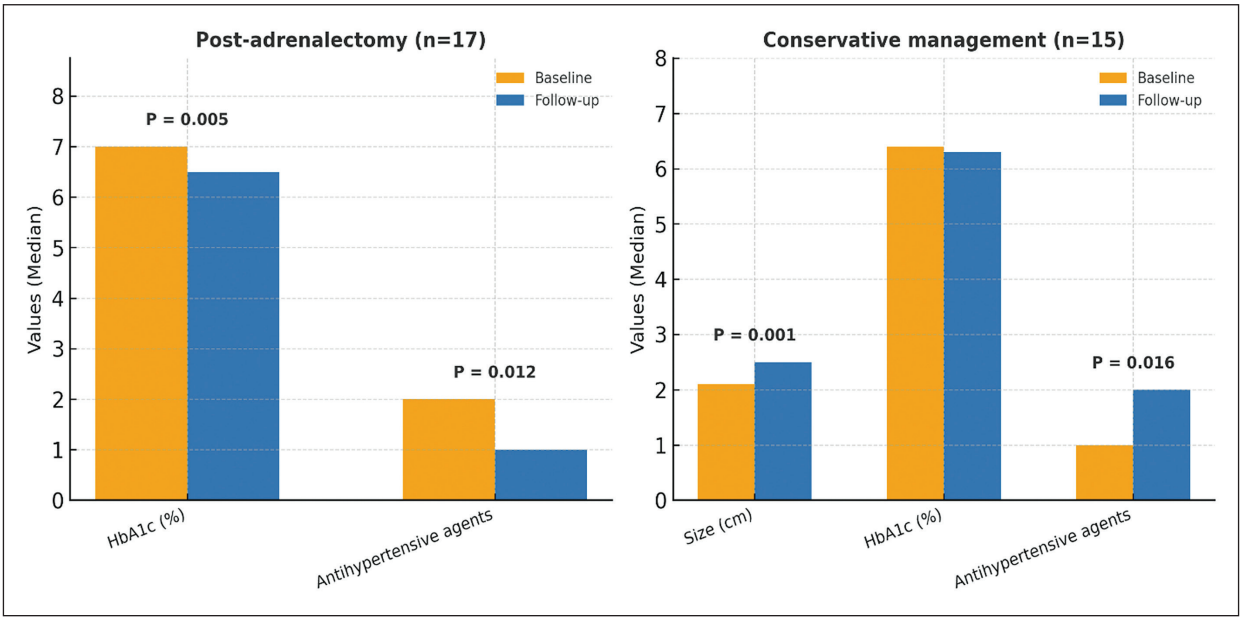

Figure 5. Outcomes of patients with MACS undergoing surgical versus conservative management.

Values are expressed as median (IQR). *P*-values were obtained using the Wilcoxon signed-rank test for continuous paired outcomes (HbA1c, size, HU) and McNemar's test for categorical paired outcomes (antihypertensive use). *P* value <0.05 was considered statistically significant.

(p=0.001) and the number of antihypertensive medications after a median follow-up of 50 months (Figure 5).

DISCUSSION

Population-based epidemiological data on the prevalence of malignant and hormonally active adrenal tumors and their natural history are vital for devising a cost-effective diagnostic and follow-up strategy for incidentally discovered adrenal tumors. Here, we describe the first Malaysian cohort of patients with AI. The high prevalence of hypertension (63%), diabetes (42%) and obesity (30%) in patients with benign non-functioning AIs aligns with existing literature that indicates their association with metabolic syndrome.[9,13] This is attributed to a mild hypercortisolemic state, where even small amounts of cortisol secretion can lead to insulin resistance and resultant hyperinsulinemia, exacerbating conditions like hypertension and diabetes.[14] Notably, studies by Terzolo et al., and Androulakis highlight the critical link between mild hypercortisolism and metabolic disturbances, underscoring the need for metabolic monitoring in patients diagnosed with BNAI.[15,16]

In this study cohort, both HU cut-offs below 10 and 20 were highly specific for non-malignant lesions, as all malignant AIs had HU above 20, consistent with the established evidence that low HU on non-contrast CT strongly indicates benign adenoma.[17,18] Among the ten patients who underwent adrenalectomy for benign non-functioning AIs due to their size (greater than 4 cm), half presented with HU values less than ten. These findings highlight the utility of HU thresholds, rather than tumor size, in guiding the surgical management of adrenal incidentalomas.[5] The absolute contrast washout of less than 60% was also useful in our cohort, demonstrated in 80% of the malignant AIs compared to only 8.7% of benign AIs.

Functioning adrenal lesions were present in 27.3% of all benign AIs, with MACS being the most prevalent diagnosis at 13.9%. This corresponds with the literature reporting that 15-30% of AIs display hormonal activity, with MACS being the commonest functional lesion (5-20%), followed by primary aldosteronism (1-10%) and pheochromocytomas (2-7%).[4,5,13,19-21] Only 1 out of the 158 benign non-functioning AIs treated conservatively progressed to become functional, which again corresponds with the current literature reporting a very low risk of functional progression, typically less than 1% thus supporting conservative management strategies for most patients as per current guideline recommendations.[5,22,23] None of the benign AIs in our cohort experienced a significant change in the radiological characteristics, including HU and contrast washout, supporting the recommendation that small, radiologically and biochemically stable lesions do not require extensive serial imaging and hormonal re-evaluation.[5]

A total of 10 out of 63 (15.8%) patients with functioning AI presented with bilateral adrenal lesions, 80% of which were MACS-associated, with macronodular lesions suggestive of primary bilateral macronodular adrenocortical hyperplasia (PBMAH).[4,24] Unfortunately, none of them had an adrenal biopsy done. This underscores the importance of tailored clinical management in these patients, as systemic causes or genetic predispositions are often at play in bilateral functioning AIs. All patients with malignant AIs, including those with metastases, had unilateral lesions suggesting a low probability of malignancy in bilateral AIs. Bilateral adrenal lesions are more commonly associated with benign conditions such

Table 5. Prevalence and outcomes of adrenal incidentalomas and macs in asian cohorts: A literature review

Author (Year)	Country	Study Design	N	MACS Prevalence (%)	Key Outcomes
Cho et al., 2013[35]	South Korea	Retrospective	282	7.1%	First Korean AI cohort: MACS patients had higher prevalence of diabetes and hypertension; emphasized long-term follow-up.
Liu et al., 2024[36]	China	Prospective	36	Not specified	MACS patients showed cognitive impairment compared to non-functioning adenomas; adrenalectomy improved memory function.
Luk et al., 2025[37]	Hong Kong	Retrospective	340	23.5% among functioning AIs	Female sex, larger size, hypertension, and prediabetes predicted MACS; surgery, when done, prevented metabolic progression
Current study, 2025	Malaysia	Retrospective	251	12.7%	Bilateral lesions and osteoporosis are significant predictors of MACS. Improvement in HbA1c and reduction in antihypertensive requirements after adrenalectomy.

as adrenal hyperplasia or systemic diseases, whereas unilateral adrenal lesions require careful consideration of the probability of malignancy. Bilateral adrenal lesions were independently associated with MACS in our cohort. Studies by Vassiliadi et al., and Di Dalmazi et al., suggested that the larger adrenal mass in bilateral lesions increases the risk of subclinical cortisol overproduction, potentially due to dysregulation of the hypothalamic-pituitary-adrenal axis.[25,26] The increased tissue volume may result in low-grade autonomous cortisol secretion that escapes normal feedback mechanisms. Clinically, this may substantiate the need for closer hormonal monitoring for autonomous cortisol secretion in patients with bilateral non-functioning adenomas.

Our patients with MACS had significantly higher rates of diabetes, hypertension, dyslipidemia, obesity, and osteoporosis compared to the non-MACS cohort, a finding consistent with the current literature. Chiodini et al. reported that MACS patients are 60-80% more likely to develop type 2 diabetes due to cortisol-induced insulin resistance, while Araujo-Castro et al. found that hypertension is 2-3 times more common in MACS due to cortisol's impact on the renin-angiotensin system.[10,27] Additionally, Barzon et al., documented a 50-70% higher prevalence of dyslipidemia and central obesity in MACS patients, likely due to cortisol's role in fat redistribution and lipid metabolism.[28] However, osteoporosis was the only comorbidity that was independently associated with MACS in our cohort. Even mild hypercortisolism significantly increases bone resorption and decreases bone formation by suppressing osteoblast activity and promoting osteoclast activity, leading to an increased risk of osteoporosis and vertebral fractures.[29-33] The strong and independent association between MACS and osteoporosis in our cohort underscores the importance of routine bone health assessment and early intervention to diagnose osteoporosis and prevent fragility fractures, in addition to periodic monitoring of diabetes, hypertension, dyslipidemia and obesity in patients with MACS, as recommended by the European Society of Endocrinology.[5]

Patients with MACS who underwent surgical intervention experienced significant improvement in blood pressure and glycemic control, while those managed conservatively showed worsening of blood pressure control and increased tumour size. These findings are consistent with the recent CHIRACIC trial, which demonstrated improved blood pressure control after adrenalectomy compared with conservative management.[34] The improvement is largely attributed to the removal of the adrenal tumour, which reduces hormone secretion that drives hypertension, while persistent tumour activity in conservatively managed patients may contribute to progressive growth and worsening metabolic comorbidities over time.[35] The decision to manage such tumours non-surgically should therefore be weighed carefully against the potential for progressive growth and related metabolic complications.

Table 5 summarizes published Asian studies on adrenal incidentalomas and MACS,[36-38] While earlier cohorts from Korea, China, and Hong Kong reported variable prevalence and outcomes, our Malaysian data add to the limited regional evidence, particularly by highlighting improvements in glycemic control and antihypertensive requirements following surgery.

This study provides a comprehensive analysis of a Malaysian cohort, an underrepresented population in the global literature on adrenal incidentalomas and mild autonomous cortisol secretion (MACS). Its multicentre design, incorporating data from three urban tertiary centres, and relatively large sample size compared with most Asian studies, enhance representativeness and statistical power. The evaluation of readily available clinical and radiological parameters as potential predictors of MACS supports applicability in routine clinical practice and may facilitate personalised follow-up strategies. In addition, the findings provide a foundation for future research, including the potential development of a regional risk-stratification or scoring system for adrenal incidentalomas. The study was conducted in accordance with ethical standards and employed a well-structured retrospective methodology, further strengthening its credibility.

Nevertheless, several limitations should be acknowledged. The retrospective design is inherently subject to selection bias, incomplete medical records, and inconsistent documentation, which may limit generalisability. The inclusion of patients with different subtypes of functioning adrenal incidentalomas introduces population heterogeneity and may reduce predictive accuracy. Not all patients underwent bone mineral density assessment, potentially leading to an underestimation of osteoporosis

prevalence. Furthermore, most patients underwent only a single 1 mg dexamethasone suppression test without routine confirmatory testing, raising the possibility of misclassification due to false-positive results. Follow-up duration was variable and may have been insufficient to detect delayed hormonal progression or malignant transformation in some patients.

These strengths and limitations highlight the need for prospective, multi-center, longitudinal studies to validate predictive factors for MACS and malignant adrenal pathologies, with longer follow-up to clarify the natural history of both functioning and non-functioning AIs. Randomized controlled trials are also required to determine the long-term impact of adrenalectomy in MACS, refine treatment guidelines, and define the comparative benefits of surgical versus conservative management.

CONCLUSION

This study demonstrated that most benign non-functioning AIs exhibit minimal risk of progression in terms of functionality or malignancy, suggesting that after an initial period of stability, the frequency of imaging and hormonal assessments can be safely reduced or omitted for the majority of patients. Bilateral adrenal lesions and osteoporosis emerged as the most robust independent predictors of MACS. This reinforces the importance of monitoring for autonomous cortisol secretion in patients with bilateral AIs and evaluating bone health in patients with MACS to prevent metabolic complications or spinal fractures associated with cortisol overproduction.

Statement of Authorship
All authors fulfilled ICMJE authorship criteria.

CRediT Author Statement
VD: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation; **SR:** Validation, Resources, Supervision, Project administration; **VMM:** Validation, Resources, Supervision, Project administration; **FSH:** Conceptualization, Methodology, Validation, Resources, Writing – review and editing, Supervision, Project administration.

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