

ARTICLE



Prevalence and clinical correlates of positive aldosterone-to-renin ratio screening in obese hypertensive patients with obstructive sleep apnea: a Southeast Asian cross-sectional study

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Although routine screening for primary aldosteronism (PA) is increasingly recognized among patients with obstructive sleep apnea (OSA), data regarding aldosterone-to-renin ratio (ARR) screening positivity among Southeast Asian OSA populations remain limited, particularly in resource-limited settings. This study aimed to determine the prevalence and clinical correlates of ARR positivity screening among obese hypertensive OSA patients. In this cross-sectional study, obese hypertensive adults with confirmed OSA were recruited. Blood samples were analyzed for plasma aldosterone concentration (PAC), plasma renin concentration (PRC), serum potassium, and standard metabolic indices. Therapeutic intensity score (TIS) was used to quantify antihypertensive burden. ARR-based categories were applied to stratify patients into (i) positive ARR (Group 1), (ii) low renin/negative ARR (Group 2), or (iii) negative ARR (Group 3). Among 160 patients, 11.9% were classified in Group 1 and 20.0% as Group 2. Serum potassium levels were significantly lower in Group 2 compared with Group 3. An inverse association between PRC and uric acid was observed in the overall cohort, although the model fit was weak. In males, serum potassium, uric acid, and TIS were significantly associated with RAAS activity and were associated with greater likelihood for ARR positive screen. A substantial proportion of obese hypertensive OSA patients demonstrated ARR positivity. However, routine clinical and metabolic parameters alone were insufficient to reliably identify affected individuals. These findings support maintaining a low threshold for PA screening in hypertensive OSA patients.

Journal of Human Hypertension (2026) 40:755–762; <https://doi.org/10.1038/s41371-026-01195-w>

INTRODUCTION

Obstructive sleep apnea (OSA) is one of the most common sleep-related breathing disorders with increasing prevalence worldwide in parallel with the rising rate of obesity [1]. This condition is strongly associated with increased cardiovascular morbidity and mortality [2]. Hypertension is a frequent co-morbidity in patients with OSA and contributes significantly to the development of resistant hypertension in these patients, further compounding cardiovascular risks [3]. In recent years, a growing body of evidence has demonstrated an association between OSA and dysregulation of the renin-angiotensin-aldosterone system (RAAS) [4]. Importantly, RAAS activation has been implicated in the increased cardiovascular risk associated with OSA [5].

Notably, emerging studies suggest a higher-than-expected prevalence of primary aldosteronism (PA) among patients with OSA [6]. Although most studies reported the prevalence of PA in OSA to range between 8.9 and 11.2% [7, 8], this figure increases to as high as 21.3% among patients with moderate-to-severe OSA [9]. PA has been increasingly recognized not only for its impact on

blood pressure (BP) control but also for its independent association with cardiovascular and renal complications [10]. Besides, overweight and obese patients with PA demonstrate a higher prevalence of metabolic syndrome [11]. Despite these risks, PA is frequently under-diagnosed.

In response to mounting evidence, the Endocrine Society recommends that all patients with OSA should be screened for PA using the aldosterone-to-renin ratio (ARR) as an initial diagnostic step [12]. Since then, the society's most recent guideline update has since broadened its recommendation, advocating ARR screening for all patients with hypertension, irrespective of OSA status [13]. Nevertheless, despite these recommendations, ARR screening for PA is rarely performed routinely in clinical practice among OSA patients in Southeast Asia, particularly in resource-limited settings [14], with an average screening rate of <10% [15]. Factors contributing to this under-utilization include the cost and availability of ARR testing, limited awareness among clinicians, and challenges in proceeding with confirmatory testing which are time-consuming and often inaccessible in many healthcare

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Received: 6 May 2026 Revised: 3 August 2026 Accepted: 3 August 2026

Published online: 8 August 2026

systems [16]. Furthermore, the lack of specific, easily identifiable features in PA may contribute to the low disease awareness and missed opportunities for screening [17]. While the prevalence of raised ARR in OSA has been reported in Western and East Asian cohorts, there is a lack of corresponding data in Southeast Asian populations.

Given the high prevalence of resistant and poorly controlled hypertension among OSA patients, identifying potentially treatable secondary causes such as PA has important implications. Therefore, the objectives of this study were first, to determine the prevalence of ARR positivity screening in a cohort of obese hypertensive OSA patients in a Southeast Asian cohort; and second, to explore whether routinely measured metabolic and biochemical parameters are associated with an elevated ARR. Estimating the frequency of a positive ARR screen in this high-risk group may help guide recommendations for broader screening implementation. Additionally, assessing the clinical correlates of ARR positivity may inform whether clinicians can rely on these parameters to guide screening decisions in resource-limited settings.

METHODS

Study design and study participants

This study stems from an investigator-initiated research project, *Cardiovascular Impacts of RAAS and Vitamin D in Obstructive Sleep Apnea (CARD-OSA)*, outlined in our previous publication [18], which aimed to improve the understanding of the role of RAAS and vitamin D in OSA and their impact on patient health. This cross-sectional study was conducted between June 2022 and May 2024, involving the OSA population residing in Kuching and Kota Samarahan areas of Sarawak. The sample size of 125 was calculated based on the prevalence of PA in OSA [7].

All patients suspected of OSA who were referred from the primary care clinics in the above areas underwent sleep study in a tertiary sleep center in Kuching and were subsequently reviewed by a sleep physician. OSA was diagnosed using either overnight polysomnography (PSG) or level 3 respiratory polygraphy. In accordance with the American Academy of Sleep Medicine (AASM) recommendations [19], level 3 respiratory polygraphy served as the primary diagnostic modality for uncomplicated adults with a high pre-test probability of moderate or severe OSA. Patients with equivocal respiratory polygraphy findings or clinically significant comorbidities subsequently underwent PSG for definitive evaluation. A lower body mass index (BMI) cut-off to define obesity was used in accordance with the World Health Organization Asian-specific obesity threshold [20]. The inclusion criteria were aged ≥ 18 years, BMI ≥ 27.5 kg/m², confirmed to have OSA (including mild, moderate, and severe), and hypertensive; whereas exclusion criteria were known secondary hypertension, factors affecting RAAS hormones such as chronic kidney disease, congestive heart failure, history of acute coronary syndrome within 6 weeks prior to recruitment, treated for OSA, and pregnancy.

In line with the Endocrine Society guidelines, antihypertensive medications were withheld before blood collection [13]. If required, antihypertensive with the least effect on RAAS (non-dihydropyridine calcium blockers and/or alpha blockers) was prescribed as per guideline. During this period, BP was monitored once to twice weekly. All patients were instructed to maintain unrestricted salt intake prior to blood sampling.

Study variables

Demographic characteristics and anthropometric measurements were recorded. Office BP was measured twice using a validated automated sphygmomanometer (Omron HEM-7130-L, Omron Healthcare), with the patient seated after at least 5 min rest, and with a 1–2 min interval between readings. The average of the two measurements was utilized for analysis. Ambulatory and home BP monitoring were not used for the diagnosis of hypertension in this study. Blood samples were collected to assess plasma aldosterone concentration (PAC), plasma renin concentration (PRC), metabolic markers including HbA1c, lipid profile, uric acid, and other biochemical parameters such as serum potassium and renal function. Blood sampling for PAC and PRC was performed in accordance with guidelines [21]. Briefly, the patients' blood was sampled after an overnight fast, in the morning between 08:00 h and 11:00 h with patients in an upright position, at least 2 h after waking. The blood samples were then processed within 30 min of collection and subsequently analyzed using the

chemiluminescence immunoassay method (Liaison® XL, DiaSorin, Italy). Hypokalemia was corrected before blood sampling for the RAAS parameters. ARR was taken as the ratio between PAC and PRC. The intensity of anti-hypertensive treatment was evaluated using the Therapeutic Intensity Score (TIS), a validated method for quantifying treatment burden [18, 22]. It was determined as the ratio of the prescribed daily dose of an antihypertensive agent to its maximum FDA-approved daily dose, as illustrated in the formula below:

$$\text{TIS} = \frac{\text{Prescribed medication dose}}{\text{Maximum FDA – approved daily dose}}$$

Definitions

Previous smokers and previous alcohol consumers were those who had abstained from smoking and alcohol intake for at least 1 year respectively. OSA was categorized based on apnea hypopnea index (AHI), ie mild (AHI 5–< 15), moderate (AHI 15–< 30), and severe (AHI ≥ 30). Hypertension was defined as having systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg on two separate occasions, or patient was on antihypertensive medication. Hypokalemia was taken as serum potassium < 3.5 mmol/L. Using ARR as the screening tool, the patients were grouped into (i) positive ARR (Group 1) if low PRC (≤ 8.2 $\mu\text{IU/mL}$) and elevated ARR (> 70 pmol/L: $\mu\text{IU/mL}$) were demonstrated, (ii) low renin/negative ARR (Group 2) if PRC was low (≤ 8.2 $\mu\text{IU/mL}$) but ARR was normal, and (iii) negative ARR (Group 3) if both PRC and ARR were normal. Elevated PAC was defined as a value of > 277 pmol/L. These values were taken in accordance with the most recent Endocrine Society guidelines [13]. A lower cut-off value for ARR was utilized as per Endocrine Society recommendations to increase sensitivity in detecting those with suspected PA [13].

Statistical analysis

Statistical analysis was conducted using SPSS software (version 29, SPSS Inc., Chicago, IL). Continuous variables were expressed as mean $\pm$ standard deviation (SD) for normally distributed data or as median (interquartile range [IQR], 25th to 75th percentile) for non-normally distributed data. Categorical variables were summarized as frequencies and percentages. Normally distributed variables were compared among the groups using One way ANOVA, whereas non-normally distributed variables were compared using Kruskal-Wallis test. The chi-squared test was used to assess differences across the groups for categorical variables. Ordinal regression analysis was conducted to explore associations between various metabolic, biochemical, and anthropometric parameters with likelihood of ARR positivity, after adjusting for various potential explanatory variables. The three ARR categories were ordered from the highest biochemical risk to the lowest (Group 1 to Group 3). Therefore, a positive regression coefficient (β) and an odds ratio (OR) greater than 1.0 indicate that an increase in the predictor variable is associated with greater odds of belonging to a biochemically lower-risk profile (Group 3; negative ARR). A p-value of < 0.05 was considered statistically significant.

RESULTS

This study was reported in accordance with the STROBE guidelines. A total of 797 patients underwent sleep study, of which 160 fulfilled the study criteria and were recruited over a period of 22 months following informed consent. Notably, as concurrent hypertension and confirmed OSA were strict inclusion criteria, all participants ($n = 160$) met the specific indication for PA screening under the 2016 Endocrine Society guideline [12]. Within this target subgroup, the prevalence of a positive ARR screen (Group 1) was 11.9% while 20.0% were categorized as Group 2. The demographic, clinical, biochemical, and anthropometric characteristics across the three groups are presented in Table 1. Only three patients had hypokalemia (range 2.9–3.4 mmol/L), with one patient in each group. Serum potassium differed among the groups ($p = 0.024$). Post-hoc analysis showed that patients with Group 2 ($n = 32$) had significantly lower serum potassium than those with Group 3 ($n = 108$, $p = 0.019$).

No significant differences were observed in age, ethnicity, comorbidities, smoking or alcohol use, and OSA severity. Majority of

Table 1. Demographic, co-morbidities, and biochemical characteristics of obese hypertensive patients with obstructive sleep apnea categorized based on aldosterone-to-renin ratio screening.

Variables	Group 1 <i>n</i> = 19	Group 2 <i>n</i> = 32	Group 3 <i>n</i> = 109	<i>p</i>
Age, years	45.0 ± 12.9	48.9 ± 9.6	44.7 ± 12.2	0.146
Sex, <i>n</i> (%)				0.049
Male	11 (57.9)	11 (34.4)	64 (58.7)	
Female	8 (42.1)	21 (65.6)	45 (41.3)	
Ethnicity, <i>n</i> (%)				0.989
Malay	8 (42.1)	16 (50.0)	46 (42.2)	
Chinese	4 (21.1)	5 (15.6)	20 (18.3)	
Iban	3 (15.8)	4 (12.5)	17 (15.6)	
Bidayuh	4 (21.1)	6 (18.8)	21 (19.3)	
Others	0 (0)	1 (3.1)	5 (4.6)	
Co-morbidities, <i>n</i> (%)				
Type 2 diabetes	14 (73.7)	19 (59.4)	63 (57.8)	0.426
Dyslipidaemia	18 (94.7)	31 (96.9)	100 (91.7)	0.575
Hyperuricemia	12 (63.2)	21 (65.6)	103 (64.4)	0.983
Smoking, <i>n</i> (%)				0.193
Yes	5 (26.3)	3 (9.4)	24 (22.0)	
No	12 (63.2)	23 (71.9)	57 (52.3)	
Previous	2 (10.5)	6 (18.8)	28 (25.7)	
Alcohol use, <i>n</i> (%)				0.254
Yes	7 (36.8)	4 (13.3)	28 (25.9)	
No	11 (57.9)	23 (76.7)	64 (59.3)	
Previous	1 (5.3)	3 (10.0)	16 (14.8)	
AHI, /hour	39.5 ± 24.3	44.2 ± 28.1	47.7 ± 27.7	0.424
OSA category, <i>n</i> (%)				0.719
Mild	3 (15.8)	3 (9.4)	7 (6.4)	
Moderate	5 (26.3)	9 (28.1)	29 (26.6)	
Severe	11 (57.9)	20 (62.5)	73 (67.0)	
Family history of hypertension, <i>n</i> (%)				0.382
Yes	15 (78.9)	27 (84.4)	99 (90.8)	
No	4 (21.1)	4 (12.5)	9 (8.3)	
Unsure	0 (0)	1 (3.1)	1 (0.9)	
TIS score	1.29 ± 0.72	1.02 ± 0.77	1.05 ± 0.85	0.459
Systolic BP, mmHg	155.1 ± 13.9	151.3 ± 20.3	152.5 ± 17.4	0.801
Diastolic BP, mmHg	96.5 ± 12.9	95.3 ± 13.7	97.9 ± 12.7	0.708
BMI, kg/m ²	37.8 ± 6.1	40.8 ± 7.7	41.4 ± 7.2	0.143
Neck circumference, cm	42.4 ± 3.9	42.3 ± 4.3	44.0 ± 4.1	0.082
Waist circumference, cm	114.0 ± 11.3	117.1 ± 14.9	121.8 ± 14.0	0.047
Uric acid, mmol/L	407.8 ± 82.7	413.2 ± 86.7	438.1 ± 93.4	0.143
HbA1c, %	6.2 ± 0.5	6.7 ± 1.1	6.9 ± 1.8	0.316
Lipid profile, mmol/L				
Total	4.65 ± 1.12	4.86 ± 1.14	4.70 ± 1.0	0.831
LDL-C	2.73 ± 1.0	2.80 ± 0.91	2.71 ± 0.82	0.931
HDL-C	1.24 ± 0.21	1.31 ± 0.25	1.27 ± 0.25	0.684
Triglycerides	1.73 ± 0.96	1.73 ± 0.75	1.77 ± 0.87	0.985
Serum potassium, mmol/L	4.15 ± 0.43	4.04 ± 0.33	4.23 ± 0.32	0.024
PAC, pmol/L	310.2 (206.4, 506.9)	186.4 (126.7, 257.8)	263.2 (183.5, 325.5)	<0.001
PRC, μIU/mL	2.1 (1.4, 4.2)	5.7 (4.5, 7.1)	18.7 (13.3, 34.7)	<0.001
ARR, pmol/L:μIU/mL	133.7 (102.8, 167.6)	34.1 (22.5, 45.8)	12.8 (7.7, 19.4)	<0.001

Numerical variables are presented as the mean ± standard deviation or median (IQR), categorical variables are defined as percentage. Non-normally distributed variables were compared using Kruskal-Wallis test.

Group 1: positive ARR; Group 2: low renin/negative ARR; Group 3: negative ARR; AHI: apnea hypopnea index; OSA: obstructive sleep apnea; TIS: therapeutic intensity score; BP: blood pressure; BMI: body mass index; PAC: plasma aldosterone concentration; PRC: plasma renin concentration; ARR: aldosterone-to-renin ratio.

Table 2. a Multiple linear regression analysis between plasma renin concentration and covariates in obese hypertensive patients with obstructive sleep apnea. b Ordinal logistic regression analysis on likelihood of positive ARR in obese hypertensive patients with obstructive sleep apnea.

a				
Independent variable	Dependent variable: Plasma renin concentration ^a Adjusted R ² = 0.040			
	β	95% CI		p
Sex	−0.158	−17.758, 2.098		0.121
Smoking history	0.087	−3.294, 11.487		0.275
Body mass index	−0.089	−1.060, 0.295		0.267
Serum potassium	0.122	−3.568, 25.751		0.137
Uric acid	−0.216	−0.129, −0.018		0.010
HbA1c	0.080	−1.528, 4.653		0.319
b				
	β	SE	OR	95% CI (lower and upper limits)
Dependent variable: likelihood of positive ARR				
Group 1	5.000	2.365		0.366, 9.635
Group 2	6.310	2.383		1.640, 10.980
Independent variable				
Serum potassium	0.728	0.517	2.071	0.751, 5.703
Uric acid	0.003	0.002	1.003	0.999, 1.007
Waist circumference	0.024	0.013	1.024	0.999, 1.051
Model fitting information:				Pseudo R2 values:
Log-likelihood = 256.551				Cox & Snell = 0.067
χ ² (degree of freedom) = 11.095 (3)				Nagelkerke = 0.082
p-value = 0.011				McFadden = 0.041

^aControlled for age, apnea hypopnea index, systolic blood pressure, therapeutic intensity score.

Group 1: Positive ARR; Group 2: Low renin/negative ARR.

the patients had severe OSA across all 3 categories. All groups had similar prevalence of family history of hypertension, TIS, and BP. All patients met the study's hypertension criterion (systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg, or current anti-hypertensive use). The mean office BP was within the hypertensive range in every group and BP severity did not differ significantly by ARR screening category (systolic BP $p = 0.801$, diastolic BP $p = 0.708$). Similarly, there was no difference in metabolic parameters including BMI, neck circumference, uric acid, glucose control, and lipid profile. Those in Group 3 had significantly higher waist circumference than the other two groups.

Baseline characteristics of participants were further stratified by sex (Supplementary Table 1) and OSA severity (Supplementary Table 2). A progressive increase in anthropometric and metabolic burden was observed across both the OSA severity categories and sex-stratified cohorts. Specifically, higher BMI, larger waist and neck circumferences, and higher serum uric acid levels were associated with increasing OSA severity and were more pronounced in male participants compared to females. However, no statistically significant differences in RAAS hormones or the prevalence of positive ARR screening were observed across OSA severity categories. In contrast, the overall distribution of patients across the three ARR risk categories differed significantly between sexes ($p = 0.049$). Notably, male patients demonstrated a higher prevalence of ARR screen-positivity (Group 1) compared to female patients (12.8 vs 10.8%).

Correlation analysis in the overall cohort demonstrated that elevated uric acid was the only metabolic parameter significantly associated with PRC, showing an inverse relationship. No other statistically significant correlations were observed between RAAS

markers – including PAC, PRC, and ARR – and other key metabolic parameters, such as BMI, waist and neck circumferences, HbA1c, and lipid profile, as well as OSA severity.

In addition, multiple linear regression analysis demonstrated that only uric acid is negatively correlated with PRC ($\beta = -0.216$, $p = 0.010$) (Table 2a) although the model's explanatory power was limited, with a pseudo R² of <0.1. Following stepwise model selection, ordinal regression analysis retained serum potassium, uric acid, and waist circumference as variables that improved model stability. The threshold coefficients remained statistically significant, suggesting a consistent gradient across the groups. However, none of these variables exhibited a statistically significant independent association with likelihood of a positive ARR (Table 2b).

Sensitivity analyses of PRC and PAC were subsequently performed after stratification by sex, BMI, and TIS (Tables 3a and 3b). Associations varied across subgroups. PRC correlated inversely with uric acid in males, patients with BMI < 40 kg/m², and those with TIS ≤ 1, but positively with HbA1c in females and patients with TIS > 1. PAC correlated positively with TIS and inversely with serum potassium among patients with TIS > 1, whereas no significant associations were observed in females, patients with BMI < 40 kg/m², or those with TIS ≤ 1.

Ordinal regression analysis was then performed on the male subgroup, as this was the only subgroup in which both PRC and PAC demonstrated significant, independent associations with relatively higher adjusted R² values indicating greater explanatory power, whereas findings in other subgroups (female, BMI category, TIS strata) were less consistent and with limited proportion of variance. Serum potassium remained the only

Table 3. a Sensitivity analyses of plasma renin concentration stratified by sex, BMI, and therapeutic intensity score. b Sensitivity analyses of plasma aldosterone concentration stratified by sex, BMI, and therapeutic intensity score.

a								
Subgroup	N	Outcomes showing significant correlation	Pearson's correlation		Multiple regression analysis			
			r	p	Adjusted R ²	β	95% CI	p
Sex								
Male	86	Uric acid	−0.284	0.008	0.113	−0.355	−0.236, −0.060	0.001
Female	74	HbA1c	0.294	0.011	0.085	0.295	1.104, 8.052	0.011
Body mass index								
<40 kg/m ²	78	Uric acid	−0.244	0.031	0.205	−0.451	−0.229, −0.096	<0.001
≥40 kg/m ²	82	None	NA	NA	NA	NA	NA	NA
Therapeutic Intensity Score								
≤1	94	Uric acid	−0.285	0.005	0.179	−0.414	−0.236, −0.081	<0.001
>1	66	HbA1c	0.310	0.011	0.127	0.372	2.038, 9.305	0.003
b								
Subgroup	N	Outcomes showing significant correlation	Pearson's correlation		Multiple regression analysis			
			r	p	Adjusted R ²	β	95% CI	p
Sex								
Male	86	TIS	0.213	0.048	0.136	0.246	0.244, 2.603	0.019
		Potassium	−0.295	0.006	0.136	−0.233	−6.256, −0.351	0.029
Female	74	HbA1c	NA	NA	NA	NA	NA	NA
Body mass index								
<40 kg/m ²	78	NA	NA	NA	NA	NA	NA	NA
≥40 kg/m ²	82	TIS	0.279	0.011	0.079	0.269	0.298, 2.55	0.014
Therapeutic Intensity Score								
≤1	94	NA	NA	NA	NA	NA	NA	NA
>1	66	Potassium	−0.291	0.018	0.086	−0.258	−6.666, −0.238	0.036

variable with an independent association with likelihood of positive ARR, supported by significant threshold coefficients (Table 4).

DISCUSSION

This study provides the first population-level screening data from Southeast Asia exploring the prevalence of ARR screening positivity in obese, hypertensive OSA patients. It demonstrates two important findings. First, in this cohort, there was a high prevalence of ARR screening positivity. Second, across the overall cohort, conventional metabolic and biochemical parameters failed to reliably differentiate or predict which individuals would screen positive on the ARR.

A total of 11.9% of patients had a positive ARR screen, and another 20.0% had low renin but a negative ARR. These numbers, which account for almost one-third of this high-risk population, suggest some form of RAAS dysregulation among these patients. The larger proportion of patients having low renin may represent early-stage aldosterone excess without a high enough aldosterone leading to a negative ARR. Collectively, these support the Endocrine Society's earlier recommendation of screening all OSA

patients with hypertension [12]. This is to ensure early identification of potentially underdiagnosed cases and hence enable timely initiation of targeted therapy to improve long term outcomes.

In the overall cohort, RAAS activity was not strongly associated with metabolic or biochemical variables, and the explanatory power of the regression models was limited. Likewise, none of the metabolic or biochemical parameters were significantly associated with positive ARR likelihood categories. The modest adjusted R² values observed across all subgroup analyses further suggest that these measured variables explain only a small proportion of the variability in RAAS activity.

Clinically, this suggests that biochemical profiling should not be used to determine which obese hypertensive patients with OSA should undergo ARR screening, nor should it be used to exclude PA. Although ancillary findings such as hypokalemia or higher TIS may increase clinical suspicion in settings where ARR testing is less accessible, these features should only be regarded as supportive clues and should never replace or delay formal ARR screening. Indeed, hypokalemia has been reported in only up to one-third of patients with PA in primary care studies, with normokalaemic hypertension being the more common presentation [23]. Confirmatory testing remains essential for diagnosis; these clinical and

Table 4. Ordinal logistic regression analysis on ARR positivity in obese hypertensive men with obstructive sleep apnea.

	β	SE	OR	95% CI
(lower and upper limits)				
Dependent variable: likelihood of positive ARR				
Group 1	7.546	3.837		
0.025, 15.066		0.049		
Group 2	8.514	3.863		
0.943, 16.086		0.028		
Independent variable				
Body mass index	0.008	0.034	1.008	
0.942, 1.078		0.820		
Serum potassium	2.238	0.882	9.375	
1.664, 52.826		0.011		
Uric acid	-0.001	0.003	0.999	
0.993, 1.005		0.814		
LDL-C	0.234	0.343	1.264	
0.645, 2.477		0.496		
Model fitting information:				Pseudo R ² values:
Log-likelihood = 117.116				Cox &
Snell = 0.122				
χ^2 (degree of freedom) = 11.188 (6)				
Nagelkerke = 0.157		p-value = 0.083		
McFadden = 0.087				

Group 1: Positive ARR; Group 2: Low renin/negative ARR.

metabolic surrogates may serve as complementary evidence to help prioritize screening, particularly in obese hypertensive men with OSA and in a resource-limited settings, but they are not a substitute for it.

Although previous studies have reported associations between PA and multiple metabolic dysfunctions [11], this was not observed in our cohort of obese OSA patients. This suggests that the mechanisms driving metabolic dysfunction in these patients may be multifactorial beyond RAAS dysregulation alone. Insulin resistance and dyslipidemia in OSA may be driven by hypoxia-induced oxidative stress [24], hypothalamic-pituitary-adrenal axis activation [25], and altered adipokines [26]. This is further amplified by the presence of pro-inflammatory cytokines and angiotensinogen from adipose tissue in obesity that promotes metabolic dysfunction [27]. In addition, chronic intermittent hypoxia in OSA may lead to sympathetic activation which is known to elevate renin [28]. In view of this, clinical judgement based on metabolic risk factors alone may underestimate the likelihood of a positive ARR, potentially delaying screening and diagnosis. Collectively, these findings suggest that metabolic dysfunction in obese patients is multifactorial and not solely driven by RAAS dysregulation. Consequently, metabolic risk factors alone are unlikely to reliably identify patients with a positive ARR screen.

Interestingly, when the data were stratified by sex, serum potassium, uric acid, and TIS correlated with RAAS activity in men, but not in women, suggesting a possible complex biological heterogeneity. Sex-related differences in RAAS activity have been widely reported in the literature [29, 30]. Estrogen contributes to this variation by affecting substrate availability, regulating enzyme and receptor expression, and influencing protein synthesis [29]. As

such, these may blunt the observable impact of biochemical markers on RAAS activity. It is important to note that these sex-specific signals are a secondary, exploratory finding that suggests possible biological differences in RAAS dysregulation and merits future validation. However, they should not be used as a basis for selectively screening men over women, or any other subgroup. Taken together, these sex-specific inconsistencies suggest that conventional clinical characteristics cannot be relied upon as robust screening filters for aldosterone dysregulation among patients with OSA.

At the same time, the inverse association between PRC and uric acid in men should not be over-interpreted as evidence of direct causal link between RAAS activity and hyperuricemia. Notably, the negative ARR group (Group 3) had numerically higher uric acid level compared to the other two groups, albeit the difference was not statistically significant. This is more readily explained by the fact that hyperuricemia is a well-established component of the metabolic syndrome, which is closely linked to obesity, insulin resistance, and renal urate handling, rather than a significant relationship with RAAS activity. Additionally, the entire cohort was obese with a high background prevalence of metabolic syndrome features, which likely explains the regression associations observed between uric acid and the RAAS hormones in men.

Beyond the associations explored in this study, the relationship between OSA and aldosterone excess is increasingly recognized as bidirectional [31]. Aldosterone excess promotes salt and fluid retention, which may exacerbate upper airway oedema and worsen OSA severity. Conversely, sleep fragmentation and recurrent arousals in OSA lead to heightened sympathetic activation, which in turn activates the RAAS. Together, these mechanisms create a self-perpetuating pathological cycle characterized by chronic intermittent hypoxia, RAAS dysregulation, and arterial hypertension. Although these associations were not observed in our cohort, this should not be interpreted as evidence that no relationship exists. Rather, the predominance of severe OSA in our study likely limited the variability in disease severity and reduced the statistical power to detect such associations.

This study has a few limitations. First, in the absence of confirmatory testing, classification of participants into the positive ARR groups was based solely on screening thresholds, thereby limiting diagnostic certainty. Accordingly, these categories should be regarded as ARR screening categories rather than definitive diagnoses of PA. Nevertheless, this reflects the original scope and design of our study. Confirmatory testing such as the saline suppression test was not incorporated into the study protocol or funding application because the primary objective was to determine the prevalence and clinical correlates of a positive ARR screen, rather than to establish the prevalence of confirmed PA.

Importantly, this approach mirrors real-world clinical practice in many resource-constrained Southeast Asian public healthcare infrastructures, where access to specialized confirmatory testing is limited and ARR often serves as the principal screening tool for identifying patients who warrant further evaluation and referral. Therefore, although confirmatory testing was not performed, the prevalence of a positive ARR screening results reported in this study remains clinically meaningful, as it provides valuable insight into the potential burden of aldosterone dysregulation that may otherwise go unrecognized in this population. Accordingly, the reported prevalence should be interpreted as the prevalence of positive ARR screening results rather than the prevalence of confirmed PA. Second, the cross-sectional single-center design of the study limits the ability to establish causality and generalizability to other OSA populations. Moreover, as the patients of this study were recruited from a tertiary sleep center, it may have led to selection bias and thus, may not represent all OSA patients in primary care. Despite controlling for multiple confounders, other unmeasured variables could have influenced RAAS markers.

In addition, the possibility of false elevation of PRC due to sympathetic overactivation and chronic intermittent hypoxia in OSA may have resulted in missed identification of suspected PA cases.

Notwithstanding, this study addressed a clinically relevant but underexplored area by investigating RAAS markers and positive ARR likelihood in OSA patients, a specific high-risk group, where the prevalence and screening strategies for PA remain uncertain. Importantly, this study adds region-specific evidence to existing literature and provides valuable insight given the high burden of obesity, OSA, and hypertension in Southeast Asia. Such regional data are crucial, as RAAS activity and optimal ARR screening approaches may be influenced by differences in ethnicity, environment, and healthcare access.

The observation that male patients, but not females, demonstrated distinct associations of potassium, uric acid, and hypertensive severity with RAAS activity provides novel insight into potential sex-specific regulation. Although the variance explained was modest, these findings raise important hypotheses about differences between sexes that warrant further confirmation. Equally important, the largely negative findings in the overall cohort suggest that currently available metabolic biochemical markers have limited utility for identifying ARR-positive individuals, highlighting the need for improved risk-stratification strategies.

Future research should validate these findings by adding PA confirmatory tests, particularly whether sex-specific associations reflect true biological variations. Besides, cost-effectiveness analysis of universal vs. targeted PA screening should be performed in this patient cohort in resource-limited settings. A screening algorithm that integrates ARR testing in OSA management can help raise awareness among clinicians for early detection and intervention of PA in these high-risk individuals.

CONCLUSIONS

In this cohort of obese hypertensive patients with OSA, 11.9% had a positive ARR screen. Across the overall cohort, routine metabolic and biochemical markers showed limited ability to distinguish patients who screened positive from those who did not, reinforcing that clinical and metabolic profiles alone are not reliable tools for deciding who should undergo ARR screening. Taken together, these findings support the Endocrine Society's recommendation to maintain a low threshold for ARR screening in all hypertensive patients, including those with OSA, regardless of ancillary parameters. Further studies with larger sample sizes and confirmatory testing are warranted to refine PA screening strategies in this population in resource-limited settings.

DATA AVAILABILITY

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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ACKNOWLEDGEMENTS

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

AUTHOR CONTRIBUTIONS

HHL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Writing – original draft; **SPT:** Investigation, Validation, Writing – review and editing; **AJK:** Data curation; **MCY:** Data curation, Validation; **AS:** Data curation, Validation; **CSC:** Resources; **NMAM:** Data curation; **ATS:** Formal analysis, Writing – review and editing; **BBCT:** Data curation; **FHST:** Supervision; **EAA:** Supervision, Writing – review and editing; **NS:** Funding acquisition, Methodology, Supervision, Writing – review and editing

FUNDING

This work was supported by the Malaysian Ministry of Higher Education under Fundamental Research Grant Scheme FRGS/1/2021/SKK01/UNIMAS/02/1 and the National University of Malaysia (UKM) under Grant FF-2022-066, GP-2020-K013181, GP-2021-K013181, and TAP-K013181. The sponsors had no role in the design or conduct of this study.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL CONSIDERATION

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was provided by Medical Research Ethical Committee of Malaysia (NMRR-21-1472-60812), UNIMAS Medical Ethics Committee (UNIMAS/TNC(P1)/09-65/01), and Universiti Kebangsaan Malaysia Ethics Committee (UKM PPI/111/8/JEP-2022-029). All patients gave written informed consent.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41371-026-01195-w>.

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