Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

A parsimonious hormone-based triage model for selected endocrine causes of hypertension: a prospective single-center cohort study

Chengjing Xia
Shenzhen University of Advanced Technology General Hospital
Fen Ma
Shenzhen University of Advanced Technology General Hospital
Fuhai Huang
Shenzhen University of Advanced Technology General Hospital
Zhongqun Zhan
zzqun0316@163.com

Shenzhen University of Advanced Technology General Hospital

Research Article

Keywords: hypertension, secondary hypertension, endocrine hypertension, primary aldosteronism, clinical prediction model, biomarkers

Posted Date: September 27th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10826956/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Endocrine causes of secondary hypertension carry important cardiovascular consequences but require different disease-specific diagnostic pathways. We evaluated whether a small set of baseline endocrine measurements could support triage among adults already undergoing etiologic evaluation for hypertension.

Methods

In this prospective single-center cohort, adults evaluated for hypertension in Shenzhen between July 2023 and January 2025 underwent baseline measurement of adrenocorticotropic hormone, plasma renin activity (PRA), angiotensin II, aldosterone, and cortisol before final endocrine adjudication. Participants with complete candidate-predictor and independent reference-standard data were included. Nested logistic models were compared using a stratified 70:30 development-validation split. Discrimination, calibration, Brier score, sensitivity, specificity, predictive values, and likelihood ratios were assessed.

Results

Among 5,986 participants in the screening cohort, 1,502 completed the reference-standard pathway and 412 had confirmed primary aldosteronism, pheochromocytoma/paraganglioma, or Cushing syndrome. In the validation cohort (n = 451; 124 events), the aldosterone-PRA-cortisol model achieved an area under the receiver operating characteristic curve of 0.889 (95% CI 0.852–0.922), sensitivity of 72.6%, specificity of 86.9%, positive predictive value of 67.7%, negative predictive value of 89.3%, and Brier score of 0.109. Adding angiotensin II and adrenocorticotropic hormone did not materially improve the linear model. An exploratory nonlinear five-marker model achieved an area under the curve of 0.900 with higher sensitivity but lower specificity.

Conclusions

A three-marker model retained most of the discrimination of the five-marker panel and may help prioritize disease-specific confirmatory evaluation in selected patients undergoing hypertension work-up. It should not replace established endocrine testing or be used to withhold guideline-recommended primary aldosteronism screening. External validation is required before clinical implementation.

Background

Hypertension is a leading modifiable cause of stroke, ischemic heart disease, heart failure, and chronic kidney disease worldwide [1, 2]. Although most patients are classified as having primary hypertension, a clinically important subgroup has an identifiable secondary cause. Endocrine disorders are particularly relevant because recognition of the causal hormonal abnormality can change treatment, surveillance, and cardiovascular prognosis [3, 4].

Primary aldosteronism, pheochromocytoma/paraganglioma (PPGL), and Cushing syndrome are among the most important endocrine causes of hypertension. Primary aldosteronism is common in hypertension, particularly in higher-risk clinical settings, and is associated with excess cardiovascular and target-organ risk compared with blood pressure-matched primary hypertension [5–10]. PPGL is less prevalent but potentially life-threatening because catecholamine excess can precipitate hypertensive crises, arrhythmias, myocardial injury, and other cardiovascular complications [13–16]. Hypercortisolism contributes to hypertension through sodium retention, increased vascular responsiveness, metabolic dysfunction, and activation of multiple neurohormonal pathways [17–20].

The diagnostic pathways for these disorders are disease-specific. Contemporary guidance recommends screening for primary aldosteronism with aldosterone and renin, interpreted together with clinical context and followed by further disease-specific evaluation when appropriate [5, 11, 12]. PPGL is investigated primarily using plasma free or urinary fractionated metanephrines under standardized sampling conditions [13–16]. Suspected Cushing syndrome requires high-accuracy cortisol testing, often with more than one concordant test [17–20]. Therefore, a nonspecific baseline hormone panel cannot serve as a stand-alone diagnostic test for endocrine hypertension.

In hypertension practice, however, clinicians often need to decide which patients should be prioritized for more extensive endocrine evaluation. The five measurements available in our study center—adrenocorticotropic hormone (ACTH), plasma renin activity (PRA), angiotensin II, aldosterone, and cortisol—sample complementary components of pituitary-adrenal and renin-angiotensin-aldosterone physiology. We therefore asked a workflow-oriented question: whether a reproducible and sufficiently parsimonious combination of these baseline markers could help triage patients already undergoing etiologic evaluation for hypertension. The primary aim was to develop and internally validate a model for the composite outcome of confirmed primary aldosteronism, PPGL, or Cushing syndrome. Secondary objectives were to compare nested marker sets, assess calibration and clinically interpretable classification performance, explore disease-specific discrimination, and examine the incremental contribution of angiotensin II.

Methods

Study design and setting

This prospective observational cohort study was conducted at Shenzhen University of Advanced Technology General Hospital, formerly University of Chinese Academy of Sciences Shenzhen Hospital

(Guangming), from July 2023 to January 2025. The hospital is a general hospital serving Guangming District and surrounding areas of Shenzhen. Adults referred for hypertension or high-risk blood pressure evaluation were screened consecutively. The present model-development analysis was restricted to participants who met the study definition of hypertension, had complete baseline candidate-predictor measurements, and completed the independent reference-standard pathway. The study was reported in accordance with the STROBE statement for observational research and the TRIPOD + AI statement for clinical prediction models developed using regression methods [23, 24].

Participants

Eligible participants were aged 18 years or older and had hypertension documented by repeated office blood pressure measurements, current antihypertensive treatment, or resistant hypertension requiring etiological evaluation. Exclusion criteria were pregnancy or lactation; clinically important exogenous glucocorticoid exposure; advanced kidney disease that precluded valid biochemical assessment; known renovascular or major aortic causes of hypertension; active malignancy or severe hepatic failure likely to affect hormone interpretation; and incomplete candidate-predictor or reference-standard data.

Candidate predictors and preanalytical assessment

The candidate predictors were ACTH, PRA, angiotensin II, aldosterone, and cortisol measured at baseline before final endocrine adjudication. Hormone concentrations were natural-log transformed because of right-skewed distributions and were standardized using the means and standard deviations of the development cohort. Preanalytical variables considered clinically relevant included collection time, fasting status, posture, serum potassium, sodium intake, and use of medications that may alter PRA, aldosterone, cortisol, or catecholamine-related testing [11–16]. Medication classes of particular interest were angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium-channel blockers, beta-blockers, thiazide or loop diuretics, mineralocorticoid receptor antagonists, glucocorticoids, and alpha-blockers.

Independent reference standard

The target outcome was the presence of at least one confirmed selected endocrine cause of hypertension. Baseline candidate-hormone values were not used as the sole basis for outcome classification. Final disease status was assigned from the specialist record and the disease-specific diagnostic pathway:

1. Primary aldosteronism: positive case detection followed by confirmatory evaluation, such as saline infusion or captopril challenge, unless a guideline-recognized exception applied; imaging and adrenal venous sampling were considered when clinically indicated [5, 11, 12].

2. PPGL: biochemical confirmation using plasma free metanephrines or urinary fractionated metanephrines, followed by anatomical or functional localization when appropriate [13–16].

3. Cushing syndrome: at least two concordant abnormal high-accuracy tests or documented specialist adjudication using urinary free cortisol, late-night salivary cortisol, and/or dexamethasone suppression testing, with etiologic evaluation when indicated [17–20].

Outcomes

The primary outcome was discrimination and calibration of the final model for any confirmed selected endocrine cause. Secondary outcomes were the performance of nested one- to five-marker models and the classification characteristics of the selected model at a probability threshold determined in the development cohort. Exploratory outcomes were disease-specific discrimination, the incremental contribution of angiotensin II, and model performance after excluding participants receiving a diuretic or mineralocorticoid receptor antagonist at baseline sampling.

Sample size and missing data

The model-development cohort contained 412 outcome events for five candidate predictors, providing more than 80 events per candidate predictor for the main linear analysis. The primary analysis used complete candidate-predictor and reference-standard data. Participants who did not complete the independent reference-standard pathway were not included in model development; the implications of this partial verification are addressed in the Discussion. The event count was also considered adequate in relation to contemporary sample-size guidance for multivariable prediction-model development [25].

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), and categorical variables as number (percentage). Group differences were assessed using the independent-samples t test, Mann-Whitney U test, chi-square test, or Fisher exact test, as appropriate. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

The modeling cohort was divided using a stratified 70:30 development-validation split. Nested logistic models were prespecified in the following sequence: aldosterone alone; aldosterone plus PRA; addition of cortisol; addition of angiotensin II; and addition of ACTH. Differences between correlated areas under the receiver operating characteristic curve (AUCs) were assessed using the DeLong method [26]. The parsimonious model was selected by balancing discrimination, Brier score, interpretability, and assay burden rather than by statistical significance alone.

Validation performance was summarized using AUC with bootstrap 95% confidence intervals (CIs), calibration intercept, calibration slope, Brier score, sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios [27, 28]. A decision threshold was selected using the

Youden index in the development cohort and was locked before validation. A nonlinear five-marker model using spline-transformed predictors and penalized logistic regression was evaluated as an exploratory analysis. Treatment-response and hormone-change analyses were not retained because disease-specific therapy, adherence, co-interventions, and time-varying confounding were not sufficiently characterized.

Ethics approval and consent

The protocol entitled "Prospective cohort study of etiological screening for endocrine hypertension" was approved by the Ethics Committee of University of Chinese Academy of Sciences Shenzhen Hospital (Guangming) on January 16, 2023 (Approval No. LL-KT-2022066). Written informed consent was obtained before enrollment. The study was conducted in accordance with the Declaration of Helsinki.

Use of generative AI

OpenAI ChatGPT was used only to support English-language editing and manuscript formatting. It was not used to generate, alter, or analyze study data or to determine study outcomes. All scientific content, numerical values, references, and interpretations were reviewed and verified by the authors, who take full responsibility for the final manuscript.

Results

Study population

A total of 7,842 adults were assessed for hypertension evaluation. After exclusion of 1,856 individuals, 5,986 participants entered the screening cohort. Of these, 1,502 completed the independent reference-standard pathway and formed the modeling cohort. A confirmed selected endocrine cause was present in 412 participants (27.4%): primary aldosteronism in 304, PPGL in 48, and Cushing syndrome in 60. No diagnostic-category overlap was observed. The development cohort included 1,051 participants with 288 events, and the validation cohort included 451 participants with 124 events (Fig. 1).

Baseline characteristics

Participants with a confirmed selected endocrine cause were older, had a higher body mass index, higher systolic and diastolic blood pressure, lower serum potassium, higher fasting glucose, and a greater frequency of resistant hypertension, obstructive sleep apnea, and diabetes. Diuretic and mineralocorticoid receptor antagonist use was also more common in the confirmed group. Sex distribution, kidney function, LDL cholesterol, and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium-channel blockers, and beta-blockers did not differ materially between groups (Table 1).

Table 1
Baseline characteristics of the complete-reference-standard cohort

Characteristic	No confirmed selected cause (n = 1,090)	Confirmed selected cause (n = 412)	P value
Age, years	45.0 ± 10.4	47.6 ± 10.7	< 0.001
BMI, kg/m²	25.9 ± 3.5	26.8 ± 3.5	< 0.001
Systolic blood pressure, mmHg	154.5 ± 15.5	159.4 ± 15.0	< 0.001
Diastolic blood pressure, mmHg	91.5 ± 10.5	93.5 ± 9.6	< 0.001
Serum potassium, mmol/L	4.1 ± 0.4	3.7 ± 0.4	< 0.001
eGFR, mL/min/1.73 m²	87.7 ± 18.4	86.6 ± 18.2	0.319
Fasting glucose, mmol/L	5.9 ± 1.3	6.3 ± 1.3	< 0.001
LDL-C, mmol/L	3.0 ± 0.8	3.1 ± 0.8	0.096
Male sex	564 (51.7%)	226 (54.9%)	0.308
Resistant hypertension	232 (21.3%)	160 (38.8%)	< 0.001
Obstructive sleep apnea	98 (9.0%)	57 (13.8%)	0.008
Diabetes	176 (16.1%)	99 (24.0%)	< 0.001
ACE inhibitor or ARB	631 (57.9%)	223 (54.1%)	0.209
Calcium-channel blocker	692 (63.5%)	255 (61.9%)	0.610
Beta-blocker	317 (29.1%)	130 (31.6%)	0.384
Diuretic	291 (26.7%)	144 (35.0%)	0.002
Mineralocorticoid receptor antagonist	57 (5.2%)	58 (14.1%)	< 0.001

Values are mean ± standard deviation or n (%), unless otherwise indicated. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol.

Hormone profiles by confirmed subtype

Hormone distributions differed across confirmed subtypes. Primary aldosteronism showed the expected combination of suppressed PRA and higher aldosterone. PPGL had the highest median ACTH, PRA, angiotensin II, and cortisol concentrations, whereas Cushing syndrome had the highest cortisol concentration. The opposing disease-specific patterns indicate that a single linear direction for every biomarker is unlikely to characterize all endocrine causes equally well (Table 2).

Table 2
Hormone concentrations according to confirmed subtype

Group	n	ACTH, pg/mL	PRA, ng/mL/h	Angiotensin II, pg/mL	Aldosterone, ng/dL	Cortisol, nmol/L
No confirmed selected endocrine cause	1,090	24.8 (18.6–34.8)	1.6 (1.1–2.3)	49.0 (35.2–68.9)	11.3 (7.8–15.3)	367.8 (294.4-456.5)
Primary aldosteronism	304	24.5 (17.7–34.5)	0.5 (0.4–0.8)	37.7 (26.6–50.9)	23.5 (16.5–31.5)	380.6 (292.6-483.7)
PPGL	48	35.6 (25.8–50.8)	2.4 (1.7–3.4)	75.4 (56.7-104.6)	17.6 (11.6–22.2)	497.7 (396.4-612.2)
Cushing syndrome	60	19.7 (13.8–35.1)	1.1 (0.8–1.7)	62.0 (43.7–85.1)	15.1 (9.2–18.8)	562.9 (506.3–670.0)

Values are median (interquartile range). ACTH, adrenocorticotropic hormone; PRA, plasma renin activity; PPGL, pheochromocytoma/paraganglioma.

Comparison of nested candidate models

Aldosterone alone provided moderate discrimination. Adding PRA significantly improved the AUC, and adding cortisol produced a further improvement. Angiotensin II and ACTH did not materially improve the linear model for the composite endpoint. Aldosterone, PRA, and cortisol were therefore retained as the parsimonious primary model (Table 3).

Table 3
Validation performance of nested linear models

Model	Predictors	Validation AUC	Brier score	DeLong comparison
M1	Aldosterone	0.814	0.144	Reference
M2	Aldosterone + PRA	0.866	0.117	P = 0.003 vs M1
M3	Aldosterone + PRA + cortisol	0.889	0.109	P = 0.002 vs M2
M4	M3 + angiotensin II	0.889	0.109	P = 0.329 vs M3
M5	M4 + ACTH	0.888	0.110	P = 0.744 vs M4

AUC, area under the receiver operating characteristic curve; ACTH, adrenocorticotropic hormone; PRA, plasma renin activity.

Parsimonious model specification

The parsimonious model was fitted using standardized natural-log hormone concentrations. The prediction equation was: logit(p) = -1.552 + 1.290 z[ln(aldosterone)] − 1.167 z[ln(PRA)] + 0.500 z[ln(cortisol)]. The standardized terms were calculated using development-cohort values:

z[ln(aldosterone)] = (ln value − 2.573)/0.578; z[ln(PRA)] = (ln value − 0.221)/0.734; and z[ln(cortisol)] = (ln value − 5.934)/0.348. The predicted probability was p = 1/[1 + exp(-logit(p))]. The fitted coefficients are provided in Table 4.

Table 4
Coefficients of the parsimonious three-marker model

Term	Beta coefficient	Odds ratio	95% CI
Intercept	-1.552	-	-
ln(Aldosterone), per 1 SD	1.290	3.63	2.90–4.54
ln(PRA), per 1 SD	-1.167	0.31	0.25–0.38
ln(Cortisol), per 1 SD	0.500	1.65	1.37–1.98
CI, confidence interval; PRA, plasma renin activity; SD, standard deviation.			

Internal validation

In the validation set, the parsimonious model achieved an AUC of 0.889 (95% CI 0.852–0.922). At the locked probability threshold of 0.339, sensitivity was 72.6%, specificity 86.9%, positive predictive value 67.7%, negative predictive value 89.3%, positive likelihood ratio 5.52, and negative likelihood ratio 0.32. The calibration intercept was 0.126, the calibration slope 1.047, and the Brier score 0.109. The confusion matrix contained 90 true positives, 34 false negatives, 284 true negatives, and 43 false positives. Detailed validation metrics are summarized in Table 5. The validation receiver operating characteristic curves are shown in Fig. 2, and model calibration is shown in Fig. 3.

Table 5
Internal validation of parsimonious and full-panel models

Model	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Brier score
Parsimonious three-marker linear model	0.889 (0.852–0.922)	72.6%	86.9%	67.7%	89.3%	0.109
Full five-marker linear model	0.888	74.2%	88.7%	71.3%	90.1%	0.110
Exploratory nonlinear five-marker model	0.900 (0.867–0.930)	85.5%	80.1%	62.0%	93.6%	0.106
AUC, area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.						

Exploratory contribution of angiotensin II

Angiotensin II added almost no discrimination for the composite endpoint or primary aldosteronism, whereas its largest numerical contribution was observed in PPGL. The PPGL estimate was imprecise because the validation set contained only 13 PPGL cases; this result should therefore be regarded as hypothesis-generating rather than evidence for clinical implementation (Table 6).

Table 6
Exploratory subtype-specific contribution of angiotensin II

Subtype	Validation cases	AUC without Ang II	AUC with Ang II	Difference
Primary aldosteronism	90	0.934	0.937	0.003
PPGL	13	0.903	0.944	0.040
Cushing syndrome	21	0.866	0.890	0.023

Ang II, angiotensin II; AUC, area under the receiver operating characteristic curve; PPGL, pheochromocytoma/paraganglioma.

Sensitivity analysis for medication interference

After exclusion of validation participants using a mineralocorticoid receptor antagonist or diuretic at baseline hormone sampling, 302 participants with 64 confirmed events remained. The exploratory nonlinear model retained an AUC of 0.879, sensitivity of 82.8%, specificity of 82.8%, and negative predictive value of 94.7%. These findings suggest that the model signal was not entirely explained by these medication classes, although the remaining medication and preanalytical effects could not be eliminated.

Discussion

This prospective single-center study evaluated a workflow-oriented approach to endocrine secondary hypertension in adults already undergoing etiologic evaluation. The main finding was that a three-marker model based on aldosterone, PRA, and cortisol retained essentially all of the discrimination of the full five-marker linear model. In the held-out validation cohort, the parsimonious model achieved an AUC of 0.889 with specificity of 86.9% and a negative predictive value of 89.3%. The result is most relevant to prioritization of disease-specific endocrine testing within hypertension care, rather than to stand-alone diagnosis.

The composite endpoint deserves explicit interpretation. Primary aldosteronism, PPGL, and Cushing syndrome are biologically distinct disorders and were not combined because they share a single pathophysiological mechanism. They were combined because the clinical workflow question was whether a patient undergoing hypertension work-up had any selected endocrine cause that warranted disease-specific confirmation. The subtype analyses therefore remain important for understanding where the composite signal originated, and the small PPGL and Cushing syndrome samples limit disease-specific inference.

The modeling cohort represented a selected subgroup of the overall screening population. Only 1,502 of 5,986 screened participants completed the independent reference-standard pathway, and 412 of these had a confirmed selected endocrine cause. The 27.4% event proportion therefore reflects enrichment among patients who underwent confirmatory evaluation and must not be interpreted as the prevalence of endocrine hypertension in the broader hypertensive population. Referral patterns, clinician suspicion, test availability, and completion of the diagnostic pathway are all likely to have influenced verification. Selective completion of the reference standard may introduce partial-verification bias [29], and this remains one of the principal limitations of the present analysis.

The subtype-specific hormone patterns support biological plausibility while also illustrating why a universal linear signal is challenging. Primary aldosteronism was characterized by suppressed PRA and higher aldosterone, consistent with autonomous mineralocorticoid activity and explaining the large gain in discrimination when PRA was added to aldosterone [5–7, 11, 12]. Cushing syndrome showed the highest cortisol concentrations, whereas ACTH varied across disease forms [17–20]. PPGL showed higher ACTH, PRA, angiotensin II, and cortisol, compatible with catecholamine-related hemodynamic and stress-axis activation [13–16]. These patterns provide a mechanistic basis for the candidate markers but do not imply that angiotensin II, ACTH, or the combined panel can replace metanephrine-based PPGL testing or established Cushing syndrome testing.

The nested-model results favor parsimony. Aldosterone alone yielded an AUC of 0.814; addition of PRA increased the AUC to 0.866, and addition of cortisol increased it to 0.889. Angiotensin II and ACTH did not materially improve the linear composite model or reduce overall prediction error. This is clinically relevant because additional assays can add cost and preanalytical variability without improving classification. Importantly, the 2025 Endocrine Society guideline recommends primary aldosteronism screening with aldosterone and renin for individuals with hypertension [5]. The present model should therefore not be used to withhold guideline-recommended primary aldosteronism screening; its potential role is downstream prioritization of broader disease-specific endocrine evaluation in selected patients.

The locked threshold also defines the limits of clinical use. Sensitivity of 72.6% means that the model would miss a clinically important proportion of cases if used as a rule-out test. Likewise, a positive predictive value of 67.7% means that a positive model result cannot establish an endocrine diagnosis. The positive likelihood ratio of 5.52 represents a meaningful but not definitive increase in post-test odds, whereas the negative likelihood ratio of 0.32 is insufficient to exclude disease without clinical judgment. Future work should assess clinically motivated thresholds, including higher-sensitivity operating points, and should evaluate net benefit using decision-curve analysis rather than relying on discrimination alone [27, 30].

Calibration was acceptable overall, with an intercept of 0.126, a slope of 1.047, and a Brier score of 0.109, although deviations were evident in intermediate-risk groups. This matters because good discrimination does not guarantee accurate absolute risk estimates [28]. Recalibration may be required in populations with different referral patterns, medication use, and disease spectra. Angiotensin II

showed its largest numerical increment in the PPGL subgroup, but the apparent AUC increase was based on only 13 PPGL events in the validation cohort and should be treated as hypothesis-generating.

Medication interference remains an important source of uncertainty. After exclusion of participants receiving a diuretic or mineralocorticoid receptor antagonist, discrimination persisted but decreased in the exploratory nonlinear analysis. Residual effects from angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, glucocorticoids, sodium intake, posture, potassium status, and sampling time may also remain [5, 11, 12, 21]. Future validation should use standardized sampling conditions and prespecified medication-handling strategies.

The study has several strengths. The outcome was assigned through disease-specific confirmation pathways rather than by the same baseline hormone thresholds used as candidate predictors, reducing circular validation. The analysis compared prespecified nested marker sets, separated development and validation data, reported calibration and Brier score in addition to AUC, and provided predictive values and likelihood ratios that are easier to interpret clinically. The study also directly addresses a practical hypertension-care question: how a simpler biomarker combination might help prioritize confirmatory endocrine evaluation rather than replace it.

Several limitations require emphasis. First, this was a single-center study and transportability to community, outpatient, and specialist referral settings is unknown. Second, restricting model development to participants who completed the reference-standard pathway creates potential partial-verification and referral bias. Third, the composite endpoint combined three biologically distinct disorders and was dominated numerically by primary aldosteronism. Fourth, the PPGL and Cushing syndrome subgroups were small. Fifth, medication exposure and preanalytical conditions may have influenced the candidate hormones. Sixth, split-sample internal validation uses data inefficiently and does not establish external validity. Finally, the model has not undergone independent external validation or prospective impact assessment.

These findings support further evaluation rather than immediate clinical implementation. Priority next steps include comparison of verified and nonverified participants, methods that explicitly address partial verification, standardized medication and sampling protocols, resampling-based internal validation, external validation at another institution, disease-specific assessment of false negatives, and evaluation of whether use of the model improves testing efficiency or cardiovascular care pathways.

Conclusions

Among adults who completed definitive endocrine evaluation during hypertension work-up, a parsimonious model based on aldosterone, PRA, and cortisol showed good internal discrimination for the composite outcome of confirmed primary aldosteronism, PPGL, or Cushing syndrome and performed similarly to the full five-marker linear model. The model may help prioritize disease-specific testing in selected patients, but its residual false-negative rate precludes use as a stand-alone diagnostic

or rule-out test. Independent external validation and explicit assessment of partial-verification and medication-related bias are required before clinical implementation.

Abbreviations

ACTH
adrenocorticotropic hormone
AUC
area under the receiver operating characteristic curve
CI
confidence interval
LDL-C
low-density lipoprotein cholesterol
NPV
negative predictive value
PPGL
pheochromocytoma/paraganglioma
PPV
positive predictive value
PRA
plasma renin activity
RAAS
renin-angiotensin-aldosterone system
SD
standard deviation.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Ethics Committee of University of Chinese Academy of Sciences Shenzhen Hospital (Guangming) on January 16, 2023 (Approval No. LL-KT-2022066). Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

The work submitted did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contribution

C.X. performed data curation, formal analysis, investigation, and drafted the manuscript. F.M. contributed to data curation, investigation, and methodology. F.H. contributed to investigation and validation. Z.Z. conceived and supervised the study and critically revised the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgements

The authors thank the clinical and laboratory staff of Shenzhen University of Advanced Technology General Hospital for their support in participant evaluation, laboratory testing, and data collection.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available because public release may compromise participant privacy and is subject to institutional approval, but deidentified data are available from the corresponding author on reasonable request and subject to applicable institutional and ethical restrictions.

References

1. NCD Risk Factor Collaboration. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398:957–80. 10.1016/S0140-6736(21)01330-1.
2. McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45:3912–4018. 10.1093/eurheartj/ehae178.

3. Rimoldi SF, Scherrer U, Messerli FH. Secondary arterial hypertension: when, who, and how to screen? Eur Heart J. 2014;35:1245–54. 10.1093/eurheartj/eht534.
4. Young WF Jr, Calhoun DA, Lenders JWM, Stowasser M, Textor SC. Screening for endocrine hypertension: an Endocrine Society scientific statement. Endocr Rev. 2017;38:103–22. 10.1210/er.2017-00054.
5. Adler GK, Stowasser M, Correa RR, et al. Primary aldosteronism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2025;110:2453–95. 10.1210/clinem/dgaf284.
6. Rossi GP. Primary aldosteronism: JACC state-of-the-art review. J Am Coll Cardiol. 2019;74:2799–811. 10.1016/j.jacc.2019.09.057.
7. Turcu AF, Yang J, Vaidya A. Primary aldosteronism - a multidimensional syndrome. Nat Rev Endocrinol. 2022;18:665–82. 10.1038/s41574-022-00730-2.
8. Monticone S, D'Ascenzo F, Moretti C, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2018;6:41–50. 10.1016/S2213-8587(17)30319-4.
9. Brown JM, Siddiqui M, Calhoun DA, et al. The unrecognized prevalence of primary aldosteronism: a cross-sectional study. Ann Intern Med. 2020;173:10–20. 10.7326/M20-0065.
10. Käyser SC, Dekkers T, Groenewoud HJMM, et al. Study heterogeneity and estimation of prevalence of primary aldosteronism: a systematic review and meta-regression analysis. J Clin Endocrinol Metab. 2016;101:2826–35. 10.1210/jc.2016-1472.
11. Mulatero P, Rabbia F, Milan A, et al. Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. Hypertension. 2002;40:897–902. 10.1161/01.HYP.0000038478.59760.41.
12. Stowasser M, Taylor PJ, Pimenta E, Ahmed AH, Gordon RD. Laboratory investigation of primary aldosteronism. Clin Biochem Rev. 2010;31:39–56.
13. Lenders JWM, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:1915–42. 10.1210/jc.2014-1498.
14. Lenders JWM, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA. 2002;287:1427–34. 10.1001/jama.287.11.1427.
15. Eisenhofer G, Prejbisz A, Peitzsch M, et al. Biochemical diagnosis of chromaffin cell tumors in patients at high and low risk of disease: plasma versus urinary free or deconjugated O-methylated catecholamine metabolites. Clin Chem. 2018;64:1646–56. 10.1373/clinchem.2018.291369.
16. Lenders JWM, Eisenhofer G, Mannelli M, Pacak K, Phaeochromocytoma. Lancet. 2005;366:665–75. 10.1016/S0140-6736(05)67139-5.
17. Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93:1526–40. 10.1210/jc.2008-0125.
18. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing disease: a guideline update. Lancet Diabetes Endocrinol. 2021;9:847–75. 10.1016/S2213-8587(21)00235-7.

19. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BMK, Colao A. Complications of Cushing syndrome: state of the art. Lancet Diabetes Endocrinol. 2016;4:611–29. 10.1016/S2213-8587(16)00086-3.
20. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing syndrome. Lancet. 2006;367:1605–17. 10.1016/S0140-6736(06)68699-6.
21. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension. 2018;72:e53–90. 10.1161/HYP.0000000000000084.
22. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58:811–7. 10.1161/HYPERTENSIONAHA.111.179788.
23. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 2007;4:e296. 10.1371/journal.pmed.0040296.
24. Collins GS, Moons KGM, Dhiman P, et al. TRIPOD + AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ. 2024;385:e078378. 10.1136/bmj-2023-078378.
25. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. BMJ. 2020;368:m441. 10.1136/bmj.m441.
26. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837–45. 10.2307/2531595.
27. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology. 2010;21:128–38. 10.1097/EDE.0b013e3181c30fb2.
28. Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW. Calibration: the Achilles heel of predictive analytics. BMC Med. 2019;17:230. 10.1186/s12916-019-1466-7.
29. Begg CB, Greenes RA. Assessment of diagnostic tests when disease verification is subject to selection bias. Biometrics. 1983;39:207–15. 10.2307/2530823.
30. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Mak. 2006;26:565–74. 10.1177/0272989X06295361.

Figures

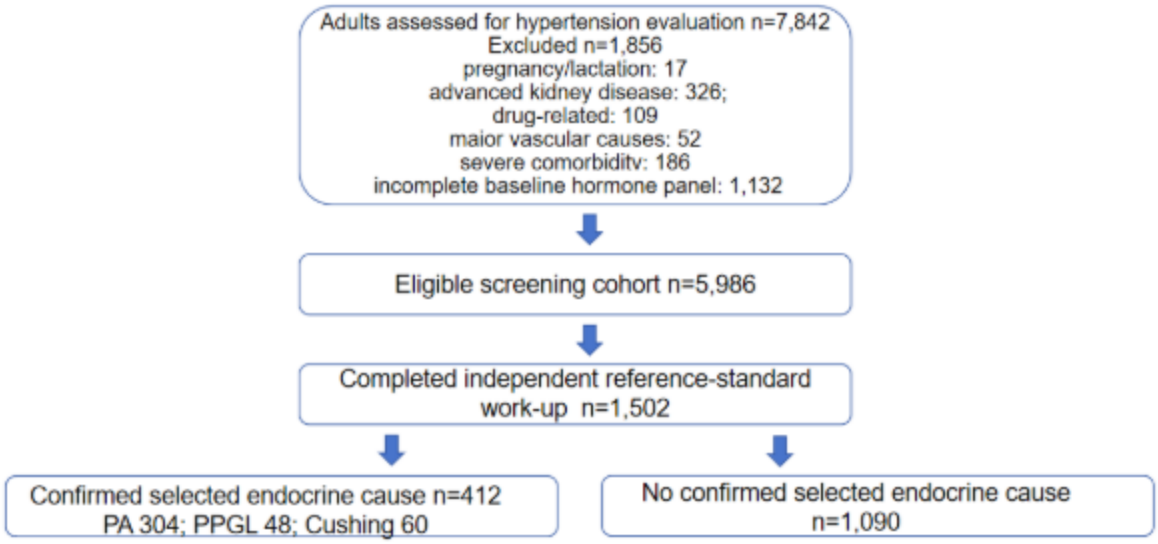


Figure 1

Patient selection and formation of the model-development cohort.

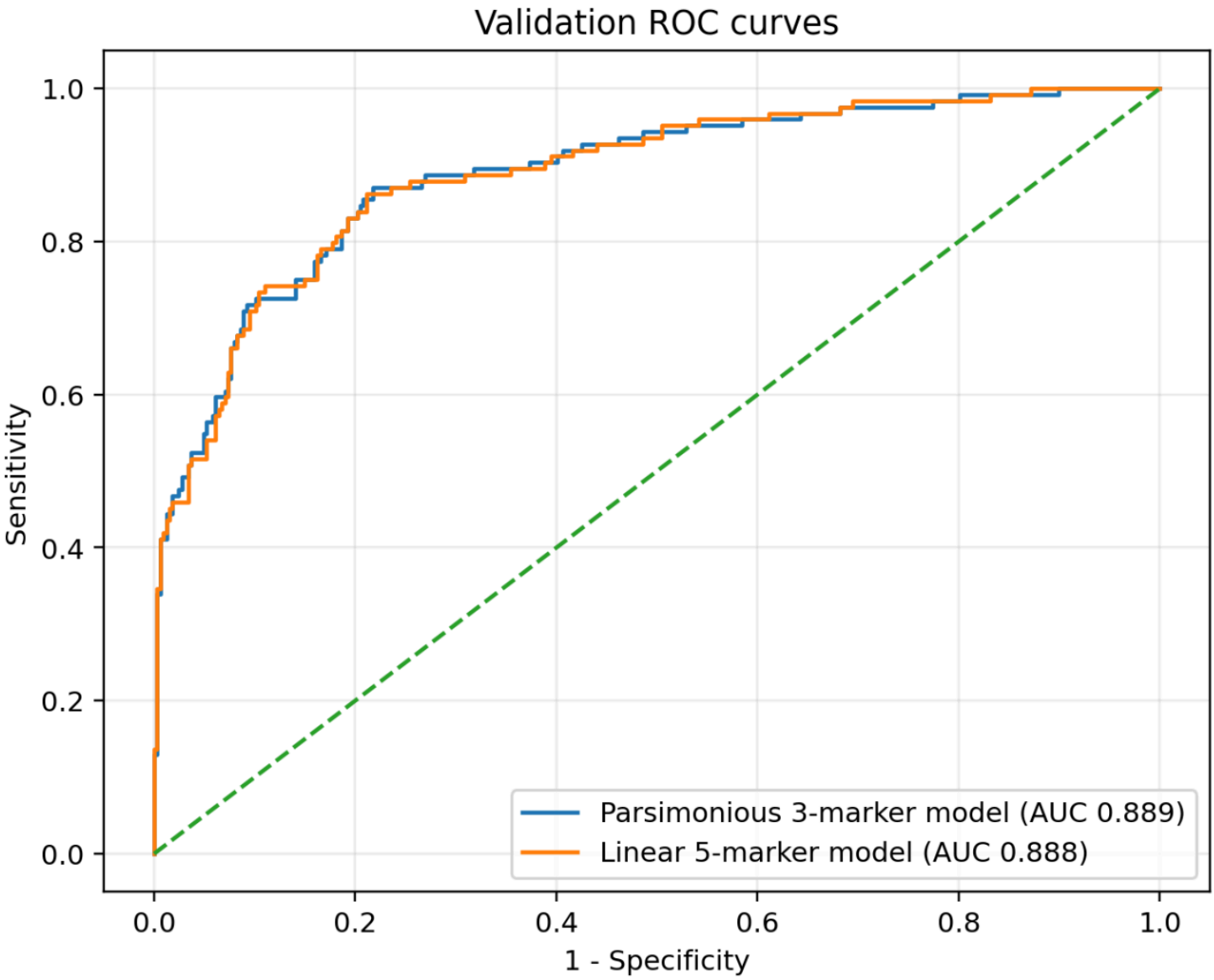


Figure 2

Validation receiver operating characteristic curves for the parsimonious and full linear models

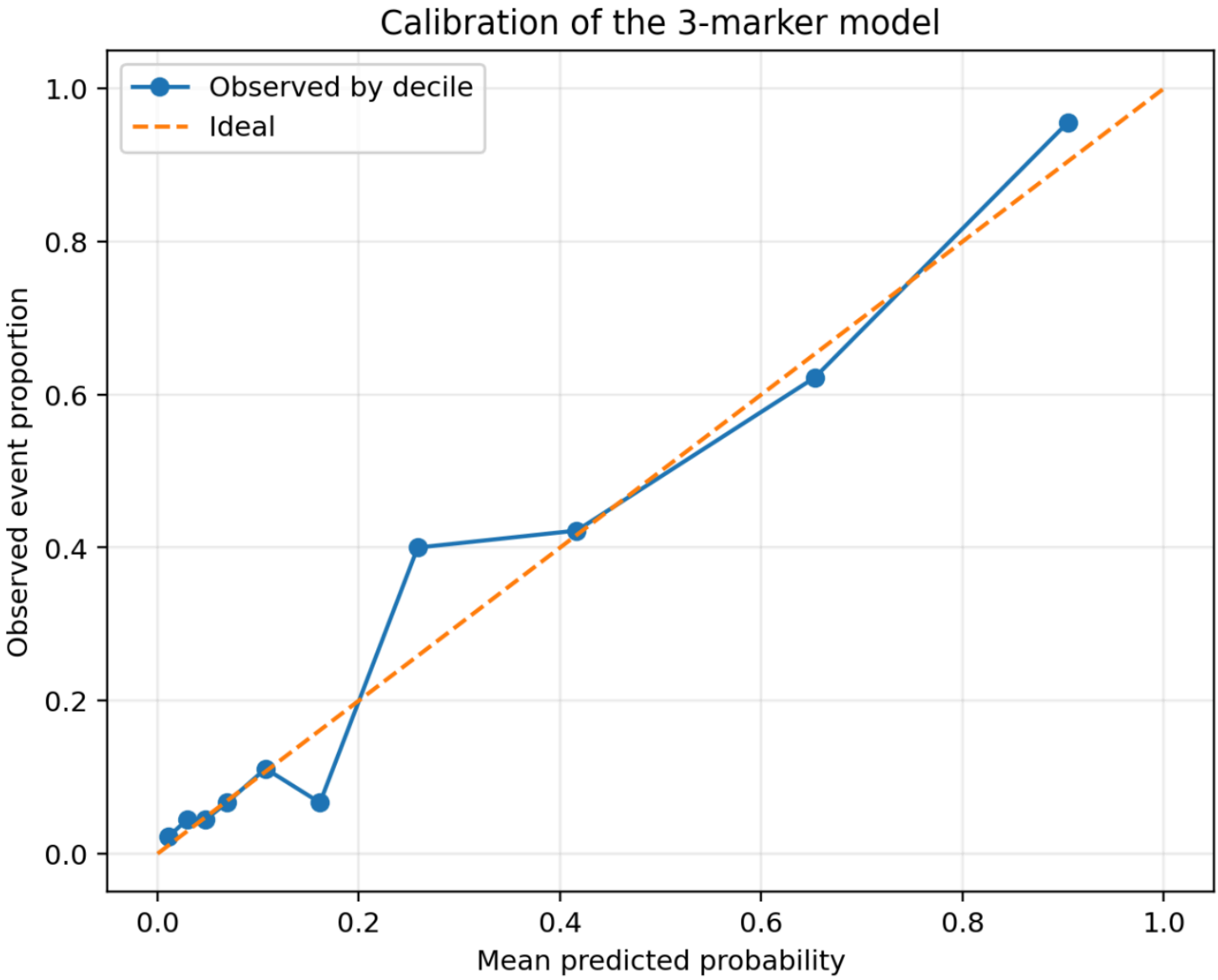


Figure 3

Calibration of the parsimonious three-marker model in the validation set.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GraphicalAbstract.jpg