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Prevalence and determinants of apparent treatment-resistant hypertension among patients in South African primary care: a single-centre observational study

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Abstract

Introduction The surge in cardiovascular disease across Sub-Saharan Africa is largely driven by hypertension along with other cardiometabolic risk factors. South Africa, like other low-middle-income countries, faces a disproportionate burden due to the increasing prevalence of hypertension, exacerbated by low awareness, treatment, and control rates. Treatment-resistant hypertension (TRH) is a complex clinical entity and poses significant obstacles to achieving therapeutic goals. The prevalence of TRH in South Africa and its associated factors remain underexplored despite its significant cardiovascular and economic burden. Accordingly, we aimed to evaluate the prevalence, clinical and biochemical profiles, and therapeutic patterns associated with TRH among hypertensives in primary care.

Methods An observational analytical study was conducted at a district hospital in KwaZulu-Natal, South Africa, from March to April 2024. Data from 400 systematically randomised hypertensive patients aged > 30 years were analysed. Participants underwent automated office blood pressure monitoring, anthropometric assessments and completed structured interviews on health behaviours and medication adherence. Clinical parameters and antihypertensive medication profiles were reviewed. Determinants of apparent TRH were identified using multivariate logistic regression.

Results The mean age of the participants was 64.4 years (SD = 10.8), with a female preponderance ($n = 260$,65%), and nearly two-thirds comprised of Black Africans (35.3%) and Indians (30.5%). The prevalence of apparent TRH was 18.8%, comprising 11% uncontrolled and 7.8% controlled TRH. Factors significantly associated with TRH included Black African ethnicity (Odds Ratio (OR) = 2.33, $p < 0.001$), waist circumference (OR = 1.03, $p < 0.001$), left ventricular hypertrophy (OR = 3.57, $p < 0.001$), chronic kidney disease (OR = 3.12, $p < 0.001$), and dyslipidaemia (OR = 2.46, $p = 0.039$). Mineralocorticoid receptor antagonists were underused (10.8%).

Conclusion This first report of apparent TRH prevalence in South African primary care underscores its complex association with cardiometabolic risk factors and the disproportionate burden among Black Africans. These findings

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highlight the urgent need for targeted, multifaceted interventions and the development of locally relevant TRH-specific guidelines to mitigate cardiovascular risks among this high-risk population.

Keywords Resistant hypertension, Africa, Primary care

Background

Hypertension remains a significant global public health concern, affecting an estimated 1.3 billion adults and is the leading modifiable risk factor for cardiovascular disease (CVD) and premature death [1]. An epidemiological transition, driven by population growth, urbanisation, sedentary lifestyles, and atherogenic diets, has placed over two-thirds of the hypertensive burden disproportionately on low- and middle-income countries (LMICs) [1]. Sub-Saharan Africa, particularly South Africa, is unfavourably positioned at the intersection of infectious and non-communicable disease syndemics. Despite the availability of effective therapeutic agents, levels of hypertension awareness, treatment, and control remain low [2]. Contributing factors such as non-adherence, incorrect blood pressure techniques, and therapeutic inertia are significant challenges to achieving blood pressure (BP) control, with treatment-resistant hypertension (TRH) emerging as a critical concern among them.

People living with hypertension (PLWHTN) who fail to achieve blood pressure targets despite treatment with three or more antihypertensives of different classes, including a diuretic, at maximally tolerated doses, are classified as having TRH [3]. Additionally, blood pressure controlled by four or more antihypertensive medications from different antihypertensive classes is classified as controlled TRH [3]. Apparent treatment-resistant hypertension (aTRH) is designated when pseudo-resistance factors, such as medication non-adherence, therapeutic inertia, white-coat hypertension, and incorrect BP measuring techniques cannot be excluded [4].

The pathogenesis of TRH is multifactorial, involving physiological disturbances of the renin-angiotensin-aldosterone system (RAAS), inappropriate activation of the sympathetic nervous system (SNS), endothelial dysfunction, and arterial stiffness [5]. TRH is associated with an overall increased cardiovascular risk and increased major adverse cardiovascular events (MACE) such as myocardial infarction, heart failure, and cerebrovascular disease [6]. Studies conducted in high-income settings have found male sex, advanced age, obesity, established hypertensive-mediated organ damage (HMOD), a history of MACE, and a higher prevalence of comorbid conditions to be frequent among patients with TRH [7].

The reported prevalence of TRH is highly variable, ranging from 3–30%, [8, 9] due to heterogeneous study settings, non-uniform definitions, varying BP targets, and failure to exclude pseudo-resistance. Noubiap et al. [10] report a global prevalence of TRH at 10.3% and aTRH at 14.7%. While estimates of aTRH exceed true TRH, it remains valuable as it identifies individuals for therapy intensification or who may have potentially reversible causes that warrant further investigation and treatment.

From an African perspective, Nansseu et al. [11] reports a pooled prevalence of TRH at 12.1% (95% CI 8.0–17.7%) across five African countries, ranging from 4.9 to 19%. In South Africa, epidemiological data is limited to speciality clinics, with an aTRH prevalence of 12.6% among patients at tertiary hypertension clinic [12], and 18.37% among those attending a specialist diabetic clinic [13]. The prevalence of resistant hypertension among a treated hypertensive population in a South African primary care setting, where the majority of PLWHTN are managed, remains unknown.

There is a dearth of research on resistant hypertension in South Africa, which is concerning, particularly as Black African individuals exhibit distinct pathophysiological characteristics that predispose them to earlier onset and more severe hypertension, accompanied by increased HMOD [14]. Several mechanisms contribute to these differences, which include altered renal sodium handling, heightened salt sensitivity leading to volume overload hypertension, low plasma renin activity, endothelial dysfunction, and increased arterial stiffness [14, 15]. Despite these significant findings, research on TRH within this inherently high-risk group remains limited. Understanding these unique pathophysiological traits is crucial for generating targeted interventions and improving management strategies for TRH in Black African populations.

We sought to address a critical gap by determining the prevalence of aTRH among treated hypertensive patients in primary care and identifying context-specific factors associated with aTRH in the African setting. Identifying patients with aTRH will assist with preliminary investigations, as referrals to specialist hypertension clinics are not always feasible. While American [16], European [17], and Asian countries have well-established TRH guidelines [18, 19], Africa currently lacks such guidelines. This gap is significant given the unique ways in which hypertension presents and affects Black African populations, highlighting the need for region-specific strategies. These guidelines may guide generalists in management and referral pathways, thereby optimising medical care, improving long-term outcomes, and increasing cost-effectiveness in primary healthcare.

Methods

Study design, setting and participants

This observational, analytical, cross-sectional study was conducted between March and April 2024 at the medical outpatient department of Wentworth Hospital, a district-level hospital in Kwa-Zulu Natal, South Africa. The chronic comorbidity clinic, staffed by family medicine medical officers and medical interns, operates on weekdays and receives referrals from nearby local clinics, general practitioners, and other hospitals.

Participants included PLWHTN aged ≥ 30 with a diagnosis of essential hypertension, who had been receiving hypertension management for at least a year and had attended the past two appointments. Exclusion criteria were a diagnosis of secondary hypertension, pregnancy, or lack of routine laboratory investigations within the preceding 12 months.

Sample size and sampling

Cochran's formula for sample estimation $N = \frac{Z^2\,P(1-P)}{D^2}$ was used to determine the prevalence of resistant hypertension among PLWHTN in primary care. Assuming a prevalence (P) of 30% based on previous literature [9], a margin of error (D) of 5% (0.05), and a confidence level of 95% (Z = 1.96), the minimum required sample size was determined to be approximately 323. However, the sample was increased to 400 participants to enhance the precision of prevalence estimates, increase generalisability, and allow for more robust subgroup analyses. Systematic random sampling was employed, with every fourth hypertensive patient meeting the selection criteria included in the study.

Study procedure

Blood pressure measurement

Blood pressure was measured using automated office blood pressure measurements overseen by trained staff using a calibrated, automated electronic sphygmomanometer (Northern Meditec, China) with an appropriate-sized BP cuff. Before measurement, standard patient preparation was adhered to, and readings were set at 2-minute intervals, with the average of two readings used for analysis.

Participant assessment

A structured questionnaire assessed health behaviours, detailed medical history, risk scores and medication adherence via the Medication Adherence Report Scale-5 (MARS-5). The MARS-5, which has been validated for use in multiple chronic diseases, consists of five questions that assess non-intentional and intentional behaviours scored on a 5-point Likert scale with a cutoff point of adherence determined to be ≥ 96% of the aggregated MARS-5 scores (i.e., MARS-5 score ≥ 23) [20]. The risk of obstructive sleep apnoea (OSA) was assessed via the STOPBANG questionnaire [21], which includes four questions referring to snoring, daytime somnolence, observed apnoea, blood pressure and four objective measures. A summed score between 0–2,3–4, and 5–8 corresponded to low, intermediate and high risk of OSA, respectively. Cardiovascular risk assessments were conducted using the Framingham 10-year risk score tables according to the South African dyslipidaemia guidelines [22].

Chart review

A chart review obtained clinical data regarding comorbidities, results of investigations (electrocardiograms, fundoscopy, urine dipstick), complications, and current therapeutic regimen. Details extracted included doses and anti-hypertensives classified according to drug classes: RAAS inhibitors encompassing angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers (BB), calcium-channel blockers (CCB), diuretics (thiazide, loop), mineralocorticoid receptor antagonists (MRA), vasodilators, and alpha-blockers. Drugs prescribed solely for alternative indications were not included in the total anti-hypertensive count. Concurrent drug use was evaluated, including lipid-lowering agents, systemic corticosteroids, tricyclic antidepressants, and chronic use of nonsteroidal anti-inflammatory drugs. Laboratory test results within the past year were collected, including electrolytes, urea, creatinine, estimated glomerular filtration rate (eGFR), glycated haemoglobin (HbA1c %), total cholesterol (TC), triglyceride level (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and haemoglobin.

Variables, definitions and measurements

Blood pressure control

Blood pressure control was defined as BP ≤ 140/90 mmHg according to the South African Hypertension Society guidelines [23].

Apparent treatment-resistant Hypertension (aTRH) is the outcome variable, as white-coat hypertension was not assessed in this study.

- Uncontrolled Resistant Hypertension: Uncontrolled BP despite concurrent use of ≥ 3 anti-hypertensive medications from different drug classes, including a diuretic, at maximally tolerated doses.
- Controlled Resistant Hypertension: Controlled BP requiring the prescription of ≥ 4 antihypertensive medications from different drug classes, including a diuretic, at maximally tolerated doses.
- Pseudo-Resistance: PLWHTN on three or more antihypertensives that remain uncontrolled due to

identifiable causes. These include non-adherence to therapy (defined by a MARS-5 score ≤ 23) or inadequate treatment (e.g., not on guideline-directed therapy or receiving suboptimal doses). In such cases, they were classified as pseudo-resistant due to non-adherence or under-treatment respectively.

Health behaviour variables

Physical activity Defined as engaging in exercise for at least 30 min a day and categorised by frequency per week.

Alcohol consumption Excess consumption was defined as more than seven standard units of alcohol for females and more than fourteen units of alcohol for males per week.

Salt intake Was estimated using a dietary questionnaire, as the gold standard 24-hour urinary sodium collection is resource-intensive and not feasible in our resource-constrained setting.

Anthropometric Measurements

Weight and height were measured by a calibrated scale and stadiometer (SECA 787, SECA, Germany), recorded to the nearest decimal.

Waist Circumference (WC) Was measured to the nearest centimetre using an inelastic measuring tape at the end of expiration, at a point midway between the lower ribcage and the superior iliac crest.

Neck circumference Was measured using an inelastic tape, placed perpendicular to the long axis of the neck just below the laryngeal prominence.

Body Mass Index (BMI) Derived from weight(kg) and height(m) and categorised into underweight (< 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (≥ 25–29.9 kg/m²), and obese (≥ 30 kg/m²). Obesity was further categorised into class I (30–34.9 kg/m²), class II (35–39.9 kg/m²), and class III obesity (≥ 40 kg/m²).

Clinical Variables

Diagnosis of medical comorbidities was confirmed by individual clinical records.Chronic kidney disease (CKD) was defined as an eGFR < 60 mL/min/1.73 m² calculated by the CKD-EPI equation and persisting for more than three months [24].

Hypertensive-mediated organ damage (HMOD) was identified based on clinical record documentation. Organ specific target organ damage was classified as follows:

- Brain: History of stroke or computed tomography evidence of lacunar infarcts, and microbleeds.
- Heart: Electrocardiographic left ventricular hypertrophy (LVH) assessed using Sokolow-Lyon index as SV1 + RV5 greater than 3,5 mV.
- Kidney: Proteinuria was assessed using dipstick urinalysis due to limited access to routine albumin-to-creatinine ratio testing in our resource-constrained setting.

Statistical analysis

Data were transferred from an electronic data form to Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Further statistical analysis was performed using STATA version 18 (Stata Corp., College Station, TX, USA). Categorical data were described by frequencies and percentages and compared using the Chi-squared test or Fisher's exact test were applicable. Continuous variables were tested for normality using the Shapiro-Wilk test and represented as mean ± standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Comparative analysis across groups was analysed using the student's T-test and Man-Whitney U-test for parametric and non-parametric data, respectively. Univariate logistic regression was performed to investigate the relationship between aTRH and independent predictors using odds ratio (OR) and 95% confidence interval (CI). To identify the factors most strongly associated with the development of aTRH, a multivariable logistic regression model was used, with a significance cutoff of $p < 0.05$ for variable inclusion and retention. The model included aTRH as the primary outcome variable and was adjusted for identified covariates. Covariates were selected based on a priori knowledge and the significant results of univariate analyses.

Ethics

The study was approved by the Biomedical Research Ethics Council of the University of Kwa-Zulu Natal (Reference: BREC/00005737/2023), Kwa-Zulu Natal Provincial Department of Health and Wentworth Hospital management. Each participant provided written informed consent for participation and for the use of non-identifiable data.

Results

Patient characteristics and prevalence of aTRH (Table 1)

Of the four hundred PLWHTN sampled, the mean age was 64.4 ± 10.8 years, predominantly female (65.0%), and almost two-thirds constituted by Black African (35.8%) and Indians (30.5%) combined. The proportion of people achieving target blood pressures was 58.8% ($n = 235/400$); with a median systolic blood pressure of 138 mmHg (IQR 21.7) and mean diastolic blood pressure of 76.1 ± 10.4 mmHg.

Table 1 Baseline demographic, anthropometric, and blood pressure characteristics of people living with hypertension

Variable	Total *N* = 400	No aTRH *N* = 325	aTRH *N* = 75	*p*-value	Uncontrolled aTRH *N* = 44	Controlled aTRH *N* = 31	*p*-value
Demographics							
Age (years) mean(± SD)	64.4 (10.8)	64.2(10.7)	65.4(11.1)	0.383	63.5(11.5)	68.1(10.0)	0.074
Age category, n (%)							
30–39	4 (1.0)	4 (1.2)	0 (0)	1.00	0(0)	0(0)	
40–49	30 (7.5)	22(6.8)	8(10.7)	0.248	6(13.6)	2(6.5)	0.457
50–59	94 (23.5)	78 (24.0)	16(21.3)	0.623	10(22.7)	6(19.4)	0.782
60–69	139 (34.8)	117 (36.0)	22(29.3)	0.274	13(29.5)	9(29.0)	0.962
70–79	100(25.0)	79 (24.3)	21(28.0)	0.506	11(25.0)	10(32.3)	0.475
80–89	32(8.0)	25 (7.7)	7(9.3)	0.637	4(9.1)	3(9.7)	0.931
90–99	1(0.3)	0 (0)	1(1.3)	0.187	0(0)	1(3.2)	0.230
Gender n (%)							
Female	260(65.0)	213(65.5)	47(62.7)	0.638	30(68.2)	17(54.8)	0.239
Ethnicity, n (%)							
Caucasian	54(13.5)	46(14.2)	8(10.7)	0.426	3(6.8)	5(16.1)	0.263
Black African	143(35.8)	104(32.0)	39(52.0)	**< 0.001**	26(59.1)	13(41.9)	0.143
Mixed	81(20.3)	69(21.2)	12(16.0)	0.310	4(9.1)	8(25.8)	0.063
Indian	122(30.5)	106(32.6)	16(21.3)	**0.056**	11(25.0)	5(16.1)	0.405
Family history of hypertension in first-degree relative n (%)	286(71.5)	229(70.5)	57(76.0)	0.338	35(79.6)	22(71.0)	0.392
Family history of premature cardiovascular disease in first-degree relative n (%)	106(26.5)	81(24.9)	25(33.3)	0.137	16(36.4)	9(29.0)	0.507
Health behaviours							
% Adherence (MARS-5), median ± IQR	96(12)	96(12)	96(4)	< 0.001	96(4)	96(4)	0.875
Smoking status							
Current smoker	52(13.0)	41(12.6)	11(14.7)	0.634	6(13.6)	5(16.1)	0.754
Past smoker	105(26.3)	91(28.0)	14(18.6)	0.098	5(11.4)	9(29.0)	0.073
Never smoker	243(60.8)	193(59.4)	50(66.7)	0.244	33(75.0)	17(54.8)	0.068
Excess alcohol consumption n (%)							
Yes	80(20.0)	64(19.7)	16(21.3)	0.749	8(18.2)	8(25.8)	0.568
Dietary salt reduction n (%)							
Yes	93(23.3)	76(23.4)	17(22.6)	0.397	11(25.0)	6(19.3)	0.843
Physical activity							
1–3 times a week	122(30.5)	104(32.0)	18(24.0)	0.175	11(25.0)	7(22.6)	0.389
3–5 times a week	27(6.8)	22(6.8)	5(6.7)	0.975	3(6.8)	2(6.5)	0.998
> 5 times a week	2(0.5)	2(0.6)	0(0)	0.496	0(0)	0(0)	0.793
None	249(62.3)	197(60.6)	52(69.3)	0.160	30(68.2)	22(71.0)	0.362
Anthropometric measurements							
Body mass index (BMI) kg/m^2, Median (IQR)	31.19 (8.2)	29.93(7.8)	32.89(10.3)	**< 0.001**	34.5(21.5)	30.5(6.5)	**0.0386**
BMI Categories, n (%)							
Underweight	4(1.0)	4(1.2)	0(0)	0.334	0(0)	0(0)	
Normal	67(16.8)	62(19.1)	5(6.7)	0.009	3(6.8)	2(6.5)	0.950
Overweight	118(29.5)	96(29.5)	22(29.3)	0.972	9(20.5)	13(41.9)	**0.044**
Obese Class I	117(29.3)	97(29.9)	20(26.7)	0.585	11(25.0)	9(29.0)	0.697
Obese Class II	56(14.0)	44(13.5)	12(16.0)	0.580	9(20.5)	3(9.7)	0.338
Obese Class III	38(9.5)	22(6.8)	16(21.3)	**< 0.001**	12(27.2)	4(12.9)	0.162
Waist circumference (cm), median (IQR)	99.3(18.8)	97.6(18.0)	106.5(17.4)	**< 0.001**	108.2(18.3)	102.4(14.7)	0.064
Blood pressure parameters							
Systolic BP (mmHg), median (IQR)	138.0(21.7)	137.0(20.3)	146.3(25.0)	**0.003**	151.2(13.3)	126.7(10.6)	< 0.001
Diastolic BP (mmHg), mean (± SD)	76.1(10.4)	75.8(10.2)	77.2(11.4)	0.315	81.5(11.8)	70.9(7.2)	< 0.001
Pulse pressure mean (± SD)	61.0(19.5)	59.6(18.4)	67.3(21.7)	**0.013**	73.2(11.1)	55.7(9.9)	**< 0.001**
Blood pressure control, n (%)							
Controlled	235(58.75)						

Table 1 (continued)

Variable	Total *N* = 400	No aTRH *N* = 325	aTRH *N* = 75	*p*-value	Uncontrolled aTRH *N* = 44	Controlled aTRH *N* = 31	*p*-value
Uncontrolled	165(41.25)						
aTRH prevalence, n (%)	75(18.8)				44(11.0)	31(7.8)	
Pseudo-resistance							
Non-adherence	76(19.0)						
Under-treatment	4(1.0)						

The prevalence of aTRH among the PLWHTN was 18.8% ($n = 75/400$), of which 11.0% was uncontrolled TRH (UTRH) and 7.8% were categorised as controlled TRH (CTRH). There were no statistically significant differences in age or gender between patients with and without aTRH. However, a significantly higher proportion of Black African patients had aTRH compared to other racial groups (39,52%, $p < 0.001$). Indian PLWHTN comprised the second highest number of aTRH cases in absolute terms; however, their proportion within the aTRH group (21.3%) was lower than in the non-aTRH group (32.6%), suggesting a lower likelihood of aTRH in this subgroup. This difference approached statistical significance, $p = 0.056$.

Health behaviour and anthropometric profile (Table 1)

There were no significant differences in cigarette smoking status, alcohol consumption, dietary salt intake, or levels of physical activity between the two groups. However, the aTRH group had the highest proportion of patients reporting no physical activity ($n = 52$, 69.3%).

Most of the sample was obese with a median BMI of 31,19 kg/m^2. The aTRH group had a significantly higher BMI compared to their non-resistant counterparts (32,89 kg/m^2 versus 29.93 kg/m^2; $p < 0.001$). An anthropometric marker of abdominal obesity, waist circumference, was found to be significantly higher among the aTRH group, with a median waist circumference of 106.5 cm ($p < 0.001$).

Clinical profile (Table 2)

Two-thirds of the PLWHTN were diagnosed and treated for more than a decade. The most frequent co-occurring comorbidity was dyslipidaemia ($n = 315$,78.8%) followed by CKD ($n = 94$,23.5%). In our study population, the prevalence of CKD was significantly higher in the aTRH group compared to those without aTRH (38.7% versus 20.0%; $p < 0.001$), underscoring the contributory role of renal impairment in TRH. Notably, moderate CKD stages were more prevalent among those with aTRH: CKD Stage 3a (18.6% versus 9.8%; $p = 0.031$) and Stage 3b (14.7% versus 7.4%; $p = 0.044$). This is further highlighted by higher serum creatinine levels among individuals in the aTRH group (88 µmol/L [IQR 37]) compared to the non-aTRH group (74 µmol/L [IQR 30]; $p < 0.001$). The eGFR was significantly lower among individuals with aTRH, with a median eGFR of 71 mL/min/1.73 m² (IQR 36) compared to a median eGFR of 80mL/min/1.73 m² (IQR 30) among individuals in the non-aTRH group ($p = 0.003$). Hypertensive-mediated organ dysfunction as represented by electrocardiographic LVH (12.0% versus 3.1%; $p = 0.001$) and positive dipstick proteinuria (34,7% versus 23.4%; $p = 0.043$) was significantly greater in the aTRH group than the non-aTRH group. The frequency of hypertensive crises was significantly increased in the aTRH group in contrast to the non-aTRH group (16% versus 6.5%; $p = 0.007$).

Biochemical profile (Table 2)

The aTRH group had a significantly higher median triglyceride level of 2.35 mmol/L (IQR 1.52) compared to 1.62 mmol/L (IQR 1.07) in the non-aTRH group ($p < 0.001$). No other significant differences were observed among the biochemical parameters that included TC, HDL, LDL, among the groups.

Risk profile (Table 2)

One-fifth of the PLWHTN had established CVD ($n = 78$,19.5%). High levels of Framingham 10-year cardiovascular risk were comparable across all the groups. A significantly higher proportion of PLWHTN at high risk for OSA was found in the aTRH group (29.3%) compared to the non-aTRH group (10.5%) ($p < 0.001$).

Therapeutic profile (Table 3)

The median total number of prescription medications per patient was 7 (IQR 4), with a median of 3 (IQR 2) antihypertensive medications. 64% of PLWHTN required treatment with three or more antihypertensive agents. Renin-Angiotensin-Aldosterone System (RAAS) blockers were the most frequently prescribed anti-hypertensive class (73.5%), followed by CCBs (68%). In contrast, MRAs were the least prescribed, accounting for only 10.8% of antihypertensive prescriptions. These prescription patterns were consistent across both the aTRH and non-aTRH groups. The most frequently

Table 2 Clinical, biochemical, and risk profiles of people living with hypertension

Variable	Total *N* = 400	No aTRH *N* = 325	aTRH *N* = 75	*p*-value	Uncontrolled TRH *N* = 44	Controlled TRH *N* = 31	*p*-value
Clinical profile							
Duration of hypertension treatment							
1–5 years	60(15.0)	53(16.3)	7(9.3)	0.149	6(13.6)	1(3.2)	0.228
5–10 years	73(18.3)	62(19.1)	11(14.7)	0.188	5(11.4)	6(19.6)	0.509
> 10 years	267(66.8)	210(64.6)	57(76.0)	0.232	33(75.0)	24(77.4)	0.809
Total number of prescription medications, median (IQR)	7(4)	7(3)	9(3)	**< 0.001**	10(3)	9(4)	0.467
Total anti-hypertensive medication, median (IQR)	3(2)	3(1)	4(1)	**< 0.001**	4(2)	4(1)	0.452
Hypertensive-mediated organ damage							
Hypertensive retinopathy n, (%)							
Present	19(4.8)	16(4.9)	3(4.0)	0.194	2(4.5)	1(3.22)	1.00
Negative	4(1.0)	2(0.6)	2(2.7)		1(2.3)	1(3.22)	
Not documented	377(94.3)						
Electrocardiographic LVH n, (%)							
Present	164(41.0)	117(36.0)	47(62.6)	**0.001**	31(70.4)	16(51.6)	**0.001**
Estimated glomerular filtration rate (eGFR) mL/min/1.73 m^2 median (IQR)	79(33.0)	80(30.0)	71(36.0)	**0.003**	68(35.0)	76(30.0)	0.228
Dipstick Proteinuria							
Negative	141(35.3)	113(34.7)	28(37.3)	0.675	12(27.3)	16(51.6)	**0.032**
Present	102(25.5)	76(23.4)	26(34.7)	**0.043**	19(43.2)	7(22.6)	0.025
1+ (30 mg/dL)	80(20)	62(19.1)	18(24.0)	0.337	14(31.8)	4(12.9)	0.098
2+ (100 mg/dL)	15(3.8)	11(3.4)	4(5.3)	0.423	2(4.5)	2(6.5)	1.0
3+ (300 mg/dL)	7(1.8)	3(0.9)	4(5.3)	**0.026**	3(6.8)	1(3.2)	0.638
Not done	157(39.2)	136(41.8)	21(28.0)		13(29.5)	8(25.8)	
Major adverse cardiovascular event (MACE) n (%)							
CVA/TIA	53(13.3)	43(13.2)	10(13.3)	0.981	4(9.1)	6(19.4)	0.302
Non- fatal myocardial infarction	27(6.8)	21(6.5)	6(8.0)	0.632	3(6.8)	3(9.7)	0.687
History of hypertensive crises in the past 6 months n (%)	33(8.3)	21(6.5)	12(16.0)	**0.007**	12(27.3)	0(0)	**0.001**
Co-morbidities, n (%)							
Type II diabetes mellitus	213(53.3)	168(51.7)	45(60.0)	0.194	30(68.2)	15(48.4)	0.085
Glycaemic control (Hba1c below 7%)	57(26.8)	42(25.0)	15(33.3)	0.216	11(25.0)	4(12.9)	0.197
Diabetic complications, n (%)							
Peripheral neuropathy	85(39.1)	60(35.7)	25(55.6)	**0.005**	18(40.9)	7(22.5)	0.003
Diabetic retinopathy	11(5.2)	8(4.8)	3(6.7)	0.463	2(4.5)	1(3.2)	0.720
Diabetic nephropathy	2(0.9)	2(1.2)	0(0)	1.000	0	0	0
Peripheral vascular disease	3(1.4)	3(1.8)	0(0)	1.000	0	0	0
Chronic kidney disease	94(23.5)	65(20.0)	29(38.7)	**0.001**	21(47.7)	8(25.8)	0.055
Dyslipidaemia	315(78.8)	248(76.3)	67(21.2)	**0.013**	40(90.9)	27(87.1)	0.711
Ischaemic heart disease	47(11.8)	38(11.7)	9(12.0)	0.941	6(13.6)	3(9.7)	0.728
Heart failure	16(4.0)	10(3.1)	6(8.0)	0.092	1(2.3)	5(16.1)	0.076
Osteoarthritis	85(21.3)	72(22.2)	13(17.3)	0.358	8(18.9)	5(16.1)	1.0
Chronic obstructive pulmonary disease	22(5.5)	20(6.2)	2(2.7)	0.396	2(4.5)	0	0.508
Asthma	20(5.0)	16(4.9)	4(5.3)	0.776	2(4.5)	2(6.5)	1.0
HIV	34(8.5)	27(8.3)	7(9.3)	0.774	5(11.4)	2(6.5)	0.693
Gastroesophageal reflux disease	47(11.6)	40(12.3)	7(9.3)	0.471	3(6.8)	4(12.9)	0.438
Biochemical profile							
Estimated GFR (mL/min/1.73 m^2) categories, n (%)							
CKD Stage 1(> 90)	114(28.5)	101(31.1)	13(17.3)	**0.017**	7(15.9)	6(19.4)	0.689
CKD Stage 2 (60–89)	189(47.2)	155(47.7)	34(45.3)	0.712	17(38.6)	17(54.8)	0.165
CKD Stage 3a (45–59)	46(11.5)	32(9.8)	14(18.6)	**0.031**	10(22.7)	4(12.9)	0.373
CKD Stage 3b (30–44)	35(8.8)	24(7.4)	11(14.7)	**0.044**	7(15.9)	4(12.9)	1.0
CKD Stage 4 (15–29)	12(3.0)	10(3.1)	2(2.7)	0.851	2(4.5)	0	0.508

Table 2 (continued)

Variable	Total *N* = 400	No aTRH *N* = 325	aTRH *N* = 75	*p*-value	Uncontrolled TRH *N* = 44	Controlled TRH *N* = 31	*p*-value
CKD Stage 5 (< 15)	4(1.0)	3(0.9)	1(1.3)	0.566	1(2.3)	0	1.0
Serum creatinine (µmol/L) median (IQR)	77(33.0)	74(30.0)	88(37.0)	**< 0.001**	93.5(48.0)	82(35.0)	0.226
Serum potassium (mmol/L) mean (SD)	4.2(0.5)	4.2(0.5)	4.2(0.4)	0.625	4.3(0.5)	4.2(0.5)	0.853
Total cholesterol (mmol/L) median (IQR)	4.62(1.51)	4.69(1.54)	4.45(1.29)	0.088	4.71(1.4)	4.17(1.0)	0.081
Triglycerides (mmol/L) median (IQR)	1.69(1.15)	1.62(1.07)	2.35(1.52)	**< 0.001**	2.43(1.55)	1.88(1.38)	0.205
HDL cholesterol (mmol/L) median (IQR)	1.10(0.390	1.10(0.40)	1.10(0.38)	0.774	1.1(0.37)	1.13(0.41)	0.412
LDL cholesterol (mmol/L) median (IQR)	2.49(1.40)	2.51(1.43)	2.43(1.44)	0.668	2.6(1.1)	2.3(1.1)	0.140
Hb median (IQR)	13.2(2.0)	13.2(1.9)	13.1(2.0)	0.783	12.7(1.9)	13.6(2.5)	**0.033**
Risk profile							
Framingham 10-year cardiovascular risk profile							
low risk < 3%	0	0	0		0	0	0
moderate risk 3–15%	51(12.8)	44(13.5)	7(9.3)	0.325	4(9.1)	3(9.7)	1.0
high risk 15–30%	65(16.3)	55(16.9)	10(13.3)	0.447	5(11.4)	5(16.1)	0.732
very high risk > 30%	165(41.3)	130(40.0)	35(46.7)	0.290	25(56.8)	10(32.3)	**0.036**
Established cardiovascular disease	78(19.5)	62(19.1)	16(21.3)	0.657	7(15.9)	9(29.0)	0.172
Not applicable	41(10.3)	34(10.5)	7(9.3)	1.00	3(6.8)	4(12.9)	
OSA RISK SCORE							
STOPBANG score	3(2)	3(1)	3(3)	**0.003**	4(2.5)	3(3.0)	**0.002**
Low risk	160(40.0)	138(42.5)	22(29.3)	**0.036**	11(25.0)	11(35.9)	0.074
Intermediate risk	183(45.8)	152(46.8)	31(41.3)	0.394	17(38.6)	14(45.2)	0.595
High risk	56(14.0)	34(10.5)	22(29.3)	**< 0.001**	16(36.4)	6(19.4)	**< 0.001**

prescribed antihypertensive drug combination was a thiazide diuretic, ACEI, and CCB ($n = 56$, 14.0%). This was followed by dual therapy with a combination of a thiazide diuretic and an ACEI ($n = 29$, 7.25%), and thiazide diuretic monotherapy ($n = 22$, 5.5%). These patterns are detailed in Table 3 and illustrated in Fig. 1. The use of second-line antihypertensive medications was significantly higher in the aTRH group compared to the non-aTRH group. Specifically, 32.0% of individuals with aTRH were prescribed MRAs versus 5.8% in the non- aTRH group ($p < 0.001$). Similarly, loop diuretics (49.3% versus 26.8%; $p < 0.001$), alpha-blockers (33.3% versus 9.8%; $p < 0.001$) and vasodilators (28.0% versus 10.2%; $p < 0.001$) were more frequently used among the aTRH group.

Controlled versus uncontrolled resistant hypertension

Among the 75 PLWHTN with aTRH, 31 participants (7.8%) achieved BP control with four or more antihypertensive agents, while 44(11%) remained uncontrolled despite treatment with three or more agents. In comparison, the uncontrolled group demonstrated a significantly higher mean BMI (34.5 kg/m² versus 30.5 kg/m²; $p = 0.038$), greater prevalence of chronic kidney disease (47.7% versus 25.8%; $p = 0.055$), a higher incidence of documented hypertensive crises (27.3% versus 0%; $p < 0.001$), and elevated mean pulse pressures (73.2 mmHg versus 55.7 mmHg; $p < 0.001$). Additionally, a significantly higher proportion of individuals in the uncontrolled group were characterised by a high CVD risk (56.8% versus 32.3%, $p = 0.036$) and high OSA risk (36.4% versus 19.4%; $p < 0.001$).

Determinants of aTRH

After adjusting for age, gender, ethnicity, smoking status, level of physical activity, and dietary salt intake, six factors remained significantly associated with aTRH (Table 4).

Black Africans were nearly two and a half times more likely to have aTRH than individuals from other ethnic groups (adjusted odds ratio [aOR] = 2.33, 95% CI = 1.30–4.20; $p < 0.001$). Among anthropometric measures, whilst both BMI and waist circumference were significant in univariate analysis, only waist circumference remained significant in the multivariable model, with each unit increase associated with a 3% increase in the odds of aTRH (aOR = 1.03, 95% CI = 1.01–1.05; $p < 0.001$).

Additionally, total medication count was significantly associated with aTRH; with each additional medication increasing the odds of aTRH by 31% (aOR = 1.31, 95% CI = 1.18–1.46; $p < 0.001$). Patients with comorbid dyslipidaemia also had significantly higher odds of aTRH (aOR = 2.46, 95% CI = 1.04–5.81; $p = 0.039$). Markers of hypertensive-mediated organ dysfunction, specifically electrocardiographic left ventricular hypertrophy (aOR = 3.57, 95% CI = 1.95–6.54; $p < 0.001$) and chronic kidney disease (aOR = 3.12, 95% CI = 1.65–5.89; $p < 0.001$),

Table 3 Therapeutic profile of people living with hypertension

	Total ***N*** **= 400**	**No aTRH** ***N*** **= 325**	**aTRH** ***N*** **= 75**	***p*-value**
Total prescription medication count median (IQR)	7(4)	7(3)	9(3)	< 0.001
Total anti-hypertensives median (IQR)	3(2)	3(1)	4(1)	< 0.001
Number of anti-hypertensive agents n (%)				
1 agent	44(11.0)	44(11.0)	0(0)	< 0.001
2 agents	100(25.0)	100(25.0)	0(0)	< 0.001
3 agents	149(37.3)	136(41.8)	13(17.3)	0.000
4 agents	58(14.5)	23(7.1)	35(46.7)	0.000
5 agents	32(8.0)	13(4.0)	19(25.3)	0.000
6 agents	15(3.8)	9(2.7)	6(8.0)	0.032
7 agents	2(0.5)	0(0)	2(2.7)	0.003
Drug class use n (%)				
RAAS Blockers	294(73.5)	226(69.5)	68(90.7)	< 0.001
ACE-I	267(66.8)	205(63.1)	62(82.7)	0.001
ARB	27(6.8)	21(6.5)	6(8.0)	0.395
Dihydropyridine Calcium Channel Blocker	272(68.0)	204(62.8)	68(90.7)	< 0.001
Beta-blocker	118(29.5)	74(22.8)	44(58.6)	< 0.001
Alpha blocker	57(14.3)	32(9.8)	25(33.3)	< 0.001
Vasodilator	54(13.5)	33(10.2)	21(28.0)	< 0.001
Diuretic				
Thiazide	225(56.3)	187(57.5)	38(50.6)	0.280
Loop	124(31.0)	87(26.8)	37(49.3)	< 0.001
Mineralocorticoid Receptor Antagonist	43(10.8)	19(5.8)	24(32.0)	< 0.001
Other drugs				
Lipid-lowering therapy	327(81.8)	260(80.0)	67(89.3)	0.059
Tricyclic anti-depressants	97(24.3)	77(23.7)	20(26.7)	0.588
Non-steroidal anti-inflammatory drugs	53(13.3)	44(13.5)	9(12.0)	0.723
Oral corticosteroids	11(2.75)	11(3.4)	0(0)	0.230

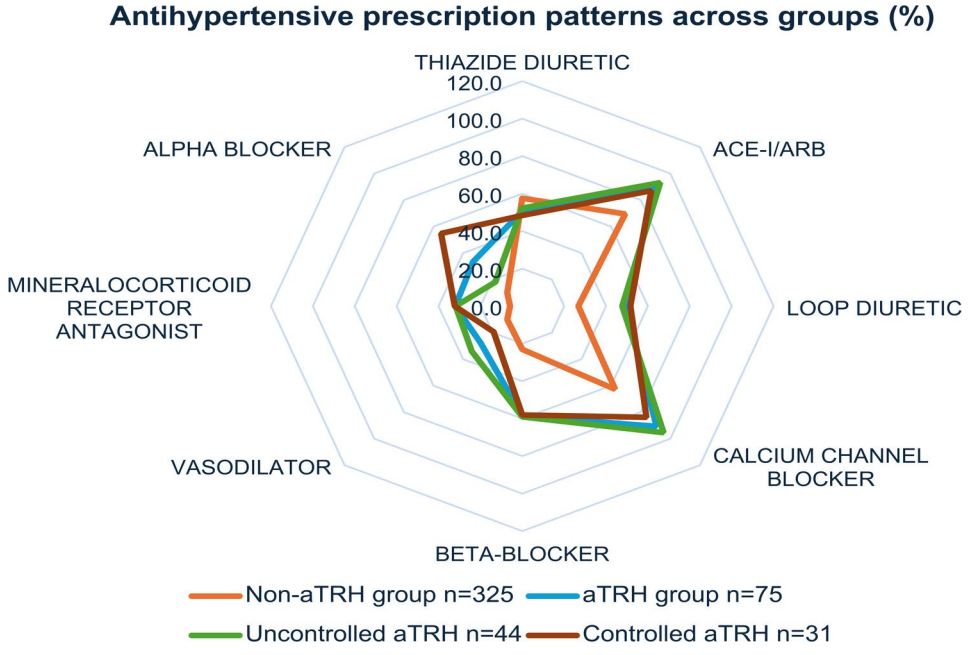

Fig. 1 Antihypertensive drug class prescription patterns among study participants (%)

Table 4 Multivariable logistic regression analysis of factors associated with apparent treatment-resistant hypertension

	aOR 95% CI	*p*-value
Black African race	2.33 (1.30–4.20)	< 0.001
Waist circumference	1.03 (1.01–1.05)	< 0.001
Total medication count	1.31(1.18–1.46)	< 0.001
Dyslipidaemia	2.46(1.04–5.81)	0.039
Chronic kidney disease	3.12(1.65–5.89)	< 0.001
Electrocardiographic LVH	3.57(1.95–6.54)	< 0.001

were the strongest factors associated with aTRH in the model.

Model performance was assessed using a receiver operating characteristic (ROC) curve analysis (Fig. 2), which yielded an area under the curve (AUC) of 0.8014 reflecting good discriminatory performance in identifying individuals with aTRH. Additionally, the Hosmer–Lemeshow goodness-of-fit test (χ^2 (8) = 6.84, $p = 0.554$) demonstrated no significant departure from an adequate fit, further supporting the model's reliability in predicting aTRH status.

Discussion

Our findings contribute to a growing body of evidence demonstrating suboptimal BP control among PLWHTN in South African primary care, consistent with previous reports [25]. Despite receiving antihypertensive treatment, a substantial proportion of patients remained uncontrolled. This suboptimal control likely reflects a complex interplay of factors, including non-adherence, subtherapeutic treatment regimens, white-coat effect, and inaccurate BP measurement techniques, with true TRH accounting for the remainder. To better approximate the burden of true TRH, we applied a pragmatic definition of aTRH, excluding cases of pseudo-resistance due to non-adherence and undertreatment. However, due to the lack of ambulatory BP monitoring, white-coat hypertension could not be definitively excluded. By quantifying the prevalence of aTRH in a real-world primary care context, our study addresses an important evidence gap and provides insights into the magnitude of this high-risk phenotype in the South African setting.

Our findings also revealed significant associations between aTRH and cardiometabolic risk factors, including obesity, dyslipidaemia, and features of HMOD, such as CKD and LVH. These associations are consistent with previously reported findings in the literature, underscoring the burden of cardiometabolic comorbidities in resistant hypertension [6, 7, 26].

aTRH prevalence

Our observed prevalence of 18.8% is comparable to other African studies, such as the 18.9% reported in Ghana [27], and the 18.0% in Egypt [28], both of which were also

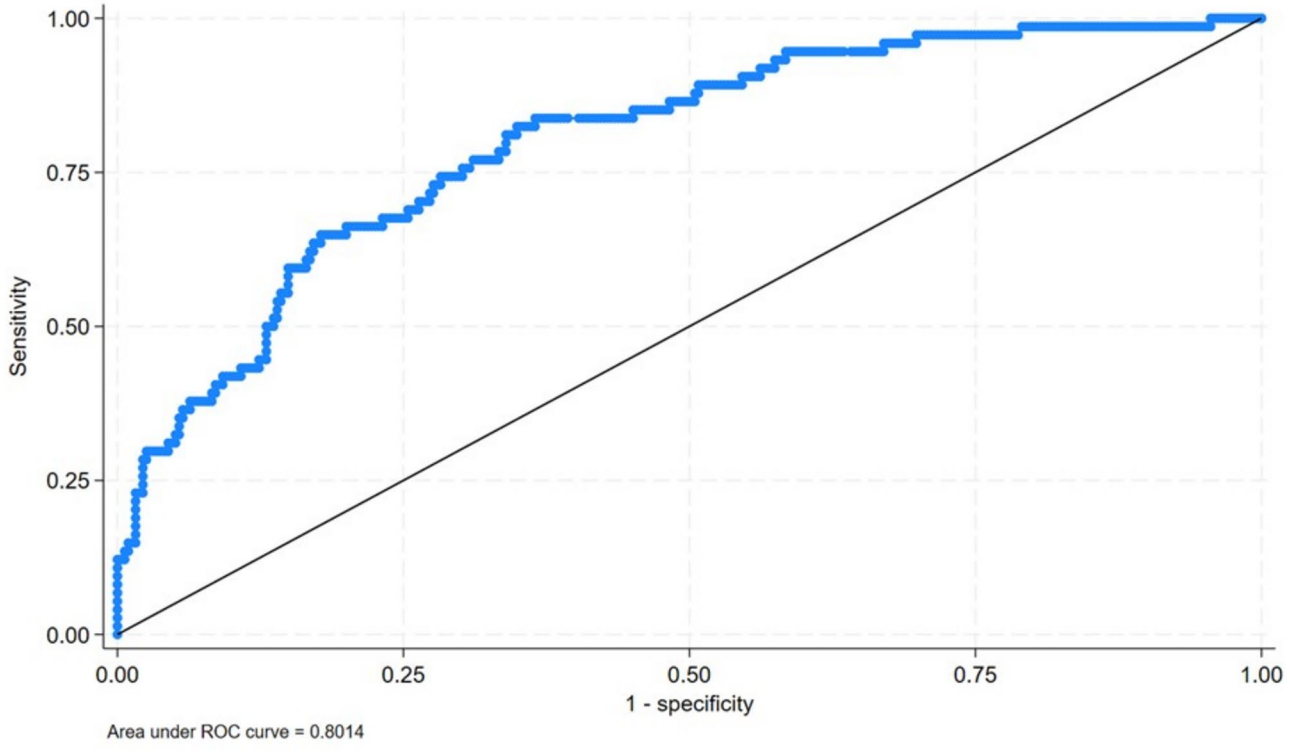

Fig. 2 Receiver operating characteristic (ROC) curve analysis of the aTRH model

conducted in outpatient populations using similar definitions of TRH. However, our prevalence is higher than the 15.5% TRH prevalence reported in Nigeria, which assessed true TRH in a tertiary cardiology clinic where stricter exclusion of pseudo-resistance and enhanced specialist management may have contributed to lower prevalence [29].

In comparison to global data, our prevalence is lower than the 24.0% reported in Malaysia [30], despite a similar level of care. This may reflect differences in population characteristics and comorbidity burden—such as a higher prevalence of type 2 diabetes in the Malaysian cohort. Our findings are comparable to the 17.0% reported in Swedish primary care [31], while exceeding prevalence rates observed in Chinese (7.4%), [32] and Irish (9.0%) primary care settings [33]. The Chinese cohort demonstrated significantly lower obesity rates compared to our study population—a difference that may partly account for the lower prevalence of aTRH. The Irish study included both insured and uninsured PLWHTN, thereby capturing a socioeconomically diverse population. Such heterogeneity may partly explain the lower observed prevalence of aTRH and underscores the potential role of socioeconomic factors such as access to care, health literacy, and lifestyle practices in its development. Variations in sampling strategy, prescribing patterns, and the degree to which pseudo-resistance was excluded may also contribute to observed differences across studies.

Ethnicity and aTRH: genetic and environmental contributions

Our findings corroborate prior research which demonstrates a higher prevalence of TRH among individuals of African descent. The REasons for Geographic and Racial Differences in Stroke (REGARDS) [34] study showed African Americans were 1.62 times more likely to have aTRH (PR = 1.62; 95% CI: 1.36–1.93). Similarly, Sim et al., [7] found a significantly higher likelihood of aTRH among African Americans (OR = 1.68; 95% CI: 1.62–1.75). In our study, Black Africans were nearly two and a half times more likely to have aTRH compared to other racial groups (aOR = 2.33, CI:1.30–4.20, $p < 0.001$), adding to the growing evidence of heightened risk among this population. Although Indian PLWHTN comprised the second largest ethnic group with aTRH, they were proportionally underrepresented compared to the non-aTRH group. This disparity may reflect underlying differences in socioeconomic status, healthcare literacy, and health-seeking behaviour—factors not directly measured in this study. Nevertheless, the variation observed between ethnic groups highlights the combined influence of biological and social determinants on aTRH risk. Beyond socioeconomic influences, biological and genetic factors likely contribute significantly to the elevated burden of aTRH among Black African populations. Genetic variations affecting blood pressure regulation and pharmacogenetic pathways may influence responsiveness to antihypertensive therapies. Among individuals of African descent, hypertension is often driven by mechanisms of salt and water retention associated with low-renin hypertension. Low renin hypertension has two primary subtypes: low renin with low aldosterone (Liddle phenotype) and low renin with high aldosterone (primary aldosteronism phenotype) [14].

The renal tubular epithelial sodium channel (ENaC), a key regulator of sodium balance in the distal nephron, is central to the Liddle phenotype. Aberrations in ENaC activity—whether through structural mutations or via regulatory dysfunction can lead to sodium retention and elevated blood pressure [14]. Notably, the *R563Q* variant, found in 6% of Black Africans and individuals of mixed ancestry in South Africa, has shown remarkable responsiveness to amiloride, an ENaC antagonist, with observed reductions in blood pressure of up to 36/17 mmHg [35]. Variants in aldosterone synthase (CYP11B2), driving the primary aldosteronism phenotype, are also more prevalent in Black populations [36]. Individualised treatment strategies based on renin-aldosterone profiling have demonstrated superior outcomes compared to standard care in African settings [37]. However, significant barriers persist in translating these findings into routine practice. Notably, amiloride remains unregistered in South Africa, limiting access to a proven therapeutic option for patients with the Liddle phenotype [38]. Advocacy efforts informed by robust evidence are essential to address this unmet need and improve access to therapies for Black Africans with TRH.

HMOD and aTRH

Hypertensive-mediated organ damage (HMOD) and TRH maintain a bidirectional relationship: persistently elevated BP leads to structural and functional alterations and progression of cerebrovascular, cardiac, renal, and vascular target organ damage [39]. In turn, established HMOD in the form of microvascular disease, atherosclerosis, CKD, LVH, and aortic stiffness render blood pressure more difficult to control [39].

Left ventricular hypertrophy arises from the mechanical pressure afterload and is augmented by neurohormonal factors (angiotensin II, aldosterone, adrenaline) and metabolic dysfunction (insulin resistance) that promote cardiac hypertrophy and fibrosis [40]. In our sample, over half were obese, and more than a third were Black African (35.3%), both factors strongly associated with LVH [40, 41]. Electrocardiographic LVH was found to be a significantly associated with aTRH in our study population. This aligns with findings from a large Spanish cohort, where LVH was identified in 18.5% of patients

with resistant hypertension (OR 1.22; 95% CI: 1.02–1.38, $p < 0.033$) [26]. Similarly, studies from African settings report higher LVH prevalence among TRH patients. For instance, Khafallah et al. [42] observed a prevalence of 59.5% using echocardiography—a method more sensitive than electrocardiography employed in our study.

CKD and TRH frequently coexist, forming a complex and interdependent relationship. CKD predisposes individuals to TRH through mechanisms such as impaired natriuresis and resultant volume expansion, while persistent hypertension accelerates renal dysfunction [39]. In our study, CKD was significantly associated with aTRH, consistent with findings from multiple other studies [6, 7, 26].

A key driver of obesity-induced hypertension is SNS activation via neurohormonal mechanisms (increased leptin, hyperinsulinaemia) which is also independently linked to increased left ventricular mass [5]. Obstructive sleep apnoea (OSA), a common comorbidity of obesity, contributes to the development of TRH through mechanisms such as endothelial dysfunction, SNS hyperactivity, and oxidative stress [43]. In our sample, 14% were at high risk for OSA, which was more prevalent among those with aTRH. This is comparable to results from a Nigerian cohort [44], however, OSA screening in Africa is underutilised and OSA as a contributor to TRH is under-recognised.

Uncontrolled TRH (UTRH) versus controlled TRH (CTRH): role of arterial stiffness and obesity-driven mechanisms

Our study reveals a greater proportion of individuals with uncontrolled aTRH (11%) compared to controlled (7.8%). This prevalence of UTRH is notably higher than that reported in other African countries, such as Nigeria (3.3%), [29] and even exceeds the findings of a US study (7.8%).[7] The lower prevalence reported in these studies may partly reflect their ability to exclude pseudo-resistance, a limitation in our study.

Controlled TRH is generally associated with volume-dependent mechanisms, whilst additional pathophysiological factors, including heightened SNS activity and increased arterial stiffness influence UTRH. Supporting these mechanisms, the UTRH group in our study exhibited a higher BMI and pulse pressure, a recognised surrogate for arterial stiffness [45], compared to the CTRH group. These findings concur with a Brazilian cohort who also described higher pulse pressures, BMI and LVH in the UTRH group [46]. Obesity-related factors, such as hyperinsulinaemia and elevated adipokines thought to stimulate aldosterone, are known to exacerbate SNS hyperactivity and lead to excess aldosterone states, which may contribute to treatment resistance [47]. These observations highlight the complex interplay of metabolic dysregulation, obesity, and cardiovascular changes in the pathogenesis of uncontrolled TRH, highlighting the need for targeted management strategies to address these underlying mechanisms.

Underuse of mineralocorticoid receptor antagonists and other treatment gaps in TRH management

Medical therapy remains the cornerstone of treatment for TRH, with MRAs established as the favoured fourth-line agents, as demonstrated by the landmark PATHWAY-2 trial [48]. Mineralocorticoid antagonists outperform other pharmaceutic and interventional procedures in lowering blood pressure [49], yet their use remains underwhelming. In our study, only 10.8% of PLWHTN were prescribed an MRA—a trend consistent in high income countries [50, 51]. This underutilisation may stem from concerns about MRAs' side effect profile and contraindications in patients with advanced renal dysfunction. Despite these challenges, MRAs have demonstrated significant efficacy in improving both office and 24-hour ambulatory blood pressure control, as well as improvement in cardiac and renal HMOD [52]. Given the frequent need for multiple medications in TRH, single-pill combinations (SPCs) offer a promising strategy to enhance adherence and improve blood pressure control compared to equivalent multi-pill regimens [53]. SPCs are preferred as they improve adherence and lead to better BP control, compared with single-drug equivalent combinations [53]. The feasibility and cost-effectiveness of SPCs in our setting warrant further investigation. Furthermore, individualised approaches, such as renin-guided therapy or pharmacogenetics-based management, offer promising alternatives to the traditional add-on strategy. However, these methods remain inaccessible in many low-resource settings, including ours. Prioritising the development and adoption of such approaches could improve compliance by reducing the reliance on escalating polypharmacy and expanding therapeutic options for patients with TRH.

Our study identified key characteristics among PLWHTN that are strongly associated with TRH, including being of Black African descent, having abdominal obesity, dyslipidaemia, chronic kidney disease, and electrocardiographic left ventricular hypertrophy. These findings underscore the need for heightened vigilance and tailored management strategies for PLWHTN with these profiles. Difficulty in achieving blood pressure control in this subgroup should prompt clinicians to consider earlier and more comprehensive evaluations to address potential underlying contributors, such as secondary hypertension. Proactive intervention in these high-risk individuals could mitigate the progression of HMOD and improve long-term outcomes.

Limitations

This study, whilst insightful, is not without limitations. Our prevalence estimate of aTRH is based on a single-centre primary care cohort of PLWHTN. As the study was conducted in a public-sector primary care setting, selection bias may have been introduced, and the findings may not be fully generalisable to hypertensive patients managed in private or tertiary care settings, where variations in healthcare-seeking behaviour, referral patterns, and treatment access may influence the observed prevalence of aTRH. Although all participants accessed care within the public healthcare sector, ensuring some degree of uniformity in service availability, we did not collect detailed socio-economic data such as education level, income, or social support. These factors may influence treatment adherence and blood pressure control and could contribute to differences observed between ethnic groups. Furthermore, the absence of 24-hour ambulatory blood pressure monitoring limited our ability to exclude white-coat hypertension and detect masked hypertension; consequently, not all contributors to pseudo-resistance could be effectively excluded. Our reliance on indirect measures of medication adherence may have introduced misclassification bias. As a cross-sectional study, causal relationships between the identified risk factors and aTRH cannot be established. Future cohort or prospective studies are needed to explore causality and better delineate the temporal and mechanistic relationships underpinning these associations. Employing robust adherence assessments, comprehensive blood pressure monitoring protocols, and inclusion of socio-economic factors in such studies will further validate and expand upon our findings.

Future practice and policy considerations

Our findings emphasise the need to strengthen guideline directed management of TRH in South Africa, including greater utilisation of MRAs as the favoured fourth-line anti-hypertensive where appropriate. Advocacy for access and availability to antihypertensive medications with proven efficacy in Black African populations such as ENaC inhibitors, like amiloride is critical. Expanding access to SPC therapies particularly in the public health sector, could significantly improve adherence by reducing pill burden and enhancing BP control among PLWHTN. Future strategies should explore the value of individualised management approaches, such as renin phenotyping and pharmacogenetic guided therapy. Furthermore, the lack of region-specific guidelines for TRH highlights an important gap in current practice.

Conclusion

This study is the first to describe the prevalence and profile of aTRH in a South African primary care setting. The inclusion of a racially diverse cohort offers valuable insights into the burden of aTRH, particularly its high prevalence among Black Africans. Our findings emphasis the need for integrated care strategies that support adherence, optimise therapy, and promote sustainable lifestyle changes. Addressing these challenges is essential to reducing the impact of TRH and its dire cardiovascular complications in this high-risk population. While our findings suggest a biological vulnerability, the potential influence of unmeasured socioeconomic factors on the observed ethnic disparities warrants further investigation.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
aOR	Adjusted odds ratio
ARB	Angiotensin receptor blocker
aTRH	Apparent treatment-resistant hypertension
BB	Beta blocker
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blocker
CI	Confidence interval
CKD	Chronic kidney disease
CTRH	Controlled treatment-resistant hypertension
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
ENaC	Epithelial sodium channel
HDL	High-density lipoprotein
HMOD	Hypertension-mediated organ damage
IQR	Interquartile range
LDL	Low-density lipoprotein
LMIC	Low-middle-income countries
LVH	Left ventricular hypertrophy
MACE	Major adverse cardiovascular event
MARS-5	Medication adherence report scale-5
MRA	Mineralocorticoid receptor antagonist
OR	Odds ratio
OSA	Obstructive sleep apnoea
PLWHTN	People living with hypertension
PP	Pulse pressure
RAAS	Renin-angiotensin-aldosterone system
ROC	Receiver operating characteristic
SBP	Systolic blood pressure
SD	Standard deviation
SNS	Sympathetic nervous system
SPC	Single pill combination
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TRH	Treatment-resistant hypertension
UTRH	Uncontrolled treatment-resistant hypertension
WC	Waist circumference

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Author contributions

Both K.C.G and M.N conceptualized and designed the study. K.C.G contributed to data collection, data analysis and interpretation, and manuscript writing. M.N contributed towards supervision and critically reviewing the manuscript. All authors have read and approved the final manuscript, and give consent for publication.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The University of KwaZulu-Natal Biomedical Research and Ethics Committee (BREC/00005737/2023), together with the Kwa-Zulu Natal Department of Health and Wentworth Hospital management, granted ethical clearance for this study. Clinical trial number: not applicable. All participants provided written informed consent to participate in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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