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Original Research Article

Prevalence and Determinants of Resistant Hypertension in a Tertiary Care Population: A Prospective Observational Study

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Abstract

Background: Resistant hypertension (RH) represents a challenging clinical entity associated with increased cardiovascular morbidity and mortality. Understanding the prevalence and determinants of RH in diverse populations is essential for developing targeted management strategies.

Methods: This prospective observational study enrolled 724 consecutive hypertensive patients attending the outpatient clinics of a tertiary care hospital. RH was defined as blood pressure ≥140/90 mmHg despite optimal doses of three antihypertensive medications including a diuretic, or blood pressure controlled on four or more agents. Comprehensive clinical, biochemical, and ambulatory blood pressure monitoring (ABPM) assessments were performed.

Results: The prevalence of RH was 14.8% (107/724). Patients with RH were significantly older (62.4 ± 9.8 vs 54.6 ± 11.2 years, p<0.001), had higher body mass index (32.6 ± 5.4 vs 27.8 ± 4.2 kg/m², p<0.001), and longer hypertension duration (14.2 ± 6.8 vs 8.6 ± 5.4 years, p<0.001). Diabetes mellitus (58.9% vs 32.4%, p<0.001), chronic kidney disease (42.1% vs 18.6%, p<0.001), and obstructive sleep apnea (34.6% vs 12.8%, p<0.001) were more prevalent in RH patients. Multivariate logistic regression identified obesity (OR=2.84, 95% CI: 1.72-4.68, p<0.001), diabetes mellitus (OR=2.36, 95% CI: 1.48-3.76, p<0.001), chronic kidney disease (OR=2.18, 95% CI: 1.34-3.54, p=0.002), and obstructive sleep apnea (OR=2.12, 95% CI: 1.26-3.56, p=0.005) as independent determinants of RH. White-coat effect was identified in 23.4% of apparent RH cases through ABPM.

Conclusion: Resistant hypertension affects approximately one in seven treated hypertensive patients in tertiary care settings. Obesity, diabetes, chronic kidney disease, and obstructive sleep apnea represent major modifiable and non-modifiable determinants requiring comprehensive evaluation and management.

Keywords: Resistant Hypertension; Prevalence; Determinants; Obesity; Chronic Kidney Disease; Ambulatory Blood Pressure Monitoring.

Introduction

Hypertension remains the leading modifiable risk factor for cardiovascular disease worldwide, affecting over 1.4 billion adults globally and contributing substantially to stroke, myocardial infarction, heart failure, and chronic kidney disease [1]. Despite the availability of numerous effective antihypertensive medications, optimal blood pressure control remains elusive in a significant proportion of treated patients, with resistant hypertension (RH) representing the most challenging subset of this population [2].

Resistant hypertension is conventionally defined as blood pressure that remains above goal despite concurrent use of three antihypertensive drug classes at optimal doses, one of which should ideally be a diuretic, or blood pressure that is controlled with four or more medications [3]. This definition, endorsed by major cardiovascular societies, distinguishes true resistance from pseudo-resistance, which may result from white-coat hypertension, medication non-adherence, or inadequate dosing [4].

The epidemiology of resistant hypertension has been extensively investigated in Western populations. The landmark analysis by Persell estimated that 8.9% of hypertensive adults in the United States met criteria for apparent resistant hypertension [5]. Subsequent investigations by

Daugherty and colleagues documented an incidence rate of 1.9% per year among newly treated hypertensive patients, with cumulative incidence reaching 10.3% over a median follow-up of 1.5 years [6]. However, prevalence estimates vary considerably based on population characteristics, healthcare settings, and definitional criteria employed.

The clinical significance of resistant hypertension extends beyond blood pressure values. Patients with RH demonstrate substantially elevated cardiovascular risk compared to those with controlled hypertension. Studies have documented increased rates of left ventricular hypertrophy, chronic kidney disease progression, stroke, and myocardial infarction in this population [7]. Furthermore, resistant hypertension serves as an important marker for underlying secondary causes including primary aldosteronism, renal artery stenosis, and obstructive sleep apnea, which require specific diagnostic and therapeutic approaches [8].

Multiple factors have been implicated in the pathogenesis of resistant hypertension. Obesity represents a particularly important contributor through mechanisms involving sympathetic nervous system activation, renin-angiotensin-aldosterone system stimulation, and volume expansion [9].

Diabetes mellitus, chronic kidney disease, and advanced age are consistently identified as major determinants across studies [10]. Additionally, lifestyle factors including excessive dietary sodium intake and physical inactivity contribute to treatment resistance [11].

Despite growing literature on resistant hypertension, significant knowledge gaps remain regarding its epidemiology in developing countries and in tertiary care referral populations. Most existing data originate from primary care settings or population-based surveys in high-income countries. Furthermore, the relative contribution of various determinants may differ based on population characteristics, comorbidity profiles, and healthcare delivery patterns [12].

The aim of this study was to determine the prevalence of resistant hypertension and identify its clinical determinants in a prospective cohort of hypertensive patients attending a tertiary care center.

Materials and Methods

Study Design and Setting: This prospective observational study was conducted at the outpatient clinics of tertiary care hospital.

Study Population: Consecutive adult patients aged 18 years and above with established diagnosis of essential hypertension on pharmacological treatment for at least six months were screened for eligibility. The target sample size of 700 participants was calculated based on an estimated RH prevalence of 12%, with 95% confidence level and 2.5% margin of error, accounting for 10% incomplete data.

Inclusion criteria comprised: age ≥18 years, diagnosis of essential hypertension, current treatment with at least one antihypertensive medication for minimum six months, and willingness to participate including adherence assessment. Exclusion criteria included: secondary hypertension with identified and potentially correctable cause at baseline, pregnancy or lactation, severe comorbidities with life expectancy less than one year, inability to provide informed consent, and prior renal denervation or baroreceptor activation therapy.

Definitions: Resistant hypertension was defined according to American Heart Association scientific statement criteria: office blood pressure ≥140/90 mmHg (≥130/80 mmHg for patients with diabetes or chronic kidney disease during the study period) despite treatment with optimal or best-tolerated doses of three antihypertensive medications from different classes including a diuretic; or blood pressure at goal with four or more antihypertensive medications.

Controlled hypertension was defined as office blood pressure <140/90 mmHg on one to two antihypertensive medications. Pseudo-resistant hypertension was defined as apparent resistance due to white-coat effect, non-adherence, or suboptimal medication dosing.

Clinical Assessment: Comprehensive clinical evaluation was performed for all participants. Detailed medical history included duration of hypertension, antihypertensive medications (drug classes, doses, and frequency), adherence assessment, cardiovascular symptoms, and comorbidities. Medication adherence was assessed using the eight-item Morisky Medication Adherence Scale (MMAS-8), with scores ≥6 indicating adequate adherence.

Anthropometric measurements included height, weight, body mass index (BMI), and waist circumference. Obesity was defined as BMI ≥30 kg/m². Office blood pressure was measured using validated automatic oscillometric devices (Omron HBP-1300) after 5 minutes of seated rest, with three readings taken at 2-minute intervals. The mean of the second and third readings was recorded.

Ambulatory Blood Pressure Monitoring: All patients meeting criteria for apparent resistant hypertension underwent 24-hour ambulatory blood

pressure monitoring (ABPM) using validated devices (Spacelabs 90207).

Readings were obtained at 20-minute intervals during daytime (0600-2200 hours) and 30-minute intervals during nighttime (2200-0600 hours). Valid recordings required ≥70% successful measurements. White-coat hypertension was defined as elevated office BP with normal 24-hour ambulatory BP (<130/80 mmHg).

Laboratory Investigations: Fasting blood samples were obtained for complete blood count, comprehensive metabolic panel including serum creatinine, estimated glomerular filtration rate (CKD-EPI equation), fasting glucose, glycated hemoglobin, lipid profile, serum electrolytes, and uric acid.

Urinalysis with albumin-to-creatinine ratio was performed. Patients with suspected secondary hypertension underwent targeted evaluation including plasma aldosterone-to-renin ratio, 24-hour urinary catecholamines, and renal artery imaging as clinically indicated.

Assessment for Obstructive Sleep Apnea: All patients were screened for obstructive sleep apnea using the STOP-BANG questionnaire. Those with scores ≥3 underwent overnight polysomnography. OSA was defined as apnea-hypopnea index ≥5 events/hour.

Statistical Analysis: Statistical analysis was performed using SPSS software (Version 27.0, IBM Corporation). Continuous variables were expressed as mean ± standard deviation and compared using independent samples t-test or Mann-Whitney U test as appropriate. Categorical variables were presented as frequencies and percentages, compared using chi-square test or Fisher's exact test. Univariate analysis identified potential determinants of RH. Variables with $p<0.10$ in univariate analysis were entered into multivariate logistic regression with backward stepwise selection. Results were expressed as odds ratios with 95% confidence intervals. Hosmer-Lemeshow test assessed model goodness-of-fit. Statistical significance was defined as $p<0.05$.

Results

Study Population Characteristics: A total of 786 patients were screened, of whom 724 met eligibility criteria and completed the study protocol. The mean age was 56.2 ± 11.4 years, with 58.4% male predominance.

Mean duration of hypertension was 9.4 ± 6.2 years. Baseline characteristics are summarized in Table 1.

Prevalence of Resistant Hypertension: Among 724 participants, 107 (14.8%) met criteria for apparent resistant hypertension. Following ABPM evaluation, 25 patients (23.4% of apparent RH) demonstrated white-coat effect, leaving 82 patients (11.3% of total) with confirmed true resistant hypertension. Controlled resistant hypertension (BP at goal on ≥4 medications) was present in 34 patients (31.8% of RH group).

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Total (n=724)	RH Group (n=107)	Non-RH Group (n=617)	p-value
Age (years)	56.2 ± 11.4	62.4 ± 9.8	54.6 ± 11.2	<0.001
Male sex, n (%)	423 (58.4%)	68 (63.6%)	355 (57.5%)	0.238
BMI (kg/m²)	28.6 ± 4.8	32.6 ± 5.4	27.8 ± 4.2	<0.001
Obesity (BMI ≥30), n (%)	284 (39.2%)	72 (67.3%)	212 (34.4%)	<0.001
Waist circumference (cm)	96.4 ± 12.8	106.2 ± 14.2	94.8 ± 11.6	<0.001
Duration of HTN (years)	9.4 ± 6.2	14.2 ± 6.8	8.6 ± 5.4	<0.001
Family history HTN, n (%)	412 (56.9%)	68 (63.6%)	344 (55.8%)	0.128
Current smoker, n (%)	124 (17.1%)	22 (20.6%)	102 (16.5%)	0.298
Alcohol use, n (%)	186 (25.7%)	32 (29.9%)	154 (25.0%)	0.274
Office SBP (mmHg)	142.6 ± 18.4	162.4 ± 16.8	138.2 ± 15.6	<0.001
Office DBP (mmHg)	88.4 ± 11.2	96.8 ± 10.4	86.8 ± 10.8	<0.001
Heart rate (bpm)	74.8 ± 12.2	78.4 ± 11.6	74.2 ± 12.4	0.002

RH: resistant hypertension; BMI: body mass index; HTN: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure

Comorbidities and Laboratory Findings: Patients with resistant hypertension demonstrated significantly higher prevalence of comorbid conditions (Table 2). Diabetes mellitus was present in 58.9% of RH patients compared to 32.4% of non-RH patients ($p<0.001$). Chronic kidney disease (eGFR <60 mL/min/1.73m²) was observed in 42.1% versus 18.6% ($p<0.001$). Obstructive sleep apnea was confirmed in 34.6% of RH patients versus 12.8% of non-RH patients ($p<0.001$). Laboratory parameters demonstrated worse metabolic profiles in the RH group.

Table 2: Comorbidities and Laboratory Parameters

Parameter	RH Group (n=107)	Non-RH Group (n=617)	p-value
Diabetes mellitus, n (%)	63 (58.9%)	200 (32.4%)	<0.001
CKD (eGFR <60), n (%)	45 (42.1%)	115 (18.6%)	<0.001
Coronary artery disease, n (%)	28 (26.2%)	98 (15.9%)	0.008
Prior stroke/TIA, n (%)	14 (13.1%)	42 (6.8%)	0.024
Heart failure, n (%)	18 (16.8%)	52 (8.4%)	0.006
Obstructive sleep apnea, n (%)	37 (34.6%)	79 (12.8%)	<0.001
Dyslipidemia, n (%)	74 (69.2%)	326 (52.8%)	0.002
Hyperuricemia, n (%)	38 (35.5%)	124 (20.1%)	<0.001
Serum creatinine (mg/dL)	1.42 ± 0.68	1.04 ± 0.42	<0.001
eGFR (mL/min/1.73m²)	62.4 ± 24.6	78.6 ± 22.4	<0.001
Fasting glucose (mg/dL)	126.4 ± 42.8	106.8 ± 32.4	<0.001
HbA1c (%)	7.2 ± 1.6	6.4 ± 1.2	<0.001
Total cholesterol (mg/dL)	198.6 ± 42.4	188.4 ± 38.6	0.016
Triglycerides (mg/dL)	186.4 ± 78.6	152.6 ± 64.2	<0.001
Serum potassium (mEq/L)	4.2 ± 0.6	4.4 ± 0.5	0.002
Serum uric acid (mg/dL)	7.4 ± 2.2	6.2 ± 1.8	<0.001
UACR (mg/g)	124.6 ± 186.4	42.8 ± 68.4	<0.001

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; TIA: transient ischemic attack; UACR: urinary albumin-to-creatinine ratio

Antihypertensive Medication Patterns: Patients with RH received a mean of 4.2 ± 0.8 antihypertensive medications compared to 1.8 ± 0.6 in non-RH patients (p<0.001).

Medication classes utilized included: angiotensin receptor blockers (86.9% in RH vs 62.4% in non-RH), calcium channel blockers (89.7% vs 48.6%), thiazide diuretics (78.5% vs 34.2%), beta-blockers (64.5% vs 28.4%), and mineralocorticoid receptor antagonists (42.1% vs 4.8%). Adequate medication adherence (MMAS-8 score ≥6) was documented in 82.2% of RH patients.

Independent Determinants of Resistant Hypertension: Multivariate logistic regression analysis identified independent determinants of resistant hypertension (Table 3). Obesity demonstrated the strongest association (OR=2.84, 95% CI: 1.72-4.68, p<0.001), followed by diabetes mellitus (OR=2.36, 95% CI: 1.48-3.76, p<0.001), chronic kidney disease (OR=2.18, 95% CI: 1.34-3.54, p=0.002), obstructive sleep apnea (OR=2.12, 95% CI: 1.26-3.56, p=0.005), age per 10-year increment (OR=1.64, 95% CI: 1.28-2.10, p<0.001), and hypertension duration per 5-year increment (OR=1.42, 95% CI: 1.18-1.72, p<0.001).

Table 3: Independent Determinants of Resistant Hypertension (Multivariate Logistic Regression)

Variable	Odds Ratio	95% CI	p-value
Obesity (BMI ≥30 kg/m²)	2.84	1.72-4.68	<0.001
Diabetes mellitus	2.36	1.48-3.76	<0.001
Chronic kidney disease	2.18	1.34-3.54	0.002
Obstructive sleep apnea	2.12	1.26-3.56	0.005
Age (per 10-year increase)	1.64	1.28-2.10	<0.001
HTN duration (per 5-year increase)	1.42	1.18-1.72	<0.001
Hyperuricemia	1.56	0.94-2.58	0.086
Male sex	1.24	0.76-2.02	0.384

Model chi-square = 126.4, p<0.001; Hosmer-Lemeshow p=0.642; Nagelkerke R^2 = 0.286
CI: confidence interval; BMI: body mass index; HTN: hypertension

Discussion

This prospective study establishes the prevalence of resistant hypertension at 14.8% among treated hypertensive patients in a tertiary care population, with true RH confirmed in 11.3% after excluding white-coat hypertension. Furthermore, we identified obesity, diabetes mellitus, chronic kidney disease, and obstructive sleep apnea as independent determinants of resistant hypertension.

Our prevalence estimate aligns with the global meta-analysis by Noubiap and colleagues, which reported pooled RH prevalence of 13.7% across 91 studies encompassing 3.2 million patients [13]. The slightly higher prevalence in our cohort likely reflects the tertiary care setting with referral bias toward more complex cases. Previous studies from specialized hypertension centers have documented prevalence rates ranging from 12% to 18%, supporting our findings [14].

The identification of white-coat effect in 23.4% of apparent RH cases underscores the importance of out-of-office blood pressure measurement in this population. This proportion is consistent with prior investigations demonstrating that 20-40% of patients with apparent RH have pseudo-resistance attributable to white-coat phenomenon [15]. The 2018 European Society of Cardiology/European Society of Hypertension guidelines mandate ABPM confirmation before diagnosing true resistant hypertension, a recommendation supported by our findings [16].

Obesity emerged as the strongest independent predictor of resistant hypertension in our analysis, with nearly three-fold increased odds. The pathophysiological relationship between obesity and treatment-resistant hypertension is well-established and multifactorial. Adipose tissue expansion promotes sodium retention, sympathetic nervous system activation, and renin-angiotensin-aldosterone system hyperactivity [17]. Furthermore, obesity frequently coexists with obstructive sleep apnea, creating synergistic effects on blood pressure regulation. Weight reduction represents a cornerstone of management in obese patients with RH.

The strong association between diabetes mellitus and resistant hypertension observed in our cohort corroborates extensive prior evidence. Diabetic patients exhibit enhanced arterial stiffness, endothelial dysfunction, and volume expansion that contribute to treatment resistance [18].

The prevalence of diabetes in our RH group (58.9%) substantially exceeds that in controlled hypertension, emphasizing the importance of glycemic optimization in comprehensive management.

Chronic kidney disease demonstrated significant association with resistant hypertension, reflecting the bidirectional relationship between renal dysfunction and hypertension. Diminished nephron mass, volume expansion, and neurohormonal activation in CKD promote treatment resistance [19]. Moreover, diuretic resistance in advanced CKD necessitates dose escalation and loop diuretic utilization, complicating blood pressure management.

Obstructive sleep apnea represented a major modifiable determinant in our cohort. The intermittent hypoxia and sleep fragmentation characteristic of OSA trigger sympathetic activation, oxidative stress, and aldosterone excess [20]. Importantly, OSA remains underdiagnosed in hypertensive populations, and our systematic screening approach identified this condition in over one-third of RH patients. Continuous positive airway pressure therapy has demonstrated modest but significant blood pressure reductions in this population [21].

The age-related increase in resistant hypertension reflects progressive arterial stiffening, reduced baroreceptor sensitivity, and cumulative end-organ damage. Similarly, longer hypertension duration associates with greater vascular remodeling and treatment resistance [22]. These non-modifiable factors identify patients warranting more intensive monitoring and therapeutic approaches.

Our study has several strengths including prospective design, comprehensive clinical evaluation, systematic ABPM assessment, and multivariate analysis adjusting for potential confounders. However, limitations should be acknowledged. The single-center tertiary care design limits generalizability to primary care settings. Medication adherence assessment relied primarily on self-report despite validated instruments. Secondary causes of hypertension, particularly primary aldosteronism, may have been underdiagnosed despite screening efforts [23].

Conclusion

This prospective study demonstrates that resistant hypertension affects approximately 15% of treated hypertensive patients in tertiary care settings, with true resistance confirmed in 11% after ambulatory blood pressure monitoring evaluation. White-coat phenomenon accounts for nearly one-quarter of apparent resistant hypertension cases, emphasizing the necessity of out-of-office blood pressure confirmation. Obesity, diabetes mellitus, chronic kidney disease, and obstructive sleep apnea represent the major independent determinants of resistant hypertension, most of which are potentially modifiable through targeted interventions. These findings support comprehensive evaluation of resistant hypertension patients including ambulatory monitoring, metabolic assessment, and sleep apnea screening. Multidisciplinary management addressing these determinants may improve blood pressure control and reduce cardiovascular risk in this high-risk population.

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