Original Article

Etiological Analysis and Targeted Management of Resistant Hypertension in a Cohort of 64 Chronic Kidney Disease Patients

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Abstract

Background: *Resistant hypertension (rHTN) is a common complication in chronic kidney disease (CKD) patients, often driven by identifiable secondary etiologies.*

Objectives: *This study aimed to identify the prevalence of specific etiological factors in CKD patients with rHTN and evaluate the hemodynamic response one month after initiating targeted treatment.*

Materials and Methods: *A prospective observational study was conducted on 64 CKD patients with rHTN. All patients were stabilized on a maximal regimen of amlodipine, prazosin, bisoprolol, and indapamide. They were screened and treated for hyperuricemia (febuxostat), secondary hyperparathyroidism (doxercalciferol), hyperprolactinemia (cabergoline), and renal artery stenosis. Blood pressure (BP) was reassessed after one month. Data were analyzed using descriptive statistics and a paired samples t-test in jamovi 2.6.44.*

Results: *The prevalence of secondary factors was high: hyperuricemia 78.1% (n=50), secondary hyperparathyroidism 76.6% (n=49), and hyperprolactinemia 46.9% (n=30). Renal artery stenosis was confirmed in 3.1% (n=2). Targeted therapy led to a significant mean reduction in BP from 191.8/101.6 mmHg to 132.7/79.2 mmHg (mean reduction: -59.1/-22.4 mmHg, p<0.001).*

Conclusion: *Resistant hypertension in CKD is frequently driven by treatable secondary factors. A systematic etiological workup followed by targeted intervention alongside conventional therapy leads to a profound improvement in BP control.*

Key words: *Resistant Hypertension, Chronic Kidney Disease, Hyperuricemia, Hyperparathyroidism, Hyperprolactinemia, Targeted Therapy.*

Date of received: *18.05.2025*

Date of acceptance: *30.06.2025*

DOI: https://doi.org/10.3329/kyamcj.v16i02.87330

KYAMC Journal. 2025; 16(02): 59-63.

Introduction

Hypertension is a leading risk factor for the development of cardiovascular disease and is increasing in prevalence.[1] Reduction in blood pressure (BP) reduces the risk for end-organ damage, and patients who do not reach BP goals despite multi drug therapy are designated as having resisant hypertension (rHTN).[2-4]

Resistant hypertension (rHTN) is defined by uncontrolled blood pressure despite treatment with three or more antihypertensive medications, including, if tolerated, a diuretic in adequate doses.[5,6] Patients with rHTN have an even higher risk of cardiovascular complications than hypertensive patients.[7] It is estimated that 10–20% of people with hypertension are resistant, underscoring the importance of understanding the determinants of this condition.[8-10] RH is common in individuals with chronic kidney disease(CKD) and becomes more prevalent with declining kidney function.[11] Among individuals with CKD, RH is associated with greater risk for kidney disease progression; therefore, an understanding of recent definitions and therapeutic options is crucial for nephrologists engaging in the care of patients with CKD.[12,13]

This resistance is often attributable to specific pathophysiological mechanisms inherent to renal dysfunction, including sodium retention, sympathetic overactivity, and secondary endocrine abnormalities. This study analyzes a cohort of 64 CKD patients with rHTN to identify the prevalence of four key etiological factors and assesses the clinical outcomes of a protocol-driven, targeted treatment approach.

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Materials and Methods

Study Design and Population

This prospective observational study was conducted in the Department of Nephrology, Khwaja Yunus Ali Medical College and Hospital (KYAMCH), from January to June 2025. The study protocol was approved by the Institutional Ethical Review Committee, and written informed consent was obtained from all participants.

A total of 64 consecutive adult patients (≥18 years) with Stage III–V Chronic Kidney Disease (CKD), as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, who were admitted with apparent treatment-resistant hypertension (rHTN), were enrolled.

Resistant hypertension was defined as blood pressure (BP) ≥ 140/90 mmHg despite the concurrent use of at least three different classes of antihypertensive agents, including a diuretic, at maximum or maximally tolerated doses.

Patients with pseudoresistant hypertension (e.g., poor adherence, white-coat effect), secondary hypertension due to causes other than those under investigation (e.g., pheochromocytoma, Cushing's syndrome), or acute kidney injury were excluded.

Study Protocol

Baseline Stabilization and rHTN Confirmation

All patients underwent a 72-hour in-patient BP monitoring period while receiving a maximized (tolerated) four-drug regimen consisting of:

Amlodipine (calcium channel blocker): 10 mg once daily
Prazosin hydrochloride (α_1-blocker): 5 mg three times daily
Bisoprolol (β_1-blocker): 5 mg twice daily
Torsemide (loop diuretic): 20 mg once daily

Resistant hypertension was confirmed if BP remained uncontrolled after this stabilization period.

Diagnosis and Targeted Interventions

The following comorbid conditions were screened and managed as part of targeted intervention:

Hyperuricemia: Serum uric acid >420 µmol/L in men or >357 µmol/L in women; treated with Febuxostat 40 mg once daily.
Secondary hyperparathyroidism: Serum parathyroid hormone (PTH) >88 pg/mL; treated with Doxercalciferol 2 µg twice weekly.
Hyperprolactinemia: Serum prolactin >20 µg/L in men or >25 µg/L in women; treated with Cabergoline 0.5 mg twice weekly.
Renal artery stenosis (RAS): Screened using renal Doppler ultrasonography.

Outcome Measure and Follow-up

The primary outcome was the change in office BP from baseline to one month after targeted intervention. BP was measured three times after a 5-minute rest period in the sitting position, and the average of the three readings was recorded.

Statistical Analysis

Data were analyzed using Jamovi software (version 2.6.44). Continuous variables are presented as mean ± standard deviation (SD) or median [interquartile range], as appropriate, and categorical variables as frequencies and percentages.
Comparisons of pre- and post-intervention BP were performed using the paired-samples t-test. A two-tailed p-value <0.05 was considered statistically significant.

Results

The cohort consisted of 64 patients with a mean age of 47 years, including 38 males (59.4%) and 26 females (40.6%). All patients had CKD (Stages III-V).The most common comorbidity profile was the presence of both hypertension (HTN) and diabetes mellitus (DM) (n=47, 73.5%), followed by HTN alone (n=15, 23.4%). Only two patients (3.1%) had DM without a documented history of HTN (Figure 1).

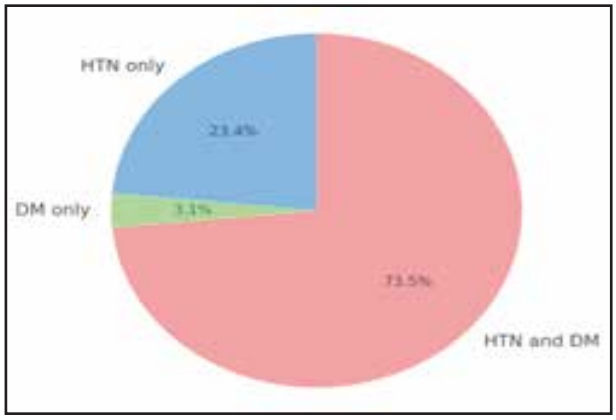

Figure 1: Distribution of Primary Comorbidities among the Study Cohort

The pie chart illustrates the prevalence of hypertension (HTN) and diabetes mellitus (DM) as underlying comorbidities in 64 patients with chronic kidney disease (CKD) and resistant hypertension. The vast majority of patients (73.5%) had both HTN and DM. Isolated HTN was present in 23.4% of patients, while only 3.1% had DM without HTN.

Prevalence of Etiological Factors

The prevalence of secondary factors was:

Hyperuricemia: 50 patients (78.1%)

Secondary Hyperparathyroidism: 49 patients (76.6%)

Hyperprolactinemia: 30 patients (46.9%)

Renal Artery Stenosis: 2 patients (3.1%)

No Identifiable Cause: 3 patients (4.7%)

The distribution of these etiological factors is presented in Figure 2.

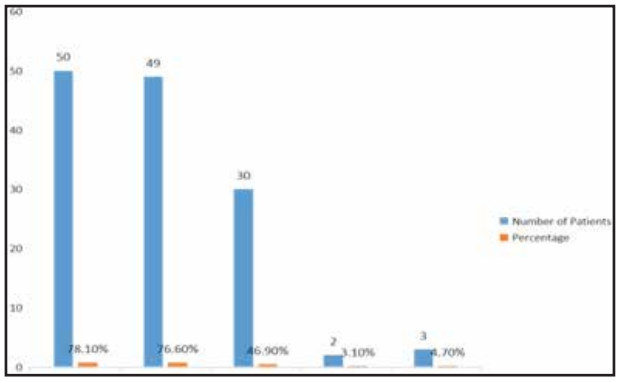

Figure 2: Prevalence of Identifiable Etiological Factors in a Cohort of Patients with Resistant Hypertension (n=64).

The bar chart illustrates the prevalence of the most common secondary causes identified in a study of 64 patients diagnosed with resistant hypertension. The most prevalent etiological factor was hyperaldosteronism (37.3%), followed closely by hyperuricemia (36.6%) and hyperprolactinemia (22.4%). Less common identifiable causes included renal artery stenosis (2.5%) and hyperparathyroidism (2.2%). A portion of the cohort had no identifiable cause for their hypertension.

Blood Pressure Response: The combined therapy resulted in a substantial improvement.

Mean BP on Admission: 191.8 / 101.6 mmHg
Mean BP after One Month: 132.7 / 79.2 mmHg
Mean Reduction: -59.1 / -22.4 mmHg ($p<0.001$)

The significant reduction in both systolic and diastolic blood pressure is visually represented in Figure 3 and Figure 4, respectively.

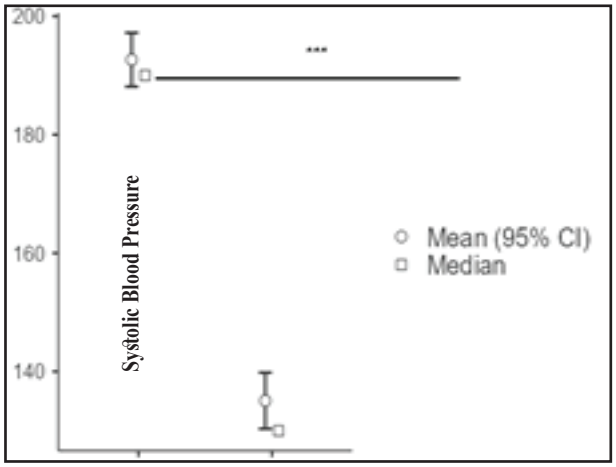

Figure 3: Box-and-whisker plot of systolic blood pressure.

The figure compares systolic blood pressure measurements on admission and after one month of combined conventional and targeted therapy in 64 patients with chronic kidney disease and resistant hypertension. The central line within the box represents the median, the box extends from the first to the third quartile, and the whiskers show the range. The plot demonstrates a significant reduction in median systolic blood pressure following treatment.

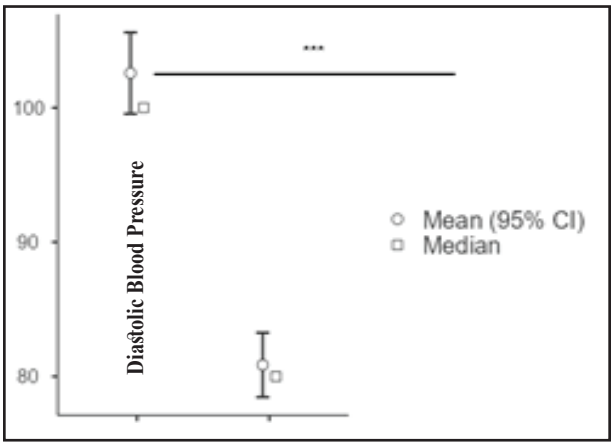

Figure 4: Box-and-whisker plot of diastolic blood pressure.

The figure compares diastolic blood pressure measurements on admission and after one month of combined conventional and targeted therapy in 64 patients with chronic kidney disease and resistant hypertension. The central line within the box represents the median, the box extends from the first to the third quartile, and the whiskers show the range. The plot demonstrates a significant reduction in median diastolic blood pressure following treatment.

Table I: Baseline Characteristics and Clinical Outcomes of the Study Cohort (n=64)

Variable	Mean	Median	SD
Demographic			
Age (years)	47.0	45.0	5.07
Laboratory Parameters			
S. Creatinine (µmol/L)	267.3	250.0	62.80
S. Uric Acid (µmol/L)	431.8	421.5	111.40
S. Prolactin (µg/L)	66.5	50.0	94.69
S. PTH (pg/mL)	228.3	209.5	108.22
Blood Pressure (Admission)			
Systolic BP (mmHg)	193.4	190.0	20.34
Diastolic BP (mmHg)	101.6	100.0	12.35
Blood Pressure (After 1 Month)			
Systolic BP (mmHg)	132.8	130.0	8.35
Diastolic BP (mmHg)	79.2	80.0	5.78

Abbreviations: SD, Standard Deviation; S., Serum; PTH, Parathyroid Hormone; BP, Blood Pressure.

Five patients were non-responders: two with renal artery stenosis, two with no identified cause, and one with a limited response despite hyperuricemia.

Discussion

This prospective study demonstrates that a systematic search for common secondary etiologies in patients with CKD and rHTN is highly warranted. Our principal finding is that after implementing targeted treatment for these identified factors alongside a standardized antihypertensive regimen, we observed a profound and statistically significant mean reduction in blood pressure of -59.1/-22.4 mmHg ($p<0.001$) within just one month. This dramatic improvement underscores the potential for reversing apparent treatment resistance by addressing its underlying causes.

The high prevalence of hyperuricemia (78.1%) and secondary hyperparathyroidism (76.6%) in our cohort aligns with the known pathophysiological landscape of CKD. Hyperuricemia is increasingly recognized not merely as a biomarker but as a contributor to hypertension and renal disease progression through mechanisms involving endothelial dysfunction, stimulation of the renin-angiotensin system, and vascular smooth muscle proliferation.[14, 15] Our findings support the growing body of evidence, such as that from a post-hoc analysis of the LIFE study, which suggested that serum uric acid is an independent predictor for the development of resistant hypertension.[16] The significant BP response to febuxostat in our patients suggests a potential causal role and a therapeutic target, a notion bolstered by experimental and small clinical studies.[17]

Similarly, the high rate of secondary hyperparathyroidism is expected in advanced CKD. Parathyroid hormone (PTH) itself has pressor effects, primarily through its influence on intracellular calcium in vascular smooth muscle cells, which can increase peripheral vascular resistance.[18] The association between hypertension and hyperparathyroidism has been established in previous observational studies.[19] The prospective cohort study by Taylor EN et al. reported increased incidence of hypertension with higher quartiles of PTH.[20] In this study, treatment of secondary hyperparathyroidism with doxercalciferol was associated with a significant reduction in systolic and diastolic blood pressure. This finding corroborates existing clinical evidence linking hyperparathyroidism to the pathogenesis of hypertension and suggests a potential beneficial role for vitamin D receptor activators in modulating blood pressure in this population.

The prevalence of hyperprolactinemia (46.9%) was notably high. CKD patients have elevated prolactinemia when compared to the general population, and those with high hormone have higher cardiovascular mortality compared to those with normal prolactinemia.[21] An interesting study in patients undergoing endarterectomy found that both fibrotic layer and atherosclerotic plaque macrophages had Prolactin(PRL) receptors. In the same study, it was also shown that PRL receptor expression was associated with the atherosclerotic lesion stage—more unstable plaques showed higher receptor expression. Thus, the study raised the hypothesis that PRL has a modulatory effect on atherogenesis.[22] A cohort study evaluating prolactinemia and incidence of cardiovascular risk found each 5 mg/dL PRL increase in men, even at normal levels, was associated with significant increase in hypertension and DM.[23] The positive response to cabergoline, a dopamine agonist, in our study suggests this may be an under-investigated and treatable secondary factor in a subset of patients with rHTN and CKD.

The low prevalence of renal artery stenosis (3.1%) is consistent with modern cohorts of rHTN, where classic fibromuscular dysplasia and atherosclerotic renovascular disease are found in a minority of cases, though they remain critical to identify.[24]

The presence of five non-responders is instructive. The two patients with renal artery stenosis who did not respond likely require more specific vascular interventions, such as angioplasty or stenting, underscoring that while medical therapy is foundational, some etiologies demand mechanical intervention.[24] The two patients with no identifiable cause may represent cases of true, multifactorial resistance, potentially related to undiscovered genetic factors, profound volume overload, or non-adherence. The single patient with a limited response despite hyperuricemia treatment highlights that individual patient factors and the multifactorial nature of rHTN can modulate the response to any single intervention.

Conclusion

Hyperuricemia and secondary hyperparathyroidism are the most common factors associated with rHTN in our CKD population. A systematic workup and targeted treatment alongside an optimized conventional regimen can lead to dramatic improvements in BP control. We recommend incorporating this protocol into standard clinical practice.

Limitations: This is a single-center observational study without a control group. Long-term outcomes require further investigation.

Acknowledgement

The authors acknowledge the support of the Department of Nephrology, KYAMCH, and thank the patients who participated in this study.

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