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Original Article

Resistant Hypertension in Chronic Kidney Disease Patients and Associated Risk Factors; A Single Tertiary Care Hospital Experience

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ABSTRACT

***Objective*:** To study the frequency of resistant hypertension in chronic kidney disease patients in our population and to analyse associated risk factors contributing to this problem.

Study Design: Cross-sectional study.

***Place and Duration of Study*:** Combined Military Hospital, Multan Pakistan from Jun to Dec 2022.

***Methodology*:** The study included all patients older than 19 who were already diagnosed with hypertension and CKD and were visiting for the usual routine check-up in the Medical/Nephrology OPD.

***Results*:** A total of 325 patients suffering from CKD were included in the study, including 226(69.5%) males and 99(30.5%) females. The mean age of study participants was 56.54±7.15 years. Mean systolic blood pressure was 140.9±19.5 mmHg, whereas mean diastolic blood pressure was 85.12±9.1 mmHg. The average BMI of the participants was measured to be 24.96±4.2 m2/kg. The average/mean eGFR of the case-study participants was calculated to be 47.80±11.6 ml/min. Out of the 325 patients, 141(43.4%) were suffering from resistant hypertension.

***Conclusion*:** The frequency of resistant hypertension in CKD patients who have a positive genealogy of hypertension and associated risk factors of diabetes mellitus and hyperlipidaemia is considerable. Worsening of CKD also increases the proportion of treatment-resistant hypertension in hypertensive patients.

Keywords: Body mass index, chronic kidney disease (CKD), diabetes mellitus, resistant hypertension.

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INTRODUCTION

The most common chronic disease in developed societies is hypertension, which affects approximately 25% of adults in our community. A linear correlation between high blood pressure (BP) and cardiovascular disease and renal events is presented.[1] Resistant hypertension (RH) is defined as blood pressures (BPs) above standard value (145/90mmHg for the general population and 130/80mmHg for those with diabetes or CKD),[2] regardless of taking at least three optimally dosed antihypertensive medications, out of which one is a diuretic. In accordance with the current definition, a patient who achieves target BP by using four or more drugs is also considered resistant.[3]

The effects of CKD extend beyond the kidneys. A decreased renal function, for example, causes hypertension, which, in conjunction with other conditions, can lead to left ventricular hypertrophy (LVH) and a disorder that ultimately leads to heart failure.[4,5] Chronic kidney disease (CKD) patients are highly vulnerable to resistant hypertension, and RH can result in other associated comorbidities. CKD can be defined as pathologies of the kidney'sanatomy or physiology, present for more than three months, affecting human health, and classified according to the causative agent, estimated glomerular filtration rate (GFR), and proteinuriacategory.[6]

Although resistant hypertension occurs in CKD at a high prevalence, the cause is unclear. CKD patients are recommended to maintain a blood pressure target of 125/80 mm Hg.[7] Due to escalated therapeutic care by the nephrologist, the frequency of RH increases significantly after the first six months.[8]

Resistant hypertension is affected by many factors associated with chronic kidney disease, including arterial senescent and autonomic disorder. As a result of chronic kidney disease, uncontrolled (especially systolic) hypertension occurs due to oedema and fluid retention, sleep disturbances, inflexible arteries, increased renin-angiotensin activities, progressive arteriosclerosis, autonomic disorders, non-functional baroreflexes, Ambulatory blood pressure monitoring (ABPM), etc.[9,10]

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Hypertensive individuals with CKD frequently suffer from RH. Nevertheless, no findings or case studies have monitored the risk factors associated with RH in hypertensive CKD populations. We must realise this relationship to avoid choosing suitable antihypertensive agents, such as diuretics or doses not adapted to kidney function. Considering that resistant hypertension in patients with chronic kidney disease (CKD) needs to be documented and understood, we designed our study to add more data to the existing database. The objective of this study is to study the frequency of resistant hypertension in CKD patients in our population and to analyse associated risk factors contributing to this problem.

METHODOLOGY

The cross-sectional study was conducted at Combined Military Hospital, Multan Pakistan, from June to December 2022 after approval was obtained from the Institutional Review Board (IRB) (Reference number 74/2023). The sample size was calculated using a WHO calculator, keeping the prevalence of Resistant hypertension among treated hypertensive patients at 30% in various population.[4] Sampling was done using the nonprobability consecutive sampling technique.

Inclusion Criteria: Patients of either gender older than 18 who were already diagnosed with hypertension and CKD and visiting for the usual routine check-up in the Medical/Nephrology Outpatient department were included.

Exclusion Criteria: The study excluded patients with non-renal secondary causes of hypertension (e.g., endocrinopathies, coarctation of the aorta, drug-induced hypertension, pregnancy), acute kidney injury, and patients on renal replacement therapy (dialysis/transplant).

Treatment-resistant hypertension (RH) was defined as blood pressure that exceeds target values (>140/90) despite the best possible regimen consisting of three antihypertensive drugs of different classes, where one should ideally be a diuretic. BP was checked by a physician using a mercury sphygmomanometer after 5 minutes of complete rest from the right hand. The mean of two readings (5 minutes apart) was recorded.

Chronic kidney disease was defined as eGFR <60ml/min for over three months. eGFR was calculated using the Kidney Disease Improving Global Outcome (KDIGO), which recommended the CKD epidemiology collaboration equation (creatinine-based).[11] Serum creatinine was checked from the last lab report within one month of the current patient encounter. A detailed history and physical exam were performed, and relevant data was filled out in a structured proforma.

For this study, all data entry and analyses were done using the IBM Statistical Package for Social Sciences (SPSS), version 24 for Windows. Frequencies with percentages were calculated for all categorical variables. Mean and standard deviation were calculated for continuous variables. One-way ANOVA was applied after grouping the study participants based on risk factors, CKD stages and comorbid conditions to determine the difference in mean values of systolic, diastolic pressure, and BMI of study participants. Independent sample t-test was applied on the systolic, diastolic blood pressures, and BMI of study participants based on the presence or absence of a family history of hypertension in a first-degree relative.

RESULTS

A total of 325 patients suffering from CKD were included in the study, of which 226(69.5%) were males and 99(30.5%) were females. The mean age of study participants was 56.54±7.15 years. Mean systolic blood pressure was 140.9±19.5 mmHg, whereas mean diastolic blood pressure was 85.12±9.1 mmHg. The mean BMI of the study participants was measured to be 24.96±4.2 m2/kg. The mean eGFR of the study participants was calculated to be 47.80±11.6 ml/min. The majority of the study individuals, 286(88%), were married. Table-I shows the frequency of other factors associated with the study participants that may lead to the cause of hypertension**.**

Out of the 325 patients, 141(43.4%) were suffering from resistant hypertension. As can be seen from the Figure, although there were a greater number of total patients with resistant and non-resistant hypertension in Stage G3a and G3b, there was an increased proportion of cases of resistant hypertension in patients of Stage G4 and Stage G5 CKD as compared to the number of cases of non-resistant hypertension in these stages.

As shown in Table-II, there was a statistically significant difference in means of systolic, diastolic pressures, and BMI of study participants based on their comorbid conditions, CKD Stages, and associated risk factors of diabetes mellitus and hyperlipidaemia as p-value < 0.05. Independent sample t-test was

applied on the systolic, diastolic blood pressures, and BMI of study participants based on the presence or absence of a family history of hypertension in a first-degree relative.

Table-I: Frequency of Different Factors Leading to the Cause of Hypertension (n=325)

Characteristics		n (%)
Drugs	None	99(30.5%)
	Steroids	118(36.3%)
	Pain Killers (NSAIDs, Acetaminophen, Tramadol)	108(33.2%)
Co-morbids	None	164(50.5%)
	Diabetes Mellitus	84(25.8%)
	Hyperlipidemia	63(19.4%)
	Diabetes Mellitus and Hyperlipidemia	14(4.3%)
Risk Factors	None	120(36.9%)
	Dietary Non-Compliance	122(37.5%)
	Smoking	76(23.4%)
	Alcohol	7(2.2%)
Family History	No History of Hypertension	140(43.1%)
	History of Hypertension (1stdegree relative)	185(56.9%)
Chronic Kidney Disease Stages	Stage G3a	222(68.3%)
	Stage G3b	71(21.8%)
	Stage G4	13(4.0%)
	Stage G5	19(5.8%)

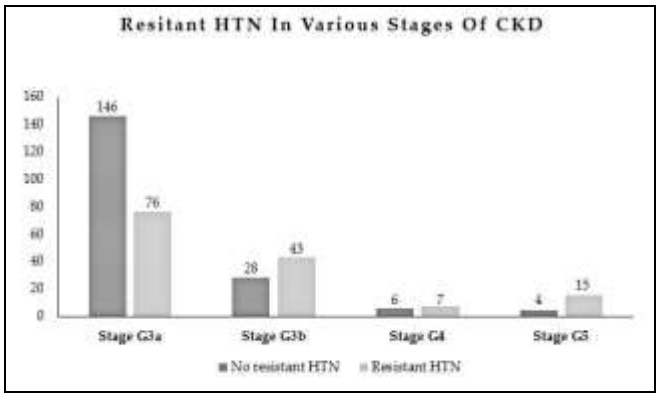

Figure: Distribution of patients according to resistant Hypertension in various groups of Chronic Kidney Disease (n=325)

DISCUSSION

A combination of factors contributes to RH in patients with CKD, including sodium retention, increased renin-angiotensin system activity, and increased sympathetic nervous system activity.[11,12] In the context of resistant hypertension, chronic kidney disease is the most frequent factor or comorbidity.[13] CKD is associated with an impaired prognosis in patients with resistant hypertension, and resistant hypertension is associated with an increased prevalence in patients with chronic kidney disease.[14]

In the current study, it was evident from our results that there was a significant difference in systolic and diastolic blood pressures of patients who had higher BMI compared to those whose BMI was within normal limits. Obesity has always been associated very strongly with resistant hypertension, which was apparent in the results of successive NHANES surveys that showed BMI ≥ 30 was independently related to treatment-resistant hypertension.[15] Similar findings were apparent in another study conducted by Calhoun *et al.*, which showed that obesity is one of the most critical risk factors of uncontrolled hypertension, and hypertension would get worse as the patient increases in weight.[16]

Similarly, in our study, it was clearly shown that there was a significant difference in means of systolic and diastolic blood pressures in patients with associated risk factors of DM and hyperlipidemia. This was in accordance with another study conducted by Carey *et al.*, which showed there was an increased prevalence of treatment-resistant hypertension in patients with Diabetes Mellitus as compared to those who did not have DM.[17] Our study showed that the proportion of patients with resistant hypertension increased with the worsening of CKD stages. This was in accordance with another study which showed an increased prevalence of resistant hypertension with CKD while also exhibiting the pattern of worsening chronic kidney disease leading to an increased frequency of resistant hypertension.[18] Our study showed statistical differences in mean systolic and diastolic blood pressures and BMI among patients who had a positive family history of hypertension in first-degree relatives as compared to the patients who did not have any such family history. In contrast to our findings, there was no significant difference in means of blood pressure among patients of resistant hypertension based on their age, gender, BMI, or even comorbid conditions in a previous study.[19] Our study results have clearly shown an association of risk factors like family history, other chronic diseases like DM, and high BMI with increased frequency of resistant hypertension in CKD patients.

LIMITATIONS OF THE STUDY

The study was conducted at a single centre with a single ethnic group. A more widespread study population needs to be included for a further and more comprehensive analysis of the association between resistant hypertension and CKD patients.

Table-II: Mean difference in Blood Pressure and Body Mass Index in the Groups of Study Participants (n=325)

Parameters	Risk factors				*p*-value
	None (n=120)	**Dietary non compliance (n=122)**	**Smoking (n=76)**	**Alcohol (n=7)**	
Body Mass Index	23.23±3.33	26.49±2.51	25.25±6.48	25.00±0.01	< 0.001
Systolic Blood pressure	126.40±8.16	145.64±18.13	154.63±20.04	162.00±0.02	< 0.001
Diastolic Blood pressure	79.45±7.86	87.84±8.65	90.20±6.85	80.00±0.01	< 0.001
	Co-morbids				
	None (n=164)	Diabetes Mellitus (n=84)	Hyperlipidaemia (n=63)	Both Diabetes Mellitus and Hyperlipidaemia (n=14)	*p*-value
Body Mass Index	24.05±3.59	26.84±2.14	24.41±6.84	26.90±0.10	< 0.001
Systolic Blood pressure	129.12±12.94	150.67±10.14	147.89±16.68	191.00±9.34	< 0.001
Diastolic Blood pressure	80.51±8.29	89.00±6.19	89.22±7.73	97.50±7.78	< 0.001
	Chronic Kidney Disease Stages				
	Stage G3a (n=222)	Stage G3b (n=71)	Stage G4 (n=13)	Stage G5 (n=19)	
Body Mass Index	24.17±4.62	27.43±2.12	26.91±0.10	23.74±3.49	< 0.001
Systolic Blood pressure	136.83±13.68	145.13±25.43	164.46±19.72	158.11±28.04	< 0.001
Diastolic Blood pressure	83.78±9.25	87.14±7.46	90.00±0.02	89.89±11.98	0.001

Table III: Of Blood Pressure and BMI based on Family History (n=325)

	Family History	Mean±SD	*p*-value
Systolic Blood Pressure (mmHg)	No history of Hypertension	131.84±10.70	<0.001
	Positive history of Hypertension	147.74±27.68	
Diastolic Blood Pressure (mmHg)	No history of Hypertension	79.12±7.58	<0.001
	Positive history of Hypertension	89.56±7.44	
Body Mass Index (m2/kg)	No history of Hypertension	24.32±3.47	0.014
	Positive history of Hypertension	25.44±4.71	

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CONCLUSIONS

There is a greater frequency of resistant hypertension in CKD patients who have a positive family history of hypertension and associated risk factors of diabetes mellitus and hyperlipidaemia. Worsening of CKD also increases the proportion of development-resistant hypertension in hypertensive patients.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MW & FI: Data acquisition, data analysis, critical review, approval of the final version to be published.

GF & MZ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AS & ARS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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