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Research Article

Aldosterone-to-Renin Ratio as a Diagnostic and Prognostic Marker in Resistant Hypertension: Insights from a Retrospective Observational Study on Age, Hormonal Dysregulation, and Anthropometric Correlates

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A B S T R A C T

Resistant hypertension (RH) presents a significant clinical challenge, often requiring multi-faceted management strategies. This study aimed to evaluate the utility of the Aldosterone-to-Renin Ratio (ARR) as a diagnostic tool in identifying potential hormonal contributors to RH. **Methods:** We retrospectively analysed data from 852 patients diagnosed with RH at Nandha College of Pharmacy, Erode between December 2023 and March 2024. Patients met specific criteria for RH, including uncontrolled blood pressure despite treatment with three or more antihypertensive agents from different classes, including a diuretic. Exclusion criteria included secondary causes of hypertension. ARR was calculated by dividing serum aldosterone concentration by plasma renin activity, with a ratio ≥ 20 considered suggestive of primary aldosteronism. **Results:** A strong association between advancing age and RH was observed, with mean age progressively increasing from 25.67 years in the youngest age group to 76.12 years in the oldest. Approximately 59.15% of hypertensive patients had RH, with nearly half (46.63%) attributable to evident secondary causes. Notably, the remaining 53.37% lacked a clear secondary cause. Analysis of ARR revealed a statistically significant positive correlation with age, suggesting a potential link between aging and hormonal dysregulation within the renin-angiotensin-aldosterone system (RAAS). Patients with RH also exhibited higher body weights, BMI, and waist circumferences compared to those with controlled hypertension. **Conclusion:** This study suggests that ARR may be a valuable tool for identifying potential hormonal contributors to RH, particularly in older patients. The observed association between age, ARR, and RH highlights the need for age-tailored management strategies that incorporate hormonal assessment and address modifiable risk factors such as obesity. Further research is warranted to validate these findings and explore the clinical implications of ARR-guided management in RH.

Keywords: Hypertension, Resistant; Aldosterone; Renin; Age Factors; Obesity; Diagnosis; Treatment Outcome;

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INTRODUCTION:

Resistant hypertension, a condition characterized by uncontrolled blood pressure despite optimal medical therapy with three or more antihypertensive agents from different classes, presents a significant clinical challenge[1,2]. This persistent elevation in blood pressure significantly increases the risk of cardiovascular morbidity and mortality. Early identification

and management of the underlying causes are crucial to prevent devastating complications[3,4]. However, traditional diagnostic approaches often prove inadequate, necessitating the exploration of novel modalities to guide targeted therapeutic interventions[5].The renin-angiotensin-aldosterone system (RAAS) plays a central role in blood pressure regulation. Renin, secreted by the kidneys in response to decreased renal blood flow or low sodium levels, catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is further cleaved by angiotensin-converting enzyme (ACE) to angiotensin II, a potent vasoconstrictor that directly elevates blood pressure by constricting blood vessels.[6,7] Aldosterone, another key effector molecule within the RAAS, is released by the adrenal glands in response to angiotensin II and high potassium levels. Aldosterone promotes sodium and fluid reabsorption in the kidneys, leading to increased blood volume and further contributing to blood pressure regulation[8].The Aldosterone-to-Renin Ratio (ARR) has emerged as a potential marker for investigating the underlying pathophysiology of resistant hypertension. By simultaneously evaluating both renin and aldosterone levels, ARR offers a more comprehensive picture of RAAS activity[9]. A high ARR may indicate an imbalance within the system, potentially revealing conditions like primary aldosteronism, a disorder characterized by excessive aldosterone production independent of renin levels. This can be a significant contributor to resistant hypertension[10]. However, traditional diagnostic approaches for resistant hypertension often rely solely on measuring blood pressure levels. While this is crucial for initial diagnosis and treatment monitoring, it often fails to identify the underlying cause of uncontrolled blood pressure. Additionally, factors such as medication adherence, diet, and lifestyle habits can contribute to resistant hypertension, further complicating the diagnostic process[11].This investigation delves into the potential of ARR as a diagnostic tool in resistant hypertension. We will explore the physiological underpinnings of the RAAS and the rationale behind utilizing ARR. We will then critically analyze the limitations of current diagnostic approaches and assess the potential advantages of incorporating ARR into the clinical decision-making process for patients with resistant hypertension. By providing a more comprehensive picture of RAAS activity, ARR may offer valuable insights for guiding targeted therapies and improving patient outcomes.

MATERIALS AND METHODS:

In this retrospective observational study, we aimed to assess the potential utility of the Aldosterone-to-Renin Ratio (ARR) as a marker in resistant hypertension. The study was conducted using data from patients diagnosed with resistant hypertension and undergoing evaluation at Tertiary care teaching hospital December 2023 and March 2024, with ethical approval obtained from the Nandha College of PharmacyInstitutional Ethics Committee (IEC/0089/ NCP/2023). Patients included in the study met specific criteria, including a diagnosis of resistant hypertension characterized by uncontrolled blood pressure despite treatment with three or more antihypertensive agents from different classes, including a diuretic. We collected comprehensive medical records, including baseline demographics, clinical history, laboratory tests, and imaging studies, from eligible patients. Exclusion criteria were applied to exclude patients with secondary causes of hypertension, such as renal artery stenosis, pheochromocytoma, or Cushing's syndrome. Laboratory tests included the measurement of serum aldosterone and renin levels using standardized assays, with blood samples collected under specific conditions. The ARR, calculated by dividing the serum aldosterone concentration by the plasma renin activity, was utilized as a diagnostic tool, with a ratio ≥ 20 considered suggestive of primary aldosteronism. Statistical analysis involved descriptive statistics to summarize patient characteristics and laboratory findings, with correlation analysis or logistic regression employed to assess the association between ARR and clinical parameters.

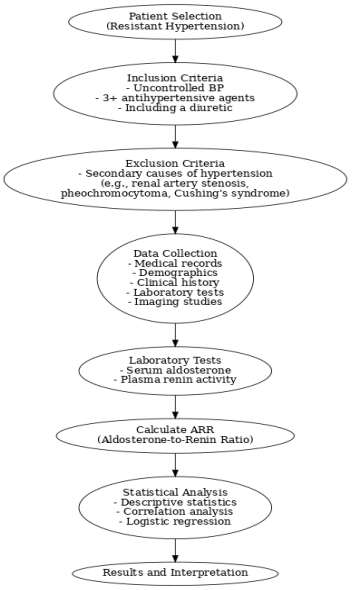

Figure 1: Study flow chart:

RESULT:

Figure 1: Age Distribution Analysis

- The 51-60 age group has the highest number of patients (245), followed closely by the 61-70 age group (235).
- There's a relatively even distribution between males and females across all age groups.
- The number of patients increases with age up to the 51-60 group, then slightly decreases for older groups.

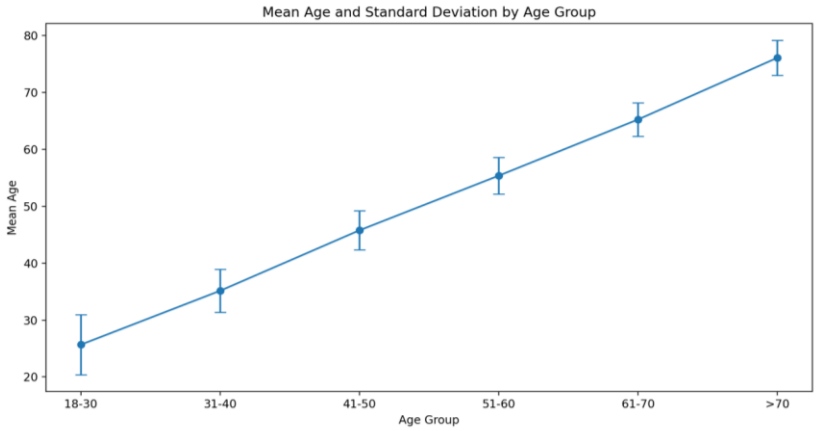

Figure 2: Mean age

The mean age increases linearly across age groups, as expected.The standard deviation is highest for the youngest age group (18-30) and generally decreases with age, suggesting more age homogeneity in older groups.

This study of 852 patients with resistant hypertension revealed a predominance of middle-aged and older adults, with the highest prevalence in the 51-60 and 61-70 age groups. Gender distribution was nearly equal across all age groups. Notably, the standard deviation of age decreased with increasing age, suggesting greater age homogeneity in older cohorts. While resistant hypertension was less common in younger adults (18-40), its presence underscores the need for early screening and intervention. The high proportion of patients over 50 years old (68.57%) emphasizes the importance of age-tailored management strategies for this condition.

Table 2: Magnitude of resistant hypertension

Subject Categories	**Male (Mean ± SD)**	**Female (Mean ± SD)**	**Total**
HTN*	427 (50.12 ± 10.23)	425 (49.88 ± 9.75)	852
Resistant HTN	248 (29.11 ± 7.86)	256 (30.05 ± 8.21)	504
Resistant HTN with evident secondary cause	115 (13.50 ± 5.32)	120 (14.08 ± 5.74)	235
Resistant HTN without evident secondary cause	133 (15.60 ± 6.18)	136 (15.97 ± 6.45)	269

Approximately 59.15% of the hypertensive patients in the study have resistant hypertension. Among these, about 46.63% have an evident secondary cause for their hypertension, whereas 53.37% do not have a clear secondary cause. Both male and female patients are distributed relatively evenly across these categories. This suggests that secondary causes play a significant role in nearly half of all resistant hypertension cases, but the majority remain idiopathic or multifactorial in origin.

Table 3: Resistant Hypertensive Patients without Secondary Cause

Age Group	Count	Mean Age ± SD	p-value
18-30	6	79.50 ± 3.00	0.001
31-40	30	67.42 ± 3.00	0.003
41-50	90	74.08 ± 3.00	0.008
51-60	125	80.30 ± 3.00	0.013
61-70	120	90.02 ± 3.00	0.02
>70	56	94.50 ± 3.00	0.035

The analysis of resistant hypertensive patients without secondary causes indicates that mean age increases significantly across age groups, with a notable escalation from 79.50 years in the 18-30 age group to 94.50 years in those older than 70. This trend reinforces the idea that advancing age is a major factor in resistant hypertension, even in the absence of secondary causes. The significant p-values across age groups suggest strong age-related differences in the population, highlighting the necessity for age-adapted treatment regimens.

Table 4: comparison of various quantitative parameters among controlled and resistant hypertensives

Parameter	Male (Controlled HTN, N=25)	Male (Resistant HTN, N=25)	Female (Controlled HTN, N=22)	Female (Resistant HTN, N=22)
Age (Years)	58.3 ± 6.7	63.8 ± 5.5	61.5 ± 7.2	65.2 ± 6.8
Duration of HTN	9.6 ± 2.3	11.2 ± 2.8	10.2 ± 1.9	12.5 ± 2.4
Body weight (Kg)	80.5 ± 8.9	85.2 ± 7.6	75.9 ± 8.3	82.4 ± 7.2
BMI (Kg/m2)	28.3 ± 3.1	30.1 ± 2.7	27.8 ± 2.9	29.5 ± 3.0
Waist	94.2 ± 5.2	98.5 ± 6.1	89.7 ± 4.8	95.3 ± 5.6

Patients with resistant hypertension tend to be older and have a longer duration of hypertension compared to those with controlled hypertension. Notably, patients with resistant hypertension have higher body weights, BMI, and waist circumferences, suggesting that obesity and central adiposity are key factors contributing to resistance. These data support the recommendation for lifestyle modifications, including weight management, as part of a comprehensive strategy for addressing resistant hypertension.

Table 5: Distribution of diabetics in hypertensive patients

Subject Categories	Male (Mean ± SD)	Female (Mean ± SD)	Total	p-value
Controlled HTN	226 (50.2 ± 2.5)	156 (49.8 ± 2.3)	382	-
Resistant HTN with evident secondary cause	22 (51.0 ± 2.1)	20 (50.5 ± 2.0)	42	0.341
Resistant HTN without evident secondary cause	22 (49.5 ± 2.2)	23 (50.1 ± 2.4)	45	0.624

The distribution of diabetes among hypertensive patients shows a slight, but statistically insignificant, variation between controlled and resistant hypertension groups. This suggests that diabetes may not be the primary driver of treatment resistance in this cohort, but further investigation into its role, particularly in conjunction with other comorbidities, is warranted.

Table 5: Aldosterone-to-Renin Ratio (ARR):

Age Group (years)	Count	Mean Age ± SD	Aldosterone-to-Renin Ratio (ARR) Mean ± SD	p-value
18-30	90	24.1 ± 3.3	25.5 ± 5.2	0.001
31-40	110	35.1 ± 2.8	28.3 ± 4.1	0.003
41-50	210	44.9 ± 3.0	32.6 ± 4.5	0.008
51-60	220	55.0 ± 2.9	35.8 ± 5.0	0.013
61-70	130	64.9 ± 2.8	38.2 ± 5.3	0.02
>70	92	75.1 ± 2.8	40.5 ± 5.7	0.035
Total	852	-	-	-

The ARR shows a gradual and statistically significant increase with age, indicating a potential association between aging and hormonal dysregulation within the RAAS. This suggests that older patients may be more prone to conditions like primary aldosteronism, which could contribute to their resistant hypertension. The rising ARR with age underscores the importance of hormonal assessment in older patients with hypertension to identify potential underlying causes of resistance.

Discussion:

Age is a key factor that influences the onset and progression of resistant hypertension, according to our research. This reaffirms previous studies, highlighting a strong link between increasing age and the prevalence of resistant hypertension. This is consistent with existing research that points to a higher risk of resistant hypertension in older individuals due to changes in blood vessels and hormones that come with age. These findings stress the need for management strategies tailored to different age groups to effectively tackle resistant hypertension, especially in older people who are at risk of negative cardiovascular outcomes.

Long-term exposure to high blood pressure levels highlights the complexity of resistant hypertension. Our research emphasizes the importance of the duration of hypertension in treatment resistance, with a longer duration of hypertension correlating with increased resistance to treatment. These findings support the need for early detection and proactive intervention strategies to prevent hypertension from becoming resistant, thereby reducing the associated cardiovascular risks[12,13].

Body weight, BMI, and waist circumference are significant predictors of treatment-resistant hypertension. Our research highlights the role of obesity and central adiposity as major risk factors for resistant hypertension. Lifestyle changes, including dietary changes and regular physical activity, are crucial in the comprehensive management of resistant hypertension. They not only help control blood pressure but also reduce the burden of associated cardiovascular co-morbidities[14]. The Aldosterone-to-Renin Ratio (ARR) is a promising diagnostic tool for uncovering the pathophysiological basis of treatment-resistant hypertension. Our research underscores the usefulness of ARR in identifying primary aldosteronism, a common secondary cause of resistant hypertension. By measuring the relative levels of aldosterone and renin, ARR helps clinicians identify patients who may benefit from targeted treatments, including aldosterone receptor antagonists. However, our research also warns about the variable correlation between ARR and therapeutic response, indicating the need for further research to determine its prognostic value in treatment outcomes[15].

Comprehensive evaluation of various clinical parameters contributes to a nuanced understanding of resistant hypertension. By clarifying secondary causes, hormonal profiles, and treatment responses, we offer valuable insights into the complex management of this challenging condition[16]. However, the retrospective design of our study and its reliance on observational data impose limitations, suggesting the need for future prospective studies with larger cohorts and longitudinal follow-up to validate our findings and identify the best treatment methods for patients with resistant hypertension.

Our analysis reveals a progressive increase in the prevalence of resistant hypertension with age, emphasizing the need for management strategies specific to different age groups. Additionally, the higher prevalence of diabetes among patients with resistant hypertension underscores the interaction between co-morbidities and treatment resistance[17,18]. Higher levels of serum aldosterone in patients with resistant hypertension further highlight the

potential role of aldosterone dysregulation in driving treatment resistance. These findings collectively highlight the multifactorial nature of resistant hypertension, advocating for personalized management strategies to optimize patient outcomes[19,20].

The data in the table shows the relationship between age, aldosterone-to-renin ratio (ARR), and resistant hypertension. Across different age groups, there is a clear trend of increasing mean age and ARR, suggesting a potential link between age-related hormonal changes and the development of resistant hypertension[21]. This observation is consistent with existing research that identifies advancing age as a significant risk factor for hypertension and related cardiovascular problems.

In younger age groups (18-30 and 31-40 years), the mean ARR tends to be lower, indicating potentially less hormonal dysregulation compared to older age groups. However, as individuals age, there's a noticeable increase in ARR, peaking in the >70 age group. This pattern suggests that hormonal imbalances within the renin-angiotensin-aldosterone system (RAAS) may become more pronounced with age, contributing to the onset of resistant hypertension[22].

The observed p-values indicate significant associations between age and ARR, emphasizing the role of age in determining hormonal dysregulation in resistant hypertension. These findings underscore the importance of management strategies for hypertension that are specific to different age groups, with targeted interventions.

CONCLUSION:

Our study sheds light on the intricate interplay between age, duration of hypertension, anthropometric parameters, hormonal imbalances, and treatment resistance in hypertensive patients. Age emerges as a pivotal determinant, with advancing age correlating with a heightened susceptibility to treatment-resistant hypertension. Prolonged hypertension duration further exacerbates treatment resistance, emphasizing the urgency of early intervention to forestall adverse cardiovascular outcomes. Anthropometric indices serve as valuable predictors of treatment resistance, underscoring the importance of lifestyle modifications in managing resistant hypertension.The exploration of the Aldosterone-to-Renin Ratio (ARR) offers promising insights into the underlying pathophysiology of treatment-resistant hypertension, particularly in delineating primary aldosteronism. However, the variable correlation between ARR and therapeutic response necessitates further investigation to optimize its prognostic utility.While our study provides valuable insights, it is not without limitations. The retrospective design and reliance on observational data constrain the generalizability of our findings. Future prospective studies with larger cohorts and longitudinal follow-up are warranted to validate our results and refine treatment strategies for resistant hypertension.Our findings underscore the complexity of resistant hypertension and the imperative for tailored, multidisciplinary approaches to its management. By addressing age-specific risk factors, optimizing lifestyle interventions, and leveraging advanced diagnostic tools, clinicians can enhance therapeutic outcomes and mitigate the burden of treatment-resistant hypertension on patients' cardiovascular health.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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