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PREDICTORS OF RESISTANT HYPERTENSION IN ADULT AMONG IRAQI SAMPLE

[*1]Amer Ahmed Abdullah Al-Qaftan, [2]Duraid Khalil Ibrahim, [3]Abdulhadi Mohammed Tarkh

[1]M.B.Ch.B./F.I.B.M.S. (Internal Medicine).
[2]M.B.Ch.B./F.A.B.M.S. (Internal Medicine).
[3]M.B.Ch.B./F.A.B.M.S. (Internal Medicine).

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***Corresponding Author: Amer Ahmed Abdullah Al-Qaftan**

M.B.Ch.B./F.I.B.M.S. (Internal Medicine).

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ABSTRACT

Background: Resistant hypertension (RH) is a subtype of hypertension that makes it difficult to achieve blood pressure targets below 140/90 mmHg even using three anti-hypertensive drugs, including diuretics, or four anti-hypertensive medications. Although the exact cause is unknown, several factors contribute to the development of resistant hypertension. **Objectives:** To show the factors which predict resistant hypertension among adult patients within a sample of Iraqi patients. **Methods:** This is a cross-sectional study. Included adult patients aged more than 18 years old who had hypertension based on a history of prior diagnosis and therapy, blood pressure ≥ 140/90 mmHg on two to three office visits two weeks apart, home blood pressure readings >130/80 mmHg, or a single blood pressure reading of ≥180/110 mmHg. The study patients were assessed at the medical consultation clinic of Azadi Teaching Hospital from May 2024 to September 2025. Patients were divided into two groups based on blood pressure control: group I (controlled hypertension) included 200 patients who achieved blood pressure measurements < 140/90 on two visits, and group II (resistant hypertension) included 100 patients whose blood pressure measurement was ≥140/90 mmHg despite adhering to medications and taking three antihypertensive drugs on the optimal dose, including the diuretic. All patients who participated in the trial provided informed consent. **Results:** The mean age ± standard deviation of the study participants was 61.64 ± 9.12 years. Male gender represents 59.66 % of the study patients. Statistically significant different was found regarding excess salt intake (P value <0.001) and BMI (P value <0.001). Moreover, statistically significant difference was found with regard to presence of chronic kidney disease (P value <0.001) and obstructive sleep apnea (P value = 0.016). Furthermore, statistically significant difference found concerning drug intake of non-steroidal anti-inflammatory drugs intake (P value <0.001), diuretics (P value <0.001), angiotensin converting enzyme inhibitors (P value <0.001), calcium channel blockers (P value <0.001), and drug compliance history (P value <0.001). Additionally, statistically significant difference found concerning systolic blood pressure (P value <0.001), diastolic blood pressure (P value <0.001), serum creatinine (P value <0.001), and estimated-GFR (P value 0.033). Lastly, patients with resistant hypertension had statistically significant cardiac structural remodeling and functional abnormalities as shown by Echocardiography. **Conclusion:** Certain factors significantly associated with resistant hypertension. These factors are excess salt intake, obesity, chronic kidney disease, obstructive sleep apnea and cardiac structural remodeling and functional abnormalities. Clinician should keep in mind these factors when treating resistant hypertensive patients.

KEYWORDS: Blood pressure, Factors, High, Sustained.

1- INTRODUCTION

Hypertension (HTN) is a reversible clinical problem that contributes to increased morbidity and death globally.[1] Around half of deaths resulting from heart disease and stroke are attributed to hypertension, which is regarded as the most significant avoidable cause of cardiovascular disorders worldwide.[1-2] It causes 7.5 million deaths annually and affects almost 1.3 billion people.[3] Additionally, hypertension accounts for 57 million years of disability-adjusted life.[4]

The incidence of hypertension (HTN) has doubled globally despite advancements in efficient medical therapy, particularly in countries with low to middle incomes with inadequate blood pressure (BP) control.[5] The USA registry states that 24% of patients with hypertension are not under control, and 47% of adults have the condition. In the USA, the burdened cost was projected to be 131 billion dollars annually.[6]

Hypertension in persons aged 18 years or older is defined as systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg on the average of two or more readings recorded at two or more visits after initial screening, as per WHO/ISH recommendations and JNC7 guidelines.[7]

Hypertension is sometimes referred to as the "silent killer" due to the absence of visible signs. Hypertension can induce symptoms including headaches, dizziness, shortness of breath, chest discomfort, palpitations, and nosebleeds. High blood pressure is consistently linked to an increased risk of cardiovascular disease events, regardless of other risk factors.[8]

Every 20 mmHg increase in systolic blood pressure (SBP) or 10 mmHg increase in diastolic blood pressure (DBP) doubles the risk of cardiovascular disease for people aged 40 to 70.[9] Numerous studies demonstrate that high blood pressure can be exacerbated by a number of risk factors that raise the likelihood of heart attack, stroke, and renal failure; some of these risk factors are unmodifiable, such as age, sex, and family history, while modifiable risk factors include smoking, bad eating habits, alcohol abuse, physical inactivity, obesity, high cholesterol, and diabetes.[10-13]

Iraq, like other countries in the area, has seen an increase in noncommunicable diseases. According to national statistics, cardiovascular disorders remain the leading cause of death in Iraq. They are responsible for one-third of all deaths and 50% of morbidities.[14]

Resistant hypertension (RH) is a subtype of hypertension that makes it difficult to achieve blood pressure targets below 140/90 mmHg even using three anti-hypertensive drugs, including diuretics, or four anti-hypertensive medications. Patients with resistant hypertension (RH) are more likely to be older, obese, diabetic, and have a history of chronic renal disease compared to those without.[15-16] Although the exact cause is unknown, several factors contribute to the development of RH. These include increased sodium and fluid retention, sympathetic nervous system activity, aldosterone levels, and the renin-angiotensin system, which can cause arterial stiffness, myocardial fibrosis, and vascular remodeling.[17]

The aim of this study is to show the factors which predict resistant hypertension among adult patients within a sample of Iraqi patients.

2- PATIENT AND METHODS

This is a cross-sectional study. Included adult patients aged more than 18 years old who had hypertension based on a history of prior diagnosis and therapy, blood pressure ≥ 140/90 mmHg on two to three office visits two weeks apart, home blood pressure readings >130/80 mmHg, or a single blood pressure reading of ≥180/110 mmHg. The study patients were assessed at the medical consultation clinic of Azadi Teaching Hospital from May 2024 to September 2025.

Patients were divided into two groups based on blood pressure control: group I (controlled hypertension) included 200 patients who achieved blood pressure measurements < 140/90 on two visits, and group II (resistant hypertension) included 100 patients whose blood pressure measurement was ≥140/90 mmHg despite adhering to medications and taking three antihypertensive drugs on the optimal dose, including the diuretic. All patients who participated in the trial provided informed consent.

The questionnaire include information about the age, sex, smoking, diabetes, dyslipidemia, physical activity, excessive salt diet consumption (>5 g sodium per day), prior history of cardiovascular, cerebrovascular, chronic kidney, and peripheral arterial diseases, obstructive sleep apnea, family history of hypertension, and medication history (including antiplatelets, statins, chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) if taken more than three times per week, antidepressants, and corticosteroid drugs) were all taken. Additionally, a questionnaire was used at each appointment to evaluate the patient's adherence to prescribed medication and the dosage of antihypertensive medicines. Additionally, the patients' place of residence, level of education, marital state and occupation were asked. All patients underwent a physical examination, which included measurements of their weight, height, body mass index (BMI), heart rate, blood pressure. Blood pressure values at baseline were average during the second and third visits following the HTN diagnosis. All patients had laboratory tests, and an electrocardiogram (ECG) was performed at baseline, at the end of a year, and at any cardiovascular events.

All patients had transthoracic echocardiography utilizing the Vivid E9 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) with an M5S phased array

transducer (2.5-5.0 MHz) following the American Society of Echocardiography recommendations.[18] Left ventricular ejection fraction (LVEF), left atrial volume index (LAVI), peak velocity of mitral early diastole (E) and late diastole (A) waves, E/A ratio, average peak of early diastolic myocardial velocity of septal and lateral walls (E'), and E/E' ratio were measured using two-dimensional, M mode, and tissue Doppler modalities. The same machine also measured carotid intimal media thickness (IMT) at 1 cm from the common carotid artery bifurcation using a 9L-D linear transducer (2.4-10 MHz).

Prior to enrolling patients, secondary causes of hypertension such as renal artery stenosis, aortic coarctation, and endocrine disorders were ruled out. Compliance with prescribed medication and doses was assessed during the initial visit, with additional follow-ups at 2nd and 4th weeks, 3, 6, 9, and 12 months. Patients who did not comply or adhere to their medicine were excluded from the study. Patients who were missing during follow-ups and had an acute systemic disease, such as COVID-19, were also excluded from the study. We employed home and office blood pressure monitoring to rule out the white-coat effect, and individuals with white coat hypertension were removed from the study. At each appointment, blood pressure and heart rate were monitored, as well as clinical assessments to record and assess the incidence of any severe cardiovascular events. The study's primary outcome was the occurrence of death or major adverse cardiovascular events (MACE), which included cardiac events (myocardial infarction, unstable angina, acute heart failure, and new-onset atrial fibrillation), cerebral events (stroke, transient ischemic attack, and cerebral hemorrhage), resuscitation after cardiac arrest, and acute peripheral vascular ischemia.

The Kolmogorov-Smirnoff test was used to assess parameter normality, while the. Quantitative data was presented as mean ± standard deviation. Qualitative data were presented as frequencies and percentages. The student's t-test was used to determine the statistical significance between the two groups in the quantitative data. The chi-square (X2) test was employed to evaluate two qualitative factors.

A two-sided P value greater than 0.05 was considered statistically significant.

3-RESULTS

The study included 300 patients, distributed into 2 groups (200 patients with controlled hypertension and 100 patients failed to controlled their hypertension). The mean age ± standard deviation of the study participants was 61.64 ± 9.12 years. Male gender represents 59.66 % of the study patients. No statistically significant difference between the two groups regarding their gender (P value = 0.737), smoking state (P value = 0.429), residence (P value =0.592), occupation (P value = 0.729), family history (P value = 0.812), physical activity (P value = 0.789), physical activity (P value =0.810) and age (P value = 0.483), while statistically significant different was found regarding excess salt intake (P value <0.001) and BMI (P value <0.001). As shown in table 1.

Table 1: Comparison between patients with controlled and resistant hypertension regarding their sociodemographic and anthropometric parameters (number = 300).

Variable	Controlled hypertension = 200		Resistant hypertension = 100		P value
	Number	Percent	Number	Percent	
Gender:					
-Male	110	55%	57	57%	0.737
-Female	90	45%	43	43%	
Smoking:					
- Yes	81	40.5%	39	39%	0.429
- No	119	59.5%	61	61%	
Residence:					
-Urban	121	60.5%	53	53%	0.592
-Rural	79	39.5%	47	47%	
Occupation:					
-Employee	113	56.5%	54	54%	0.729
-Unemployed	87	43.5%	46	46%	
Family history:					
-Positive	65	32.5%	34	34%	0.812
-Negative	135	67.5%	66	66%	
Physical activity:					
-Good	94	47%	54	44%	0.789
-Sedentary	106	53%	46	56%	
Marital status:					
- Married	131	65.5%	63	63%	
- Divorced	22	11%	13	13%	0.810
- Widow	26	13%	13	13%	

- Unmarried	21	10.5%	11	11%	
Excess salty diet: -Yes -No	 72 138	 36% 64%	 53 47	 53% 47%	**<0.001**
Mean age ± standard deviation	62.19 ± 10.32		60.26 ± 9.94		0.483
Body mass index, mean ± standard deviation	29.11 ± 4.23		33.69 ± 3.46		**<0.001**

Table 2 shows comparison between the study groups regarding their past medical history. No statistically significant difference between the two groups with regard the presence of diabetes (P value = 0.639), dyslipidemia (P value = 0.931), cardiovascular disease (P value = 0.519), cerebrovascular diseases (P value = 0.722), atrial fibrillation (0.389). While statistically significant difference was found with regard to presence of chronic kidney disease (P value <0.001) and obstructive sleep apnea (P value = 0.016).

Table 2: Comparison between patients with controlled and resistant hypertension regarding their past medical history (number = 300).

Variable	Controlled hypertension = 200		Resistant hypertension = 100		P value
	Number	Percent	Number	Percent	
Presence of diabetes:	65	32.5%	31	31%	0.639
Presence of dyslipidemia:	69	34.5%	35	35%	0.931
Presence of cardiovascular disease:	37	18.5%	21	21%	0.519
Presence of chronic kidney diseases:	31	15.5%	41	41%	<0.001
Presence of cerebrovascular diseases:	17	8.5%	12	12%	0.722
Presence of peripheral vascular diseases:	23	11.5%	14	14%	0.821
Presence of obstructive sleep apnea:	14	7%	19	19%	0.016
Presence of atrial fibrillation:	23	11.5%	15	15%	0.389

Table 3 shows comparison between the study groups regarding their drug history. No statistically significant difference between them regarding intake history of antidepressant drugs (P value = 0.391), antiplatelet drugs (0.720), corticosteroid drugs (P value = 0.251), cholesterol lowering drugs (P value 0.899) and beta-blocker (P value = 0.282). While statistically significant difference found concerning drug intake of non-steroidal anti-inflammatory drugs intake (P value <0.001), diuretics (P value <0.001), angiotensin converting enzyme inhibitors (P value <0.001), calcium channel blockers (P value <0.001), and drug compliance history (P value <0.001).

Table 3: Comparison between patients with controlled and resistant hypertension regarding their drug history (number = 300).

Variable	Controlled hypertension = 200		Resistant hypertension = 100		P value
	Number	Percent	Number	Percent	
Non-steroidal anti-inflammatory drugs use, number (%):	37	18.5%	31	31%	<0.001
Anti-depressant drugs use, number (%):	12	6%	5	5%	0.391
Anti-platelet drugs use, number (%):	83	41.5%	43	43%	0.720
Corticosteroid drugs use, number (%):	6	3%	7	7%	0.251
Cholesterol lowering drugs use, number (%):	102	51%	48	48%	0.899
Beta-blocker drugs use, number (%):	131	65.5%	68	68%	0.282
Diuretic drugs use, number (%):	142	71%	100	100%	<0.001
Angiotensin converting enzyme inhibitors or angiotensin receptor blockers drugs use, number (%):	119	59.%	91	91%	<0.001
Calcium channel blocker drugs use, number (%):	124	62%	100	100%	<0.001
Poor drug compliance, number (%):	46	23%	41	41%	<0.001

Table 4 shows comparison between the study groups regarding their different physical and laboratory findings. No statistically significant difference between them regarding heart rate (P value = 0.321), Fasting plasma glucose (0.293), 2-h post prandial plasma glucose (P value = 0.381), HbA1c (P value 0.871), Hemoglobin (P value = 0.921), TSH (P value 0.729), Total cholesterol (P value = 0.462), Triglycerides (P value = 0.419), LDL (P

value = 0.919), HDL (P value = 0.721), Albuminuria (P value = 0.632), serum potassium (P value = 0.946) and uric acid (P value = 0.620). While statistically significant difference found concerning systolic blood pressure (P value <0.001), diastolic blood pressure (P value <0.001), serum creatinine (P value <0.001), and estimated-GFR (P value 0.033).

Table 4: Comparison between patients with controlled and resistant hypertension regarding their different physical and laboratory findings (number = 300).

Variable	Controlled hypertension = 200	Resistant hypertension = 100	P value
Heart rate (beat per minute), mean ± standard deviation	78.21± 13.31	80.21 ± 14.26	0.321
Systolic blood pressure (mmHg), mean ± standard deviation	131.3 ± 11.1	158.7 ± 10.6	<0.001
Diastolic blood pressure (mmHg), mean ± standard deviation	80.02 ± 8.88	97.21 ± 8.30	<0.001
Fasting plasma glucose (mg/dl), mean ± standard deviation	116.30 ± 15.31	115.83 ± 14.77	0.293
2-h post prandial plasma glucose (mg/dl), mean ± standard deviation	167.6 ± 32.4	168.3 ± 30.9	0.381
HbA1c %, mean ± standard deviation	6.54 ± 1.61	6.44 ± 1.67	0.871
Hemoglobin, g/dl, mean ± standard deviation	12.23 ± 1.09	12.55 ± 1.11	0.921
TSH, mean ± standard deviation	4.36 ± 1.86	4.39 ± 1.82	0.729
Total cholesterol (mg/dl), mean ± standard deviation	241.8 ± 35.3	239.8 ± 36.2	0.462
Triglycerides (mg/dl), mean ± standard deviation	161.8 ± 34.7	163.1 ± 33.5	0.419
LDL (mg/dl), mean ± standard deviation	139.33 ± 27.7	139.72 ± 27.3	0.919
HDL (mg/dl), mean ± standard deviation	43.28 ± 7.11	41.98 ± 7.12	0.721
Serum creatinine (mg/dl), mean ± standard deviation	1.09 ± 0.48	1.43± 0.49	<0.001
e-GFR (mL/min/1.73 m^2), mean ± standard deviation	92.15 ± 17.70	83.05 ± 17.31	0.033
Albuminuria (mg/g), mean ± standard deviation	28.42 ± 5.38	29.31 ± 5.33	0.632
Serum potassium (mmol/L), mean ± standard deviation	4.41 ± 0.72	4.43 ± 0.73	0.946
Uric acid (mg/dl), mean ± standard deviation	5.61 ± 1.25	5.89 ± 1.27	0.620

Table 5 shows comparison between the study groups regarding their Echocardiography findings. No statistically significant difference between them regarding LVEDD (P value = 0.971), LVESD (0.099), LVEF (P value = 0.592), LVH (P value 0.803), E/A (P value = 0.981) and Carotid IMT (P value 0.480). While statistically significant difference found concerning E/E' (P value = 0.021), LAVI (P value = 0.011) and LVMI (P value = 0.024).

Table 5: Comparison between patients with controlled and resistant hypertension regarding their Echo findings (number = 300).

Variable	Controlled hypertension = 200	Resistant hypertension = 100	P value
LVEDD (cm), mean ± standard deviation	5.71 ± 0.57	5.74 ± 0.55	0.971
LVESD (cm), mean ± standard deviation	3.92 ± 0.45	3.94 ± 0.43	0.099
LVEF, (%), mean ± standard deviation	62.49 ± 3.84	62.66 ± 3.88	0.529
LVH, number (%)	89 (44.5%)	46 (46%)	0.803
E/A, mean ± standard deviation	1.34 ± 0.44	1.35 ± 0.44	0.981
E/E', mean ± standard deviation	11.7 ± 1.39	12.1 ± 1.04	0.021
LAVI (ml/m^2) mean ± standard deviation	33.3 ± 1.76	34.6 ± 2.98	0.011
LVMI (gr/m^2), mean ± standard deviation	113.27 ± 27.34	125.29 ± 25.1	0.024
Carotid IMT (mm) mean ± standard deviation	0.98 ± 0.14	0.95 ± 0.17	0.480

4-DISCUSSION

In this study the mean age of patients with resistant hypertension was not statistically significant different from patients with controlled hypertension.[19] This contrasts with other studies where a statistically significant age difference was observed, with resistant hypertension patients being older on average. The result may indicate that other risk factors or comorbidities played a larger role in determining resistance to treatment in this particular patient group. The same thing was found for patients' gender, which is found to be not significant as well, this finding contrasts with other study, however, Kumara et al had comparable results,[19] suggesting the findings can vary between studies depending on the population and other factors being examined.

Excess salt intake found in this study to be significant factor for resistance hypertension, which runs with Khalfallah et al study findings.[6] So, it's recommended to limit sodium intake to less than 2 grams per day (equivalent to 5 grams of salt) for the general population, with a particular emphasis on reduction for those with resistant hypertension. Moreover, patients with resistant hypertension found to have statistically significant obesity. Other studies found, obesity is a major risk factor for both the development of hypertension and the difficulty in achieving blood pressure control.[6-19] Multiple complex mechanisms link obesity to resistant hypertension, including; activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system hyperactivity, insulin resistance and systemic inflammation, increased intravascular volume and impaired renal sodium handling.

Chronic kidney disease shown in the current study significantly affect patients with resistant hypertension. The relationship between the two conditions is bidirectional; hypertension can cause CKD, and CKD can worsen hypertension, creating a feedback loop of damage. Shulman R and Cohen showed comparable result0s.[21] The same for obstructive sleep apnea, the study found it significantly higher among patients with resistant hypertension. The mechanisms include increased sympathetic nervous system activity, arterial stiffness, and endothelial dysfunction, similar to Oscullo et al study findings.[22]

Regarding drugs, several drugs shown in the present study to be significant affect resistant hypertension; for example, nonsteroidal anti-inflammatory drugs, primarily by inhibiting the synthesis of prostaglandins in the kidneys. These prostaglandins usually help regulate kidney function and maintain sodium and water balance, which agrees Faselis et al study findings.[23] Furthermore, antihypertensive drugs its (diuretics, ACEIs, ARBs and CCBs) but not BBs significant used from patients with resistant hypertension. As these drugs are the core recommended medications for treating resistant hypertension, while beta-blockers (BBs) are generally not a first-line or primary add-on therapy for this condition unless specific comorbidities exist. This is parallel to Khalfallah et al study findings.[6]

Patients with resistant hypertension shown in the current study to had significantly higher creatinine clearance and lower estimated GFR, increased tubular secretion of creatinine can lead to a disproportionately high Creatinine Clearance relative to the actual GFR. Many studies showed similar findings.[24-25] On the other hand, regarding the heart changes, the study found patients with resistant hypertension had significantly higher E/E', LAVI and LAMI in Echo study, indicating significant cardiac structural remodeling and functional abnormalities, specifically elevated left ventricular filling pressures and progressive diastolic dysfunction, consistent finding obtained from is Khalfallah et al.[6]

The study limitations are; as the study findings were based solely on the population of single center in Iraq. Small sample size is another limitation which might affect the result validity.

4- CONCLUSION AND RECOMMENDATION

Certain factors significantly associated with resistant hypertension. These factors are excess salt intake, obesity, chronic kidney disease, obstructive sleep apnea and cardiac structural remodeling and functional abnormalities. Clinician should keep in mind these factors when treating resistant hypertensive patients.

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CONFLICT OF INTERTEST

About this study, the authors disclose no conflicts of interest.

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