



## A Prospective, Multi-Centric, Questionnaire Survey of Demographic and Clinical Characteristics of Hypertensive Patients, Iraq (PRIME)

S Kumar<sup>1\*</sup>, AJ Jawad al-Gburi<sup>2</sup>, M Kanaan<sup>3</sup>, AS Jabur<sup>4</sup>, MA Jaber<sup>5</sup>, MT Alqurainy<sup>6</sup>, MA Aljayashy<sup>7</sup>, A Alhilli<sup>8</sup>, M Wahody<sup>9</sup>, A Almayaly<sup>10</sup>, AJ Mirza<sup>11</sup>, S D'souza<sup>12</sup>

<sup>1</sup>Ajanta Pharma, Mumbai, India.

<sup>2</sup>Al-Mustansiriyah University - College of Medicine, Baghdad, Iraq.

<sup>3</sup>Sheikh Zayed General Hospital, Baghdad, Iraq.

<sup>4</sup>Al-Kindi Teaching Hospital, Baghdad, Iraq.

<sup>5</sup>Al-Mawani teaching hospital, Basra, Iraq.

<sup>6</sup>Al Sader Teaching Hospital, Basra, Iraq.

<sup>7</sup>Alhusain Teaching Hospital, Semawa, Iraq.

<sup>8</sup>Al-Diwaniya Teaching Hospital, Diwaniya, Iraq.

<sup>9</sup>Babylon Cardiac Cath. Center, Hillah Iraq.

<sup>10</sup>Karbala Medical College, Karbala, Iraq.

<sup>11</sup>Sulemani Center for heart disease, Sulaymaniyah.

<sup>12</sup>Ajanta Pharma, Mumbai, India.

### ABSTRACT

**Background:** The prevalence of hypertension, a significant public health concern globally, continues to rise, impacting millions of individuals and contributing to millions of deaths each year. Despite advancements in understanding its epidemiology and treatment, blood pressure control rates remain poor worldwide. **Aims:** This study aims to investigate the relationship between various demographic and lifestyle factors, such as sex, body weight, physical activity, and smoking status, with blood pressure status in individuals newly or previously diagnosed with hypertension. **Methods:** A cross-sectional study in Baghdad and Iraqi primary healthcare centres (Dec 2022-Jan 2023) analysed 2,466 adults ( $\geq 18$  years) with hypertension. Using SPSS version 23.0, chi-square tests assessed correlations between blood pressure and various factors (e.g., sex, BMI, smoking, education, family history), with significance at  $P < 0.05$ . **Results:** The study revealed significant findings regarding the correlation between various factors and hypertension control. Sex ( $p = 0.006$ ), body weight ( $p = 0.0579$ ), smoking status ( $p = 0.014$ ), and diabetes mellitus ( $p = 0.000$ ) were all found to have a direct and statistically significant association with hypertension. Additionally, as the duration from the onset of hypertension increased, blood pressure control became more challenging, with a significant relation noted between duration and comorbidities such as diabetes mellitus, dyslipidaemia, kidney disease, congestive heart failure, and stroke ( $p < 0.0001$  each). **Conclusions:** These results highlight the importance of effectively managing weight, quitting smoking, and implementing comprehensive clinical care for hypertension and its related conditions. They provide insights into factors influencing blood pressure control in the Iraqi population, paving the way for further analysis.

**Keywords:** Hypertension, Blood pressure control, Body weight, Smoking status, Comorbidities.

### ARTICLE INFO

#### \*Corresponding Author

Shalini Kumar  
Ajanta Pharma  
Mumbai, India  
Contact: shalini.kumar@ajantapharma.com

#### Article History:

Received : 29 May 2024  
Revised : 28 June 2024  
Accepted : 29 July 2024  
Published : 05 Oct 2024

**Copyright© 2024** The Contribution will be made Open Access under the terms of the Creative Commons Attribution-NonCommercial License (CC BY-NC) (<http://creativecommons.org/licenses/by-nc/4.0>) which permits use, distribution and reproduction in any medium, provided that the Contribution is properly cited and is not used for commercial purposes.

**Citation:** Shalini Kumar, et al. A Prospective, Multi-Centric, Questionnaire Survey of Demographic and Clinical Characteristics of Hypertensive Patients, Iraq (PRIME). Int. J. Currnt. Tren. Pharm, Res., 2024, 12(1): 111-115.

### CONTENTS

1. Introduction. ....111

2. Materials and methods. ....	111
3. Results and Discussion .....	112
4. Conclusion .....	115
5. References. ....	115

## 1. Introduction

As per the World Health Organization, hypertension, or high blood pressure, occurs when the pressure within blood vessels is elevated, reaching 140/90 mmHg or beyond.[1] Hypertension cases in adults are rising and they are the most common cause of primary care visits, making it a major public health concern globally. It is an independent and reversible risk factor for various diseases such as stroke, renal failure, and myocardial infarction. Failure to diagnose and treat hypertension early can result in fatal outcomes.[2] Hypertension impacts 1.28 billion individuals globally, with its complications contributing to approximately 10 million deaths each year across the world.[1-3] According to the Global Burden of Disease Report, 2019, the global age-standardised prevalence of hypertensive heart disease increased by a massive 137.9% from 1990 to 2019.[3] Hypertension is also one of the primary risk factors for cardiovascular mortality, estimated to be the reason behind 20%-50% of all deaths.[2] The prevalence of hypertension increases with advancing age, i.e., it affects >60% of individuals aged >60 years. As individuals age, they adopt a more sedentary lifestyle, leading to increased body weight, thereby increasing the prevalence of hypertension. It is estimated that the prevalence of hypertension will rise further by 15%-20% by 2025, reaching approximately 1.5 billion individuals worldwide.[4]

The highest prevalence of hypertension is seen in low-income and middle-income countries.[2,5] About two-thirds of the population with hypertension is from low- and middle-income countries due to poor access to healthcare facilities and a lack of awareness of the disease. In general, the Middle Eastern countries have a high prevalence of hypertension.[1,2] In a study conducted in Iraq in 2016 involving 4,120 adults, the prevalence of hypertension was revealed to be 35.6%. [6]

Medical science has made considerable progress in understanding the epidemiology, pathophysiology and risk factors of hypertension. Considerable evidence exists to support that treating hypertension can substantially reduce premature morbidity and mortality. However, despite several proven, effective and well-tolerated pharmacological treatments and lifestyle modifications being available for hypertension, blood pressure control rates are poor globally.[4] In this study, we aimed to evaluate and analyse the correlation of sex, body weight, physical activity, smoking status, educational level, family history, and the duration of hypertension and other comorbidities with the blood pressure status of individuals with newly or previously diagnosed hypertension.

## 2. Materials and methods

A cross-sectional study was carried out in Baghdad and primary healthcare centres in Iraq from December 2022-

January 2023. The selected primary healthcare centres were Najaf, Sulemaniya, Hilla, Karbala, Diwania, Nasariya, Basara, Semawa, Erbil, Dohuk, Mosel, Amara, Kirkuk, and Tikrit.

### Methods of selection

The study population comprised a total of 2,466 adults aged  $\geq 18$  years of both sexes with newly or previously diagnosed cases of hypertension, who attended the primary health care centres in these cities. Since this was an observational study, no ethics committee approval was required.

The following method was used for measuring blood pressure in all study participants. After seating the patient in a calm environment for at least 5 minutes, their blood pressure was recorded in a seated position using a mercury sphygmomanometer with an appropriately sized cuff placed on the patient's upper arm circumference. Three readings were taken at intervals of 1-2 minutes. The mean of the last two readings was taken as the blood pressure measurement.[4] Patients were categorized as a "newly diagnosed case" if this was the first time they had high blood pressure. Patients with a medical history of high blood pressure were categorized under "previously diagnosed case". Patients were categorized into hypertension grades according to the higher value of hypertension as per the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) high blood pressure guidelines as follows:[4]

- Optimal: Systolic blood pressure less than 120 and diastolic blood pressure less than 80 mmHg.
- Normal: Systolic blood pressure between 120-129 mmHg and/or diastolic blood pressure between 80-84 mmHg.
- High normal: Systolic blood pressure between 130-139 mmHg and/or diastolic blood pressure between 85-89 mmHg.
- Grade 1 hypertension: Systolic blood pressure between 140-159 mmHg and/or diastolic blood pressure between 90-99 mmHg.
- Grade 2 hypertension: Systolic blood pressure between 160-179 mmHg and/or diastolic blood pressure between 100-109 mmHg.
- Grade 3 hypertension: Systolic blood pressure greater than or equal to 180 mmHg and/or diastolic blood greater than or equal to 110 mmHg.
- Isolated systolic hypertension: Systolic blood pressure greater than or equal to 140 mmHg and diastolic blood pressure less than 90 mmHg.

Numerous other details were recorded as well, as per the data collection form requirement. These details included age, sex, marital status, height, weight, physical activity, smoking habits, education level, family history of hypertension, clinical characteristics of hypertension, comorbidities, and any ongoing antihypertensive therapy.

Statistical analysis was done using statistical software SPSS version 23.0. Chi-square test was used to analyse the correlation between blood pressure and sex, body mass index (BMI), physical activity, smoking status, educational level, family history, duration of hypertension, and other comorbidities. A P value of <0.05 was considered significant.

**3. Results & Discussion**

**Patient disposition**

The study sample included 2,446 adult patients comprising 1,377 (56.3%) males and 1,069 (43.7%) females. A higher proportion of the patient population was married, 2,125 (86.9%), as compared to unmarried patients, 321 (13.1%). A statistically significant relation between hypertension and the sex of the patient was found in the study (p=0.006). No statistically significant relation with hypertension was observed in married and unmarried patients (p=0.754). The mean age of the patients included in the study was 55.58 years.

**Patient categorisation**

A total of 1,619 (66.2%) patients were categorised as previously diagnosed cases of hypertension and the remaining 827 (33.8%) patients were newly diagnosed cases of hypertension, with or without ongoing antihypertensive treatment. No statistically significant correlation was found between previously and newly diagnosed cases of hypertension (p=0.198).

A total of 1,892 (77.4%) patients in the study population were taking antihypertensive medications and 554 (22.6%) patients were not taking any antihypertensive medications. There was no significant relation seen between hypertension and the use of hypertension medicines (p=0.258).

Patients were categorized into various blood pressure classes as per the ESC/ESH classification of hypertension (Table 1). Of the total 2,446 patients included in this analysis, a greater proportion of patients had Grade 2 hypertension, followed by isolated systolic hypertension, Grade 3 hypertension, Grade 1 hypertension, high normal and normal.

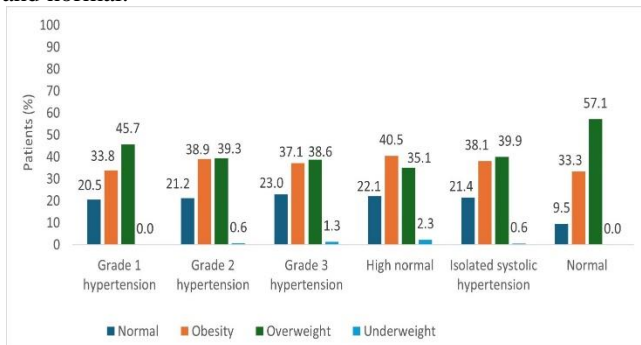


Figure 1: Correlation between hypertension and body weight

**Hypertension and body weight**

The blood pressure of the patients and their body weight were assessed, and the data was analysed to evaluate the correlation. A greater proportion of overweight 991

(40.5%) patients and obese 917 (37.5%) patients were present in the Grade 1 hypertension, Grade 2 hypertension, Grade 3 hypertension, high normal, isolated systolic and normal hypertension groups as compared to the proportion of patients with normal weight 521 (21.3%) and underweight 17 (0.7%) in these groups. This demonstrated a direct correlation between body weight and blood pressure, which was analysed and found to be statistically significant (p=0.0579) (Figure 1).

**Hypertension and physical activity**

Of the total study population, 1,722 (70.4%) patients worked out less than once a week and 724 (29.6%) patients worked out at least once a week. The correlation between the physical activity of the patient and their blood pressure status was analyzed. No significant relation between the two parameters was found (p=0.553).

**Hypertension and smoking habits**

According to the Centers for Disease Control and Prevention, a current smoker is defined as an adult who presently engages in daily smoking and has a history of consuming at least 100 cigarettes over their lifetime. On the other hand, a former smoker refers to an adult who has smoked a minimum of 100 cigarettes but has ceased smoking by the time of the interview. A never-smoker is an adult who has either refrained from smoking entirely or has smoked fewer than 100 cigarettes throughout their life.[7]

In our study, a total of 1,392 (56.9%) patients were categorized as never-smokers, 619 (25.3%) patients were categorized as former smokers and 435 (17.8%) patients were categorized as current smokers. The mean duration of smoking in current smokers was 17.07 years. Analysis of this data indicated a statistically significant relation between hypertension and the smoking status of patients (p=0.014) (Figure 2).

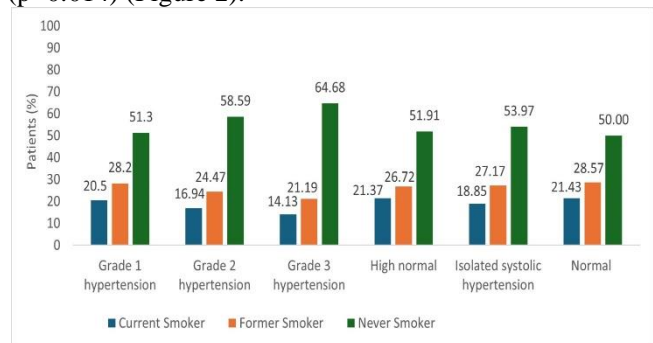


Figure 2: Correlation between hypertension and smoking status

**Hypertension and educational status**

Patients included in the study were categorized based on educational status. A total of 696 (28.5%) patients were graduates, 560 (22.9%) patients had no education, 509 (20.8%) patients had completed primary schooling, 409 (16.7%) patients had undergone less than primary schooling, 272 (11.1%) patients were post-graduate in their field of education. No statistically significant

correlation was observed between the educational status and blood pressure of the patients ( $p=0.934$ ).

### Hypertension and family history

Patients included in the study were categorised based on family history of hypertension. No statistically significant relation was found between hypertension and a family history of hypertension in the current study population ( $p=0.265$ ). A total of 1,669 (68.2%) patients had a family history of hypertension, whereas 777 (31.8%) patients had no family history of hypertension.

### Hypertension and duration of hypertension from onset

Patients included in the study were also categorized based on the duration from the onset of hypertension. A total of 965 (39.5%) patients had hypertension for <5 years, 842 (34.4%) patients had it for 5-10 years, 467 (19.1%) patients had it for 10-20 years, and 172 (7.0%) patients had it for >20 years. Duration of hypertension demonstrated no statistically significant correlation with blood pressure ( $p=0.259$ ).

### Hypertension and comorbidities

#### Hypertension and diabetes mellitus

Patients included in the study were categorised based on the presence or absence of diabetes mellitus. A total of 1,300 (53.1%) patients in the study population did not have diabetes mellitus while 1,146 (46.9%) had the condition. The blood pressure of individuals with and without diabetes mellitus was analysed and it was observed that there was a statistically significant relation between diabetes mellitus and hypertension ( $p=0.000$ ) (Figure 3).

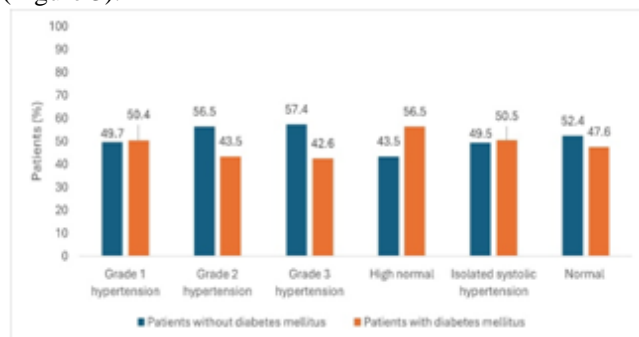


Figure 3: Correlation between hypertension and diabetes mellitus

### Hypertension and dyslipidaemia

Patients included in the study were categorised based on the presence or absence of dyslipidaemia. A total of 1,389 (56.8%) did not have dyslipidaemia and 1,057 (43.2%) patients in the study population had dyslipidaemia. Analysis revealed that there is no statistically significant correlation between patients with and without dyslipidaemia ( $p=0.240$ ).

### Hypertension and kidney disease

Patients included in the study were categorised based on the presence or absence of kidney disease. A total of 2,092 (85.5%) patients did not have kidney disease and 354 (14.5%) patients in the study population had kidney disease. Statistical analysis found no statistically significant correlation between patients with and without kidney disease ( $p=0.532$ ).

### Hypertension and congestive heart failure

Patients included in the study were categorized based on the presence or absence of congestive heart failure. A total of 2,156 (88.1%) did not have congestive heart failure and 290 (11.9%) patients in the study population had congestive heart failure. The blood pressure of individuals with and without congestive heart failure was analyzed and it was observed that there was no statistically significant correlation between patients with and without congestive heart failure ( $p=0.920$ ).

### Hypertension and stroke

A total of 2,085 (85.2%) patients did not have a history of stroke and 361 (14.8%) patients in the study population had experienced a stroke in the past. Patients included in the study were categorised based on their history of stroke. Analysis revealed that there is no statistically significant correlation between patients with and without stroke ( $p=0.545$ ).

### Duration of hypertension from onset and comorbidities

The correlation between the duration of hypertension and comorbidities, e.g., diabetes mellitus, dyslipidaemia, kidney disease, congestive heart failure and history of stroke was assessed. It was found that as the duration from the onset of hypertension increased, the proportion of patients with these comorbidities also increased. There was a significant relation between the duration from the onset of hypertension and all the mentioned comorbidities ( $p<0.0001$ , each) (Table 2).

The present study demonstrated a direct and statistically significant correlation between sex ( $p=0.006$ ), body weight ( $p=0.0579$ ), smoking status ( $p=0.014$ ) and diabetes mellitus ( $p=0.000$ ) with hypertension. It was noted that as the duration from the onset of hypertension increases, blood pressure control becomes difficult. A statistically significant relation between the duration from the onset of hypertension was also noted with the comorbidities diabetes mellitus, dyslipidaemia, kidney disease, congestive heart failure, and stroke ( $p<0.0001$  each).

The 2018 ESC/ESH guidelines present a comprehensive discourse on considerations related to sex in the management of hypertension, specifically addressing sex and gender aspects. The worldwide age-standardised prevalence of hypertension is reported as 24% in men and 20% in women. This data suggests an association between men and increased risk of cardiovascular events.[8]

In a study conducted by Sabaka et al., patients with a history of essential arterial hypertension were observed over 12 months. Of the 16,564 initially recruited patients, 13,631 (6,336 men and 7,295 women) completed the 1-year follow-up. For patients who were obese, a decrease in BMI by at least 1 kg/m<sup>2</sup> was linked to a lower likelihood of uncontrolled hypertension at the end of the follow-up period (significant for men,  $p<0.0001$ , and women,  $p<0.001$ ). A similar association was observed in patients who were overweight (significant for men,  $p<0.05$ , and for women,  $p<0.05$ ).

Conversely, an increase in BMI by at least 1 kg/m<sup>2</sup> was associated with a higher likelihood of uncontrolled hypertension in both obese (significant for men, p<0.001, and women, p<0.001) and patients who were overweight (significant for men, p<0.0001, and women, p<0.0001). The study indicates that weight loss is linked to a lower likelihood, while weight gain is associated with a higher likelihood of uncontrolled hypertension among individuals with obesity and overweight who have hypertension.[9]

A 15-year population-based cohort study conducted by Andriani et al. of 10,338 respondents in Indonesia assessed the effects of cigarette usage on systolic blood pressure, diastolic blood pressure and pulse pressure, and investigated the relationship between changes in smoking status and blood pressure changes during the study period. The results indicated that smoking has different effects on male and female smokers. Female smokers who increased smoking demonstrated significantly higher systolic blood pressure and pulse pressure (p<0.001). During the study, women and men who decided to quit smoking had the maximum change in systolic blood pressure (adjusted mean: 24.78 mmHg, standard error (SE): 23.25 in women and adjusted mean: 16.64 mmHg, SE: 21.39 in men), whereas new female and male smokers exhibited the highest change in diastolic blood pressure (adjusted mean: 7.54 mmHg,

SE: 14.39 in women and adjusted mean: 2.86 mmHg, SE: 11.50 in women).[10] Thus, our findings regarding the adverse effects of smoking on blood pressure control were corroborated by this study.

Following the Global Hypertension Practice Guidelines established by the International Society of Hypertension in 2020, it is documented that over 50% of individuals diagnosed with hypertension exhibit associated cardiovascular risk factors. Notably, among the prevalent supplementary risk factors, diabetes stands out as one of the most common, affecting approximately 15%-20% of patients with hypertension.[11] This is consistent with our study findings, where a noteworthy correlation was seen between the duration of hypertension from onset and diabetes, indicating a significant link between these two health conditions.

All the published literature and available data are in line with our cross-sectional study. To our knowledge, this is the first cross-sectional study in Iraq that assesses the effects of multiple parameters, including sex, body weight, physical activity, smoking status, educational level, family history, duration of hypertension and comorbidities on blood pressure control. However, further analysis of the data available in this cross-sectional survey can help us understand the effect of each parameter on blood pressure control in detail.

Table 1: Patient categorization based on grade of hypertension

Class of hypertension	Grade 1	Grade 2	Grade 3	High normal	Isolated systolic	Normal
N (%)	429 (17.5)	850 (34.8)	453 (18.5)	131 (5.4)	541 (22.1)	42 (1.7)

N: number of patients.

Table 2: Correlation of duration of hypertension from onset with comorbidities

Comorbidities and their presencen (%)		Duration of hypertension from onset				P value
		<5 years	5-10 years	10-20 years	>20 years	
Diabetes mellitus	No	663 (68.70)	414 (49.17)	174 (37.26)	49 (28.49)	p<0.0001
	Yes	302 (31.30)	428 (50.83)	293 (62.74)	123 (71.51)	
Dyslipidaemia	No	686 (71.09)	445 (52.85)	201 (43.04)	57 (33.14)	p<0.0001
	Yes	279 (28.91)	397 (47.15)	266 (56.96)	115 (66.86)	
Kidney disease	No	904 (93.68)	715 (84.92)	359 (76.87)	114 (66.28)	p<0.0001
	Yes	61 (6.32)	127 (15.08)	108 (23.13)	58 (33.72)	
Congestive heart failure	No	917 (95.03)	769 (91.33)	367 (78.59)	103 (59.88)	p<0.0001
	Yes	48 (4.97)	73 (8.67)	100 (21.41)	69 (40.12)	
History of stroke	No	905 (93.78)	738 (87.65)	349 (74.73)	93 (54.07)	p<0.0001
	Yes	60 (6.22)	104 (12.35)	118 (25.27)	79 (45.93)	

n: number of patients

#### 4. Conclusion

This study highlights a significant correlation of hypertension with gender, body weight, smoking status, diabetes mellitus, and the increase in comorbidities with long-term hypertension. These findings emphasise the importance of weight management, smoking cessation, and comprehensive clinical management for hypertension and associated conditions. Therefore, prioritising these interventions can be crucial for enhancing public health and promoting individual well-being.

**Acknowledgements:** The authors would like to thank Spellbound Inc. for their publication support.

#### Declarations

Ethics approval and consent to participate: The study adhered to the principles outlined in the Declaration of Helsinki. Ethical committee approval was not needed given the observational nature of the study.

#### Disclaimer:

The views expressed in the submitted article are the author's own and not an official position of the institution or funder.

**Consent for publication:** Informed consent was obtained from all participants included in the study.

**Competing interests:** The authors declare that they have no competing interests.

**Funding/Source of support:** This research did not receive any specific funding.

#### Authors' contributions:

Each author listed has contributed significantly to the research process. AJJA and MAJ played a pivotal role in study conception and design. While MAJ, MAA, MK and ASJ took charge of data collection. Both AAs, MTA, MW and AJM provided valuable insights during data analysis and interpretation of results. SK and SD conducted critical revisions of the manuscript, significantly enhancing its clarity and quality. All authors have approved the final version of the work and have committed to personal accountability and integrity throughout the research process, ensuring that any issues related to accuracy or integrity are addressed and documented appropriately in the literature.

#### 5. References

- [1] Hypertension-WHO, (<https://www.who.int/news-room/fact-sheets/detail/hypertension>). Accessed 12 December 2023.
- [2] Saka M, Shabu S, Shabila N. Prevalence of hypertension and associated risk factors in older adults in Kurdistan, Iraq. *East Mediterr Health J*. 2020; 26(3):268-275.
- [3] Mansouri A, Khosravi A, Mehrabani-Zeinabad K, Kopec JA, Adawi KII, Lui M et al. Trends in the burden and determinants of hypertensive heart disease in the Eastern Mediterranean region, 1990-2019: an analysis of the Global Burden of Disease Study 2019. *EClinicalMedicine*.2023; 60:102034.
- [4] Williams B, Mancia G, Spiering W, AgabitiRosei E, Azizi M, Burnier Met al.2018 ESC/ESH Guidelines for the management of arterial hypertension. *EurHeart J*. 2018;39(33):3021-3104.
- [5] A global brief on hypertension: Silent killer, global public health crisis-WHO, ([https://iris.who.int/bitstream/handle/10665/79059/WHO\\_DCO\\_WHD\\_2013.2\\_eng.pdf?sequence=1](https://iris.who.int/bitstream/handle/10665/79059/WHO_DCO_WHD_2013.2_eng.pdf?sequence=1)). Accessed 10 October2023.
- [6] Khaleefah MA, Al-Badri HJ, Mousa NA. Hypertension control among adult Iraqis. *J Fac Med Baghdad*. 2022; 64(3):145-152.
- [7] National Health Interview Survey-CDC, ([https://www.cdc.gov/nchs/nhis/tobacco/tobacco\\_glossary.htm](https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm)). Accessed 12 December2023.
- [8] Meinert F, Thomopoulos C, Kreutz R. Sex and gender in hypertension guidelines. *J Hum Hypertens*. 2023; 37(8):654–661.
- [9] Sabaka P, Dukat A, Gajdosik J, Bendzala M, Caprnda M, Simko F. The effects of body weight loss and gain on arterial hypertension control: an observational prospective study. *EurJ Med Res*. 2017;22(1):43.
- [10] Andriani H, Kosasih RI, PutriS, Kuo HW. Effects of changes in smoking status on blood pressure among adult males and females in Indonesia: a 15-year population-based cohort study. *BMJ Open*. 2020; 10(4):e038021.
- [11] Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International society of hypertension global hypertension practice guidelines. *Hypertension (Dallas, Tex: 1979)*. 2020;75(6):1334–1357.