



Uncontrolled blood pressure among hypertensive adults with rheumatoid arthritis in Saudi Arabia

A cross-sectional study

Ziyad S. Almalki, PhD^{a,*}, Bedor Abdullah AlOmari, SSC.PhP, SSCIMP^b, Tahani Alshammari, PharmD^c, Areej Alshlowi, PharmD^c, Mohd Faiyaz Khan, PhD^a, Ali Hazazi, BPharm^d, Maha Alruwaily, PharmD^c, Sarah Alsubaie, PharmD^c, Faten Alanazi, PharmD^c, Norah Aldossary, PharmD^c, Raseel Albahkali, PharmD^c

Abstract

Despite the availability and advancement of diagnostic and treatments with demonstrated benefits in minimizing cardiovascular morbidity and mortality, hypertension control rates remain suboptimal. Therefore, this research aimed to determine the prevalence of uncontrolled BP in rheumatoid arthritis (RA) patients and understand all potential risk factors for uncontrolled BP.

We conducted a cross-sectional study on RA patients in 2 rheumatology clinics in 2 public hospitals in Riyadh. Patients' information such as demographics, comorbidities, drug use, and other clinical data were captured through a review of medical records and supplemented by patient interviews. Multivariate logistic regression was utilized for the analysis to identify the significant factors of uncontrolled BP (systolic BP \geq 140 mm Hg or diastolic BP \geq 90 mm Hg).

In total, 834 subjects with RA and concomitant BP were involved in this cross-sectional study. The prevalence of uncontrolled BP was found to be 31.65% among all the study population. Multivariate analysis showed that males, subjects above 60 years of age, and smokers had a distinctly higher occurrence of uncontrolled BP. Among the patients with comorbid conditions, those with obesity, hyperlipidemia, diabetes, anemia, cancer, and reflex or gastroesophageal reflux disease also showed a significantly higher risk of uncontrolled BP (P < .05).

The rate of uncontrolled BP was found to be alarmingly high in the study population. Age, gender, smoking, diabetes, obesity, hyperlipidemia, cancer, gastroesophageal reflux disease, and osteoporosis are independently linked with lack of BP control.

Abbreviations: BMI = Body mass index, BP = blood pressure, CCBs = calcium channel blockers, CI = confidence intervals, CV = cardiovascular, CVD = cardiovascular disease, DBP = diastolic blood pressure, GERD = gastroesophageal reflux disease, HT = hypertension, OR = odds ratios, PSMMC = Prince Sultan Military Medical City, RA = rheumatoid arthritis, RAAS = renin-angiotensin-aldosterone system, SBP = systolic blood pressure.

Keywords: associated factors, blood pressure, prevalence, rheumatoid arthritis, Saudi Arabia

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1. Introduction

When compared to the general population, patients with rheumatoid arthritis (RA) have an increased chance of cardiovascular (CV) morbidity and mortality. [1–4] Previous studies have shown that over half of premature deaths in this population are attributable to CV events. [5] The association between RA and increased risk of cardiovascular disease (CVD) has been documented in the literature, as the risk of CV events in patients with RA is similar to the risk for CV events in patients with diabetes. [6] RA patients were associated with a twofold greater risk of a myocardial infarction event compared to non-RA patients, which is similar to the risk of myocardial infarction for patients with and without diabetes, [7] while the risk of acute coronary syndrome was found to be common among patients with RA. [8] Furthermore, patients with RA were at a twofold higher heart failure risk than non-RA patients.

The mechanisms underlying increased CV risk among this subpopulation are not well understood. However, several studies have demonstrated a close link between hypertension (HT) and increased CV risk among patients with RA. [9,10] Findings from a study that assessed the effect of changes in systolic blood pressure (SBP) on CV events found that a 20 mm Hg increase in SBP among patients diagnosed with RA would be linked to greater frequency of CV events compared to non-RA patients (i.e., an

^a Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Riyadh, Saudi Arabia, ^b Internal Medicine and Rheumatology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia, ^c Clinical Pharmacy, AlMaarefa University, Ad Diriyah, Saudi Arabia, ^d College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Riyadh, Saudi Arabia.

^{*} Correspondence: Ziyad S. Almalki, Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Riyadh, Saudi Arabia (e-mail: z.almalki@psau.edu.sa).

additional 1572 ischemic heart disease events and 602 stroke events over 12 months).^[11]

The prevalence of HT among RA patients is significantly high compared to the general population. [12] In the literature, the published estimates of the prevalence of HT in RA patients vary widely because these studies may differ in the type of the population, the number of included patients, and the definition of HT used in the study. However, the most recent comprehensive systematic review showed that the prevalence of HT in patients with RA ranged between 52% and 73%. [13] The mechanisms that may lead to HT in RA patients are not clear. However, some reports suggested that this association could be a result of several causes, including chronic systemic inflammation on the vascular endothelium, [12] physical inactivity, [14] and genetic factors. [15]

Despite the availability and advancement of diagnostic and treatments with demonstrated benefits in minimizing cardiovascular morbidity and mortality, HT control rates remain suboptimal. Only 37% of individuals undergoing antihypertensive treatment in Saudi Arabia appear to have their HT under control. [16] Despite the potential for uncontrolled blood pressure (BP) to lead to CVD complications, [17,18] There is no data on the prevalence and risk factors for uncontrolled BP in rheumatoid arthritis patients in Saudi Arabia. Improved BP monitoring and control would necessitate a better understanding of the variables affecting BP control. Therefore, this research aimed to determine the prevalence of uncontrolled BP in RA patients and to understand all potential risk factors for uncontrolled BP. This information is essential for policymakers and clinicians in planning interventions based on local influential factors to reduce the potentially preventable complications of elevated BP in clinical practice.

2. Methods

2.1. Study designs and setting

The study design was an observational, cross-sectional design. Two clinical pharmacists and 4 nurses and pharmacy interns collected data from RA patients who visited 2 rheumatology clinics in 2 public hospitals in Riyadh–Prince Sultan Military Medical City (PSMMC), King Khaled Hospital, and Prince Sultan Center for Health Care–from the beginning of October 2019 to the end of March 2020.

2.2. Eligibility criteria

Males and females aged 18 years or older diagnosed with RA and HT and who were on antihypertensive treatment were included in the study. Specifically, patients had to have received at least 6 months of treatment and ongoing treatment for HT at the time of data collection to be considered for this study. The final dataset excluded patients who were recently diagnosed, pregnant patients, and those with terminal or cognitive impairment or incomplete data. A total of 834 RA patients who fulfilled the eligibility criteria were enrolled in the study.

This research was evaluated and approved by the Ministry of Health's Institutional Review Board number 2019-0059E. The study was also approved by the Research Ethics Committee of PSMMC (project no: 1240). The permission of the MoH and the hospital administration was granted to perform this research. Everyone who agreed to participate in the study was made aware of the project's rationale and goals, and the interviews were

conducted on an entirely voluntary basis. The participants had the choice to terminate their participation in the study in any form whatsoever, for any reason. All participants gave their consent before data collection.

2.3. Study variables

2.3.1. Dependent variable: uncontrolled BP. According to the recommendations from the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP, [19] patients were subdivided into 2 groups according to BP control status. They were placed in the Controlled BP group if they were currently using BP-lowering medication associated with average SBP of less than 140 mm Hg and average diastolic blood pressure (DBP) of less than 90 mm Hg; or, in the case of patients who had a previous CVD or had been diagnosed with diabetes mellitus, they were placed in the Controlled BP group if they had an average SBP less than 130 mm Hg and an average DBP less than 80 mm Hg. They were placed in the Uncontrolled BP group if they had SBP or DBP equal to or higher than the above values while taking antihypertensive medication to manage high BP at the time of the interview. A patient was considered to have uncontrolled BP if their measured BP levels were $\geq 140/90$ mm Hg.

2.3.2. *Independent variables.* The set of independent variables was included. Patients were categorized into 2 groups according to marital status: currently married or unmarried (i.e., widowed, divorced, separated, or never married). The level of education was determined by the maximum grade level attained by the individual. According to the level of education, individuals were categorized into 5 groups: with no formal education, primary, intermediate, secondary, or post-secondary education (e.g., university and vocational). Employment status was either employed or unemployed. The participants were classified as unemployed if they had neither full-time nor part-time jobs in the formal or informal sectors. Smoking status was either a smoker or a nonsmoker. Body mass index (BMI) was calculated and classified as obese when BMI is ≥ 30 , not obese when BMI < 30kg/m². Treatment data were abstracted and recorded, including the type of BP-lowering medications. According to whether they were documented in the patient's records, comorbidities were classified as either present (yes) or absent (no). Comorbidities included were hyperlipidemia, diabetes mellitus, irritable bowel syndrome, anemia, anxiety, cancer, kidney disease, asthma, liver disease, migraine, Gastroesophageal reflux disease (GERD), osteoporosis, and depression. These comorbidities were defined using laboratory results retrieved from measurements that occurred before the latest visit. However, any lab result during an acute illness or a recent medication adjustment (<3 months) was not applicable and therefore was not used.

2.4. Data collection

The participants' information was obtained from both primary sources—interviewing the patient— and secondary sources—reviewing the patients' medical records. Patients were interviewed using a semi-structured interview to obtain sociodemographic data such as age, sex, level of education, marital status, employment status, and lifestyle factors such as smoking status. The electronic medical records were individually evaluated, and all comorbidities and types of antihypertensive drugs were identified for each eligible patient.

First, the survey was prepared in English, then translated into Arabic, and then, again, into English to ensure consistency and ensure against translation errors. A preliminary examination check was performed on 5% of the total sampling pool to verify the high quality and homogeneity of the data format and questionnaire used for the research. Any errors discovered during the pre-testing of the data were fixed, and further refining was done on the developed data abstraction tool. Data collectors were first granted the opportunity to prepare and train before being put to work. The regular correctness and accuracy of the data were checked on the spot.

2.5. BP measurement procedure

BP was assessed by nurses using the pre-tested standard mercury sphygmomanometer that uses a BP cuff covering two-thirds of the upper arm with the cuff's appropriate scale. Patients rested for at least 5 minutes and did not smoke any cigarettes or consume caffeine 30 minutes before the measurement. Excessive clothing was removed that could interfere with the BP cuff. Patients were rested and maintained relaxed during the BP measurement. The BP cuff was inflated to the point that no sounds were detected from the stethoscope. Then the cuff was deflated slowly to measure the systolic and diastolic BP. At the very least, 2 measurements were taken in 5 minutes. The mean of the 2 measures was used for analysis.

2.6. Statistical analysis

Researchers used descriptive statistics to convey the prevalence of uncontrolled BP in the RA population. Specifically, the distribution of research variables between patients with uncontrolled BP and those with controlled BP was explored using frequencies and percentages. Sample characteristics-demographic and clinical data-were reported as dichotomous or polychotomous variables. Chi-Squared test or Fisher exact test was used to compare the distribution of the groups with controlled and uncontrolled BP. We conducted univariate logistic regressions to investigate each predictor's effect on the risk of uncontrolled BP among patients with RA. The significant predictors were identified and fitted into multivariate modeling. While we concurrently adjusted for all other predictors in the model, odds ratios (OR) and 95% confidence intervals (CI) were computed to estimate each predictor's effect on the BP control status. All the data were processed using the SAS-9.4 software (SAS Institute, Inc, Cary, NC). For all tests, a P value of <.05 was taken as statistically significant.

3. Results

Table 1 shows details about the characteristics of study participants according to their BP control. In total, 834 subjects with RA and concomitant HT were enrolled in this study. The prevalence of uncontrolled BP was found to be 31.65% among all the subjects. Patients with uncontrolled BP were significantly older compared to those with controlled BP. The mean age was 58.7 + 15.1 years in the uncontrolled BP group, while it was 55 + 14.6 years in the controlled BP group. In addition, the prevalence of uncontrolled BP steadily increased with age. The prevalence increased from 9.3% among the <40 years age group to 43.6% among those more than 60 years.

Patients' characteristics according to BP control.

Variable	Uncontrolled BP n=264%=31.6	Controlled BP $n = 570\% = 68.3$	P value
Age. Mean (SD)	58.7 (15.1)	55 (14.6)	<.001
Patients, n (%)			- 001
Age Group <40	15 (9.38)	145 (90.63)	<.001
40–60	112 (31.11)	248 (68.89)	
>60	137 (43.63)	177 (56.37)	
Gender			<.001
Female Male	132 (24.63)	404 (75.37) 166 (55.7)	
Marital status	132 (44.3)	100 (55.7)	0.06
Married	164 (29.18)	398 (70.82)	0.00
Unmarried	96 (48.34)	156 (51.66)	
Level of education	00 (40 5)	00 (57.5)	0.08
Post-secondary education Secondary education	68 (42.5) 72 (51.43)	92 (57.5)	
Intermediate education	17 (26.15)	68 (48.57) 48 (73.85)	
Primary education	69 (29.61)	164 (70.39)	
No formal education	38 (16.1)	198 (83.9)	
Employment status			0.1
Employed	136 (36.96)	232 (63.04)	
Unemployed Smoking	128 (28.69)	338 (71.31)	<.001
Nonsmoker	122 (24.11)	384 (75.89)	<.001
Smoker	126 (42.57)	170 (57.43	
Obesity			<.001
No	121 (26.88)	329 (73.12)	
Yes Hyperlipidemia	124 (42.81)	167 (57.19)	<.001
No	58 (12.89)	392 (87.11)	<.001
Yes	206 (53.65)	178 (46.35)	
Diabetes Mellitus			<.001
No	68 (15.04)	384 (84.96)	
Yes Irritable Bowel Syndrome	192 (51.34)	182 (48.66)	0.7
No	204 (31.97)	434 (68.03)	0.7
Yes	60 (30.61)	136 (69.39)	
Anemia			<.001
No	196 (28.57)	490 (71.43)	
Yes Anxiety	68 (53.13)	60 (46.88)	0.5
No	188 (30.92)	420 (69.08)	0.5
Yes	36 (33.96)	70 (66.04)	
Cancer			0.01
No	236 (31.47)	514 (68.53)	
Yes Kidney Disease	20 (50)	20 (50)	0.3
No	192 (35.69)	418 (64.31)	0.5
Yes	72 (32.14)	152 (67.86)	
Asthma			0.2
No	206 (27.76)	510 (72.24)	
Yes Liver Disease	58 (49.15)	60 (50.85)	0.3
No	256 (31.6)	554 (68.4)	0.5
Yes	4 (20)	16 (80)	
Migraine			0.6
No	216 (32.83)	442 (67.17)	
Yes Castroocophagoal roflux	24 (30)	56 (70)	0.04
Gastroesophageal reflux disease (GERD)			0.04
No	160 (29.96)	374 (70.04)	
Yes	96 (36.92)	164 (63.08)	
Osteoporosis			0.04
No	100 (27.93)	258 (72.07)	
Yes Depression	164 (34.45)	312 (65.55)	0.07
No	248 (34.35)	474 (65.65)	0.07
		(00.00)	

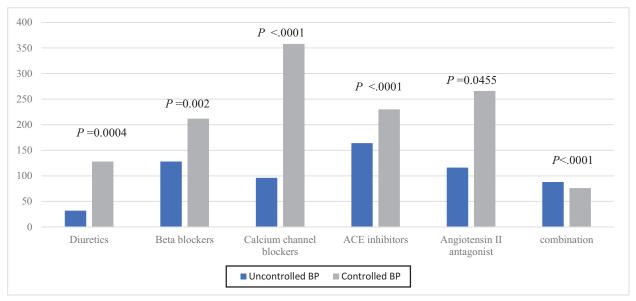


Figure 1. Number of antihypertensive classes used by RA patients.

The variables that determined uncontrolled BP on univariate analysis were age group, gender, smoking, obesity, hyperlipidemia, diabetes mellitus, anemia, cancer, GERD, and osteoporosis (Table 1).

As displayed in Figure 1, calcium channel blockers (CCBs) and angiotensin receptor blockers were the most prescribed classes of antihypertensives among the studied subjects. Treatment with different antihypertensive agents demonstrated significantly different effects on BP levels.

The most significant contributing factors associated with the increased risk of uncontrolled BP were shown in Table 2. As per the multivariate logistic regression model, it was found that the subjects who were more than 60 years of age and those who were between 40 and 60 had higher chances of uncontrolled BP compared to individuals younger than 40 years ([OR = 5.536, 95% CI: 2.954–10.375], [OR = 4.928, 95% CI: 2.657–9.14], respectively). Similarly, male subjects had higher probabilities of suffering from uncontrolled BP than female subjects (OR = 2.875, 95% CI: 2.056–4.021). Smokers were more likely to have uncontrolled BP than nonsmokers (OR = 2.332, 95% CI: 1.668–3.259)

Obese patients had a comparatively higher risk of uncontrolled BP than non-obese patients (OR = 2.456, 95% CI: 1.902–3.171). Patients with hyperlipidemia had comparatively higher chances of uncontrolled BP than nonhyperlipidemic patients (OR = 5.707, 95% CI: 3.972–8.2). Diabetic patients had a greater chance of having uncontrolled BP than patients without diabetes mellitus (OR = 9.802, 95% CI: 6.654–41.438). Patients who were anemic had 3.259 times the risk of uncontrolled BP than nonanemic patients (OR = 3.259, 95% CI: 2.174–4.884). Similarly, cancer patients had a significantly higher risk of uncontrolled BP incidence than patients free from any cancer (OR = 2.385, 95% CI: 1.255–4.534). Patients with GERD were more likely to be at a higher risk of uncontrolled BP than patients who did not have GERD (OR = 1.646, 95% CI: 1.176–2.303). Relative to patients without diagnoses of osteoporosis, the risk of

Table 2 Factors associated with uncontrolled BP among RA patients.

Variable		95%	95% CI	
	OR	Lower limit	Upper limit	P value
Patients, n (%)				
Age group				
<40	Ref			
40-60	4.928	2.657	9.14	<.001
>60	5.536	2.954	10.375	<.001
Gender				
Female	Ref			
Male	2.875	2.056	4.021	<.001
Smoking				
Nonsmoker	Ref			
Smoker	2.332	1.668	3.259	<.001
Obesity				
No	Ref			
Yes	2.456	1.902	3.171	<.001
Hyperlipidemia				
No	Ref			
Yes	5.707	3.972	8.2	0.001
Diabetes Mellitus				
No	Ref			
Yes	9.802	6.654	14.438	0.007
Anemia				
No	Ref			
Yes	3.259	2.174	4.884	<.001
Cancer				
No	Ref			
Yes	2.385	1.255	4.534	0.008
Gastroesophageal	reflux disease	(GERD)		
No	Ref			
Yes	1.646	1.176	2.303	0.003
Osteoporosis				
No	Ref			
Yes	1.413	1.017	1.963	0.03

uncontrolled BP increased 41% among patients who were suffering from osteoporosis (OR = 1.413, 95% CI: 1.017–1.963).

4. Discussion

Epidemiological studies have produced evidence that uncontrolled BP doubles the risk of CV consequences. Thus, rigorous BP control is the principal goal for preventing CV-related severe complications. ^[20] This study examined the prevalence of uncontrolled BP and found the risk factors correlated with it among RA patients in Saudi Arabia. Our study reported a prevalence of 31.65% of uncontrolled BP among the study sample, comparable with other previous studies; for example, a study conducted by Protogerou et al^[21] reported that 29% of the RA patients had uncontrolled BP.

Several of the uncontrolled BP risk factors were found among the study population. We found that people older than 60 years have a greater risk of uncontrolled BP, which is similarly evident in various other studies. [22] It is a concerning result as it has also been reported that patients who have both RA and HT and are of advanced age have more tendency to develop CVD. Hence, management of HT in the elderly is very crucial.

Our studies show that male subjects are more likely to experience uncontrolled BP than female subjects. A similar observation has been reported by previous epidemiological studies. Some studies suggested no association between uncontrolled BP and gender, whereas some reported an inverse association between them. Studies have revealed a mix-type etiology where sex hormones could be a potential factor for the results' inconsistencies. Hence, a study is needed to investigate whether sex hormones play a role in gender differences in BP regulation.

Our results showed that smoking is a significant contributor to uncontrolled BP in our study. It is well-documented in the literature that smoking is a risk factor of HT in general^[30] and is linked with HT in RA patients.^[31] Smoking acts not only as a risk factor for the occurrence of CVD but also RA. Published work has shown that smoking is linked to severe RA, such as extraarticular involvement and more abrasive diseases. The indicators of aggressive RA, that is, anti-cyclic citrullinated peptide antibody and rheumatoid factor, are more likely to be present in smokers.^[32,33]

Obesity and elevated BP go hand in hand. Many published studies have shown that obesity significantly impacts rising BP.[34-37] The present study includes obesity as another prognostic factor influencing BP regulation, in agreement with the existing literature. BMI is an independent determinant of uncontrolled BP in obese patients. Poor management of obesity in HT patients is believed to be linked with complex pathophysiological effects on renal activity. Obesity results in renal reabsorption of sodium and alters pressure natriuresis, a function of the renin-angiotensin-aldosterone system (RAAS). Impairment of intrarenal forces may also be a cause of problems in the RAAS. Changes in the structure of kidneys that eventually cause loss of nephron activities are a significant consequence of chronic obesity. Hence, it is suggested to prescribe diuretics and antihypertensives that act on RAAS in obese patients. [38] Fortunately, obesity can be controlled by adopting an appropriate prevention strategy, which includes raising public awareness and urging high-risk individuals to make various lifestyle improvements, including tailored diet and exercise plans that can aid in weight loss and BP reduction.

Hyperlipidemia, as we discovered in our work, was even more prevalent in the uncontrolled BP group. Indeed, a study of American veterans revealed that cholesterol levels were nevertheless elevated after patients were treated with more intensive lipid-lowering medications.^[39] However, in a different population, our data show similar and not encouraging results as hyperlipidemia is strongly associated with CVD.^[40]

This study shows an alarmingly high prevalence rate of uncontrolled BP in patients with diabetes mellitus. Unfortunately, this high prevalence rate was not unexpected. Various other studies have comparable findings. [41] The etiology related to this elevation of BP in diabetes mellitus patients is renal insufficiency. Another major cause is an increase in total body exchangeable sodium, which leads to the accumulation of extracellular fluid and plasma volume. Studies have also suggested that insulin resistance may result in high BP due to promoted sodium retention and the sympathetic nervous system. [42]

It was previously reported in the literature that patients with uncontrolled BP were recorded to have a lower amount of hemoglobin than anemic patients with controlled BP. In our study, anemic patients have shown an increased incidence of nocturnal systolic BP as compared to patients with a standard range of hemoglobin.^[43] This study showed that uncontrolled BP was more prevalent among anemic patients. The leading cause of this result is believed to be Leptin, which is a human obesity gene that may be associated with the rheological conduct of erythrocytes as well as microcirculation of HT.^[43]

Our results have shown a significant risk of uncontrolled BP in patients with cancer compared to patients free from malignancy. Studies have reported that HT is the most prevalent and chief comorbidity found in cancer patients. However, there were no significant differences between the general population's HT record and those of cancer patients before chemotherapy, which may indicate that elevated BP in cancer patients could be a function of chemotherapeutic agents. [44]

This study also reveals that patients with GERD have more significant risks of uncontrolled BP, which was also seen in previous studies. A comparative study was done to evaluate the risk factors of CVD in patients with reflux oesophagitis and non-ulcer dyspepsia compared with the general population. The results revealed that patients with RE had a more frequent uncontrolled BP (OR: 3.8, P<.001). Hypothetically, genetic factors may be a significant factor for this condition. In family studies, mutation of approximately 10 genes have been found to alter BP. Hence, hereditary and environmental influences may be involved in GERD's association with elevated BP. [45]

Among the aging population, osteoporosis and HT are the diseases most likely to co-exist in an individual. [46] The precise mechanism by which osteoporosis affects BP control in humans is unknown. However, several hypotheses have been proposed. For example, several of these research results suggested that elevated BP was a significant factor in the incidence of calcium deficiency, resulting in net bone remodeling and elevated parathyroid hormone levels; both had the opposite effect on bone mass and bone density. [47,48]

Although our study included a larger sample size to ensure more accurate study results, the present paper still has several limitations that are worth considering. First, we did not obtain information on lifestyle components (e.g., physical activity, salt consumption), which may influence BP control. [49] Second, while we accounted for the confounding impact of being treated with antihypertensive drugs for HT, we were unable to obtain

additional medication-use data, such as doses and length of therapy, or other relevant data indicating treatment adherence, clinical inertia, regimen complexity, and pill burden, all of which may affect the rate of uncontrolled BP. A final possible drawback of this study is BP measurements, which may have significantly overestimated the proportion of patients with uncontrolled BP as a result of the "white coat" factor.^[50] However, all patients had been on antihypertensive medication for at least 6 months, indicating that the BP levels obtained were representative; furthermore, we used 2 BP readings to confirm whether patients had control or uncontrolled BP.

These findings indicate that the policymakers' and clinicians' prompt action would help RA patients with HT achieve optimal BP control to minimize the disease's progression and related costs and poor quality of life associated with long-term poor BP control. ^[51,52] Tremendous effort is crucial to evaluate BP control among RA patients with HT and implement better approaches for achieving long-term BP control. Health education for patients was considered as the best choice to improve their self-care practices. It has been proven that DM-related self-care practices, such as diet control, being physically active, BP monitoring, and medication adherence, can contribute to achieving ideal BP control. ^[53] Besides the self-care practice, the Ministry of Health should initiate a proper screening protocol to detect and treat RA patients at risk of poor BP control.

This study contributes significantly to the design and direction of future research. For instance, future studies should examine the most effective strategies for controlling BP in this population, both pharmacological and nonpharmacological. Additionally, future studies should thoroughly control all possible confounding variables, such as lifestyle factors, and include a measure for patient adherence to antihypertensive treatments.

5. Conclusion

Despite the wide use of antihypertensive treatment, a substantial percentage of the study population had uncontrolled BP even though they were taking drugs. This study concludes significant findings that might prove beneficial in structuring policies and management criteria for uncontrolled BP among RA patients. The high prevalence of uncontrolled BP was associated with older patients, males, smokers, and people suffering from obesity, hyperlipidemia, diabetes, anemia, cancer, GERD, and osteoporosis. There is an immediate need for a diagnostic system to check on uncontrolled BP cases and structure a better management system to reduce CVD morbidity and mortality in people at higher risk.

Author contributions

Conceptualization: Ziyad S Almalki, Faten Alanazi. Data curation: Ziyad S Almalki, Bedor Abdullah AlOmari, Tahani Alshammari, Areej Alshlowi, Ali Hazazi, Maha Alruwaily, Sarah Alsubaie, Raseel Albahkali.

Formal analysis: Ziyad S Almalki, Tahani Alshammari, Areej Alshlowi, Maha Alruwaily.

Funding acquisition: Ziyad S Almalki.

Investigation: Ziyad S Almalki, Bedor Abdullah AlOmari, Tahani Alshammari, Areej Alshlowi, Ali Hazazi, Maha Alruwaily, Sarah Alsubaie, Faten Alanazi, Norah Aldossary. Methodology: Ziyad S Almalki, Tahani Alshammari, Areej

Methodology: Ziyad S Almalkı, Tahanı Alshammarı, Areej Alshlowi, Mohd Faiyaz Khan, Ali Hazazi, Raseel Albahkali. **Project administration:** Ziyad S Almalki, Bedor Abdullah AlOmari, Tahani Alshammari, Maha Alruwaily.

Resources: Ziyad S Almalki, Bedor Abdullah AlOmari, Tahani Alshammari, Areej Alshlowi, Faten Alanazi, Norah Aldossary.

Software: Ziyad S Almalki.

Supervision: Ziyad S Almalki, Sarah Alsubaie.

Writing – original draft: Ziyad S Almalki, Bedor Abdullah AlOmari, Areej Alshlowi, Mohd Faiyaz Khan, Ali Hazazi, Maha Alruwaily, Sarah Alsubaie, Norah Aldossary, Raseel Albahkali.

Writing – review & editing: Ziyad S Almalki, Bedor Abdullah AlOmari, Mohd Faiyaz Khan, Faten Alanazi, Norah Aldossary, Raseel Albahkali.

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