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Long-term blood pressure control assessment using time spent in therapeutic range among Saudi patients

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Abstract. – OBJECTIVE: Time in therapeutic range (TTR) is a new approach to monitoring blood pressure (BP), providing a more accurate picture over time compared to the standard single BP measurement during a clinic visit. Currently, no study from Saudi Arabia has explored the use of TTR in assessing BP control and its related factors. Thus, we aimed to investigate them in this study.

PATIENTS AND METHODS: Participants aged ≥ 18 years with at least three BP measurements from January 2016 to December 2020 were enrolled. Patient data were collected, including the date of hypertension (HTN) diagnosis, comorbidities, medication history, and laboratory test results. TTR values were calculated, and descriptive statistical analysis was applied to assess the differences between patients with TTR ≥ 50% and those with TTR < 50%. The Poisson regression model was used to describe the associations between patient characteristics and TTR values.

RESULTS: 30,694 patients were included, with 74% identified as having TTR < 50%. Female gender, concomitant diabetes mellitus, or cardiovascular diseases were significantly associated with TTR ≥ 50% ($p < 0.02$). Conversely, increasing age, body mass index, years with HTN, or hyperlipidemia were associated with TTR < 50% ($p < 0.001$).

CONCLUSIONS: According to the 2017 American College of Cardiology and the American Heart Association (ACC/AHA) guidelines, about three-quarters of the patients presented with TTR < 50% among the screened Saudi cohort. The results of this study may raise concerns about clinicians' adherence to the updated HTN management guidelines and patients' compliance with their treatment plans. This underscores the urgent need to improve HTN management and TTR attainment among Saudi patients.

Key Words:
Hypertension (HTN), Blood pressure monitoring, Time in therapeutic range (TTR), Saudi Arabia, 2017 ACC/AHA guidelines.

Introduction

Hypertension (HTN) is a common medical condition that increases the risk of life-threatening diseases, mainly cardiovascular diseases (CVD)[1]. Consequently, HTN is associated with a high mortality rate globally[2]. The risk of CVD escalates two-fold with each 20 millimeters of mercury (mm Hg) increase in systolic blood pressure (SBP) or 10 mm Hg increase in diastolic blood pressure (DBP)[3]. In contrast, CVD incidents and mortality rates can be reduced significantly with each 10 mm Hg reduction in SBP, as concluded by a meta-analysis involving more than 100,000 patients[4]. The World Health Organization (WHO)[2] estimated that 1.28 billion adults aged between 30 and 79

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years are affected by HTN. Essential (primary) HTN is the most common form of HTN, affecting more than 90% of hypertensive cases[5]. Essential HTN is defined as an elevated blood pressure (BP) of an unidentified cause that increases the risk for cardiovascular, cerebral, and renal events[6]. In Saudi Arabia, the estimated HTN prevalence in 2019 among individuals aged ≥ 15 years was 14%[7]. This finding is consistent with a previous national survey[8] in 2013 indicating that 15.2% of Saudis aged ≥15 years have HTN. Furthermore, a recent study by Alyabsi et al[9] in Riyadh covering 10,220 untreated individuals found that 14.1% of the surveyed Saudi adults had HTN. According to these studies[7-9], males have a higher HTN prevalence than females.

In 2003, the Seventh Report of the Joint National Committee (JNC 7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[10] released guidelines for HTN management in clinical settings. The JNC 7 classified BP levels into distinct categories. Normal BP was defined as SBP < 120 mm Hg and DBP < 80 mm Hg. Prehypertension was characterized by SBP ranging from 120 to 139 mm Hg and/or DBP from 80 to 89 mm Hg. HTN was considered when SBP readings ≥ 140 mm Hg and/or DBP readings ≥ 90 mm Hg were confirmed in at least three separate measurements[10,11]. These thresholds were recommended to be lowered thereafter based on a randomized controlled Systolic Blood Pressure Intervention Trial (SPRINT)[12] involving more than 9,000 participants. The patients in this study were followed up for over three years to evaluate whether lowering SBP values below 120 mm Hg (intensive treatment approach) had a better prognosis than maintaining SBP values below 140 mm Hg (standard treatment approach). They found that intensive BP lowering significantly reduced the incidence of CVDs and mortality events compared to standard treatment (1.65% per year *vs.* 2.19% hazard ratio, respectively)[12]. Furthermore, evidence from multiple meta-analyses of prospective and observational studies[13-16] indicated that increasing SBP above 130 mm Hg was associated with an increased risk of CVDs. Accordingly, in 2017, the American College of Cardiology and the American Heart Association (ACC/AHA) introduced a new classification of BP levels that updated the previous (JNC 7) guidelines. The main changes noted in the new classification concern the prehypertension category. This category has been divided into two distinct groups: elevated BP, manifested by SBP ranging from 120 to 129 mm Hg and/or DBP < 80 mm Hg, while SBP ranging from 130 to 139 mm Hg and/or DBP between 80 and 89 mm Hg was defined as stage 1 HTN. In addition, stage 2 HTN has been described as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg rather than the previous JNC 7 thresholds (SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg)[17]. Hence, the updated classification has lowered the level of HTN to 130/80 mm Hg and higher. The 2017 ACC/AHA guidelines were later adopted by nine other medical organizations within the United States, including the American Academy of Physician Assistants (AAPA), Association of Black Cardiologists (ABC), American College of Preventive Medicine (ACPM), American Geriatrics Society (AGS), American Pharmacists Association (APhA), American Society of Hypertension (ASH), American Society for Preventive Cardiology (ASPC), National Medical Association (NMA), and Preventive Cardiovascular Nurses Association (PCNA), and the culminating shared report was published[18]. The impact of the 2017 ACC/AHA guidelines on the prevalence of HTN among Saudis was previously assessed by Alyabsi et al[9]. Their findings revealed that HTN increased from 14.49% based on JNC 7 to 40.77%, according to the latest guidelines. However, it is crucial to recognize potential limitations in their methodology; the estimation of BP was based on average readings throughout the study. This could be misleading where episodes with abnormally high and low BP readings could be averaged out to the targeted BP despite the patient being outside of the target therapeutic range. Moreover, it is important to note their study was confined to one city in Saudi Arabia (Riyadh). The main goal in managing HTN extends beyond merely achieving targeted BP levels; long-term maintenance BP control is essential to prevent both primary and secondary end-organ complications[19].

Assessing time in therapeutic range (TTR) is a novel metric approach to monitoring patients with HTN as it provides a better prediction of clinical outcomes, such as cardiovascular prognosis, renal events, and death[20-22]. TTR provides a comprehensive disease management assessment by measuring BP over long-term follow-up to uncover current and previous BP control status rather than relying solely on incidental BP readings obtained during clinic visits[23]. Based on multiple BP recordings, TTR represents the proportion of time a patient spends in a normotensive range. Patients who consistently maintained

SBP between 120-140 mm Hg for most of their recorded time (≥ 50%) demonstrated a low risk of all-cause mortality and morbidity compared to those with intermediate (≤ 50%) or sporadic (≤ 0-25%) therapeutic BP control[20,24-26].

The TTR approach has been notably successful in monitoring patients receiving warfarin, an anticoagulant, to estimate prothrombin time within the therapeutic range over long time intervals. TTR has proven to have a significant correlation with positive thromboembolic outcomes; thus, assessment of TTR helps optimize the efficacy and safety of warfarin[27,28]. TTR assessment in patients undergoing treatment for hypertension or thrombosis is similar to measuring glycosylated hemoglobin (HbA1c) as a biomarker to assess overall long-term glycemic control. Despite the well-known benefits of TTR assessment, no study has yet investigated its application in the long-term management of HTN in Saudi Arabia. Therefore, this study aimed to fill the gap by evaluating TTR in Saudi patients with essential HTN and examining its association with patients' demographic and clinical characteristics.

Patients and Methods

Study Design

Patients' records were screened over five years (January 2016-December 2020). The required data were extracted from an electronic medical record (EMR) system called BESTCare, a patient database platform developed by the Ministry of National Guard Health Affairs (MNGHA), facilitating access to patients' EMRs. The study included patients diagnosed with essential hypertension attending primary care centers and hospitals within MNGHA, including six large medical hospitals across different regions of the Kingdom [two hospitals in the Central region (Riyadh), two in the East (Dammam and Al-Hassa), one in the West (Jeddah), and one in Madinah city], along with 24 primary care centers.

Study Subjects

The recruited participants were Saudi adults (≥ 18 years), with age determined at the time of diagnosis and the first recorded BP value. A minimum of three BP measurements in an outpatient setting were required for inclusion. Eligibility criteria were restricted to patients diagnosed with essential (primary) HTN, excluding patients with a history of a secondary form of HTN such as renal parenchymal HTN, drug-induced HTN, and renovascular HTN or those with concurrent disease-causing HTN such as coarctation of the aorta, primary hyperaldosteronism, Cushing's disease, unilateral or bilateral renal artery stenosis, pheochromocytoma, and polycystic kidney disease.

Data Analysis

All BP recorded values, documented throughout various clinic visits over the five years, were collected. These values were used to calculate the TTR, representing the percentage of time spent within a specified BP range (SBP of 90-129 mm Hg and DBP of 60-79 mm Hg). According to the 2017 ACC/AHA guidelines[29], readings of (1) SBP > 129 mm Hg and/or DBP > 80 mm Hg and (2) SBP < 90 and/or DBP < 60 mm Hg were considered above and below the targeted therapeutic range, respectively. Patients' demographics [age, gender, and body mass index (BMI)], and other variables such as the total number of antihypertensive medication (TNAHM) classes prescribed during the therapeutic journey of the patient, date of hypertension diagnosis (from which the years with hypertension was estimated), lipid profiles, and comorbidities [e.g., diabetes mellitus (DM), heart and kidney diseases] were collected to determine its association with TTR values. Furthermore, the patients were classified into eight distinct age groups (18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, and 85 years and above) to facilitate an analysis of the trends of the TTR pattern across different age cohort. Patients' characteristics were reported using mean and standard deviation (SD) for continuous parametric variables and number/frequency for binary variables.

Statistical Analysis

One way analysis of variance (ANOVA) was used to identify and compare TTR trends across different age groups. Conversely, the Chi-square test was used to compare the frequency of categorical variables between groups. Poisson regression analysis was performed to compute adjusted odds ratios (OR) and 95% confidence interval (95% CI) to elucidate the association between patients' characteristics and TTR values (as continuous variables) among the cohort. The association values were adjusted for age, gender, BMI, and duration of HTN. Covariates were included in the model if they reached a statistically significant level at $p < 0.05$ in univariate analysis. Mul-

ticollinearity was assessed using the variance inflation factor. Statistical analyses were performed using the International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) 27 (IBM Corp., Armonk, NY, USA).

Results

Patients' Characteristics

Among a cohort exceeding 70,000 hypertensive patients from Saudi Arabia, 30,694 fulfilled the inclusion criteria and were enrolled in this study. Notably, 74% of the cohort had TTR < 50% (Table I). Those patients were distinguished by older age [mean age: 62 (± 12) years *vs.* 58 (± 13) years, $p < 0.001$], high BMI values [32.7 (± 6.7) *vs.* 31.7 (± 6.5), $p < 0.001$], were prescribed more TNAHM [1.5 (± 1.4) *vs.* 1.2 (± 1.3), $p < 0.001$], and had a prolonged duration of HTN [4.7 (± 1.3) *vs.* 4.4 (± 1.4), $p < 0.001$] compared to those with TTR ≥ 50%. Regarding comorbidities, patients with TTR < 50% had a slightly higher prevalence of DM (80% *vs.* 79%), kidney diseases (16% *vs.* 15%), and hyperlipidemia (14% *vs.* 13%), though they were less susceptible to CVD (8% *vs.* 10%, $p < 0.001$) (Table I).

The Analysis of TTR Patterns Across Different Age Groups

Among younger age groups (18-24, 25-34, and 35-44 years), the percentage of TTR < 50% was remarkably lower (61%) than in the older age group. The proportion of patients with TTR < 50% began to increase significantly from the age group of 45-54 years, reaching its highest value of 80% within the 55-64 and 65-74 years age groups (Figure 1). Furthermore, a significant increase in the TNAHM prescriptions was evident with increasing age (Figure 2).

Factors Associated With TTR

After adjusting for age, gender, years with HTN and BMI, the Poisson logistic regression model shows that female gender (OR = 1.099, 95% CI = 1.05-1.26), concomitant DM (OR = 1.07, 95% CI = 1.01-1.14), or CVD (OR = 1.311, 95% CI = 1.22-1.41) were significantly associated with TTR ≥ 50% (Table II). Conversely, advancing age (OR = 1.015, 95% CI = 1.01-1.26), elevated BMI (OR = 1.02, 95% CI = 1.02-1.03), longer duration of HTN (OR = 1.04, 95% CI = 1.02-1.06), or the presence of hyperlipidemia (OR = 1.189, 95% CI = 1.11-1.28) were associated with TTR < 50%.

Discussion

Hypertension is a leading cause of cardiovascular disorders, including myocardial infarction, heart failure, renal impairment, and stroke. Effective antihypertensive pharmacotherapy, combined with lifestyle modifications, is crucial for

Table I. Clinical characteristics of patients included in the study, stratified according to their TTR values.

	Whole cohort (n = 30,694)	TTR < 50% (n = 22,566)	TTR ≥ 50% (n = 8,128)	*p*-value
TTR%, mean (±SD)	32.4 (± 26.5)	19.1 (± 14.4)	69.4 (± 14.5)	< 0.001
Age, mean (±SD)	61 (± 12)	62 (± 12)	58 (± 13)	< 0.001
Gender, female, n (%)	17,599 (57)	13,012 (58)	4,587 (56)	0.06
TNAHM, mean (±SD)	1.4 (± 1.4)	1.5 (± 1.4)	1.2 (± 1.3)	< 0.001
BMI, mean (± SD)	32.4 (± 6.6)	32.7 (± 6.7)	31.7 (± 6.5)	< 0.001
Years with HTN, mean (± SD)	4.6 (± 1.3)	4.7 (± 1.3)	4.4 (± 1.4)	< 0.001
Comorbidities				
Diabetes mellitus, n (%)	24,536 (80)	18,139 (80)	6,397 (79)	0.001
Kidney diseases, n (%)	4,881 (16)	3,666 (16)	1,215 (15)	0.006
Hyperlipidemia, n (%)	4,249 (14)	3,232 (14)	1,017 (13)	< 0.001
CVD, n (%)	2,533 (8)	1,756 (8)	777 (10)	< 0.001
Stroke, n (%)	462 (2)	351 (2)	111 (1)	0.2

TTR: Time in therapeutic range, THAHM: Total number of antihypertensive medications, BMI: Body mass index, HTN: Hypertension, CVD: Cardiovascular diseases.

Table II. Factors associated with the time in therapeutic range variability among the studied cohort. OR represents the adjusted odds ratio based on the Poisson regression model.

Characteristics	TTR	OR	95% CI	*p*-value
Gender (female)	≥ 50%	1.099	1.046-1.256	< 0.001
Age	< 50%	1.015	1.014-1.017	< 0.001
BMI	< 50%	1.02	1.016-1.025	< 0.001
Duration of HTN	< 50%	1.04	1.02-1.06	< 0.001
Diabetes mellitus	≥ 50%	1.07	1.008-1.135	0.027
Cardiovascular diseases	≥ 50%	1.311	1.219-1.409	< 0.001
Kidney diseases	< 50%	1.042	0.971-1.118	0.256
Hyperlipidemia	< 50%	1.189	1.108-1.277	< 0.001
Stroke	< 50%	1.027	0.882-1.179	0.727

BMI: Body mass index, HTN: Hypertension, TTR: Time in therapeutic range.

both symptom relief and cardiovascular protection[30]. The Global Burden of Disease study[31] in 2019 indicated that HTN is one of the leading causes of death in the Kingdom of Saudi Arabia. Despite the seriousness of the disease, only a fifth of hypertensive patients under treatment achieve adequate BP control globally[2]. According to the JNC 7 guidelines, the Saudi national survey study in 2014 revealed that 40.6% of the screened individuals were in the prehypertensive stage, 57.8% of hypertensive patients remained undiagnosed, and 55% of treated patients exhibited uncontrolled BP[8]. Additionally, if the newly recommended 2017 ACC/AHA HTN guidelines[17] were applied, it is anticipated that the prevalence of HTN will increase further. The principal finding of this observational retrospective cohort study is that the majority of the included patients demonstrated poor BP control and low TTR levels, with approximately three-quarters of the cohort showing a mean TTR of less than 20%. This rate of uncontrolled HTN is higher than the previously reported rates (55-65%) by the Saudi national survey and a recent meta-analysis study focusing on hypertensive patients undergoing treatment[8,32]. This disparity can be attributed to

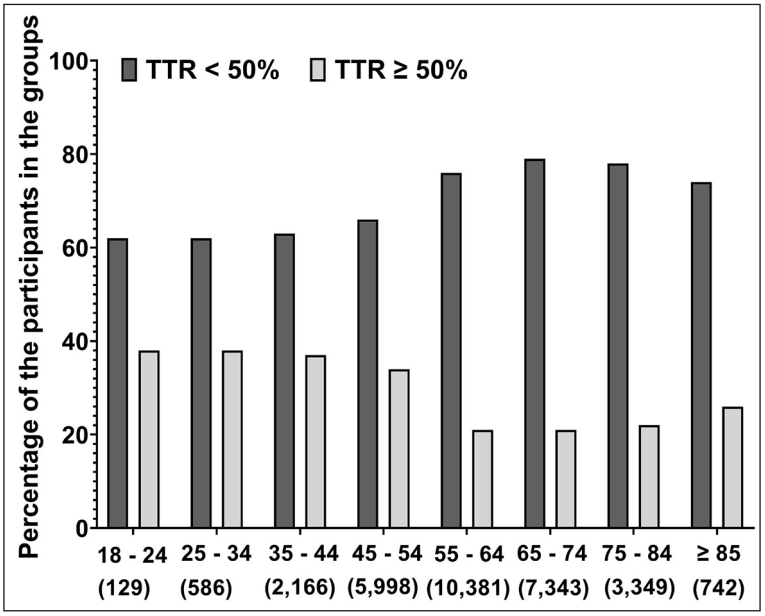

Figure 1. Differences in time in therapeutic range (TTR) among different age groups of HTN patients. Significant statistical differences were obtained ($p < 0.001$).

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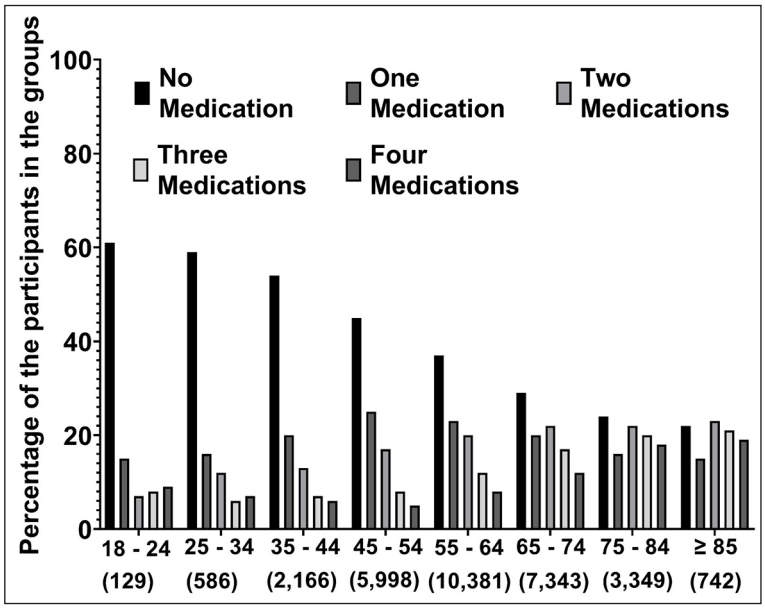

Figure 2. Differences in number of prescribed antihypertensive medications among different age groups of HTN patients. Significant statistical differences were obtained ($p < 0.001$).

the strict criteria applied in our study, which are aligned with the 2017 ACC/AHA guidelines. The low TTR rates observed in our study are consistent with findings from previous studies conducted on diverse populations, all of which adhered to the latest BP guidelines. For instance, a study[33] conducted in Korea reported that the percentage of patients with uncontrolled BP elevated from 40.9% (based on the JNC 7) to 83.9% (based on the 2017 ACC/AHA guidelines). Similarly, a study[34] on the US population revealed that more than 50% of patients receiving antihypertensive medications exhibited uncontrolled HTN when assessed using the 2017 ACC/AHA guidelines. Moreover, our study identified significant associations between TTR values and various variables. The results showed that factors including female gender, diabetes mellitus, or CVD were major contributors to high TTR rates (≥ 50%). Conversely, an increase in age, elevated BMI, longer HTN duration, or hyperlipidemia were associated with lower TTR rates. These risk factors have been previously reported to be associated with resistant HTN and poor control of BP[35-37].

Our results revealed that for each year of age increment, there was a 1.5% increase in the risk of achieving a TTR level < 50%. The majority of patients in our study cohort aged ≥ 60 years exhibited lower TTR levels. This observation aligns with previous findings in patients receiving warfarin treatment, where advanced age was associated with a reduction in TTR values measured by International Normalized Ratios (INR)[38]. Aging is frequently accompanied by the development of multiple comorbidities, requiring the usage of various medications, a phenomenon known as polypharmacy[39]. This was evident in our study, where the number of given medications (TNAHM) proportionally increased with increasing age. Consequently, patient adherence to numerous medications becomes crucial, especially among older patients who are more vulnerable to experiencing TTR < 50%. Another factor underlying lower TTR% in older age groups is the implementation of former BP guidelines, which set up BP level < 150/90 mm Hg as the treatment goal for patients aged ≥ 60 years[40]. Thus, healthcare providers should follow the latest 2017 ACC/AHA recommendations and conduct comprehensive medication reviews to assess adherence issues among their patients, thereby ensuring effective management of HTN.

Another important finding is the impact of BMI as a modifiable risk factor, with each unit increase in BMI leading to a 2% reduction in TTR levels. This finding is consistent with previous studies demonstrating a correlation between BMI and developing HTN and its influence on poor BP control in patients treated with antihypertensives[41-43]. Diabetes and HTN commonly coexist due to shared biological characteristics, making hypertension particularly concerning

for individuals with diabetes. This comorbidity significantly increases the risk of premature microvascular and macrovascular complications[44]. In our study, we found that 80% of the current hypertension cohort is also diabetics, and our adjusted regression model revealed that diabetic patients are more prone to achieve higher TTR rates. Interestingly, we recently reported that the majority (70%) of diabetic Saudi patients have comorbid hypertension[45], which emphasizes a bidirectional relationship between hypertension and DM. These findings confirm the strong correlation between HTN and DM[46-48]. In addition, we found that patients with CVD showed better TTR values than those without CVD. This could be attributed to the higher medication adherence among CVD patients. This conclusion is supported by a previous study indicating greater compliance among CVD patients using HTN medications for secondary prevention purposes compared to those using them for primary prevention purposes[49]. It is important to indicate that compliance data for our study cohort was unavailable. Using the tight BP control suggested by 2017 ACC/AHA guidelines, along with TTR methodology, is essential to reduce CVD complications, predict adverse events, and improve clinical outcomes[20,26,33,50,51].

These new data raise an important question of how clinicians adhere to and apply the current guidelines of HTN management. Therefore, continued education for healthcare providers and patients regarding the latest treatment guidelines and the significance of the TTR approach in assessing BP control is crucial to ensure safe and effective monitoring and management of HTN[52]. In a previous study, Kario et al[53] demonstrated that digital technology significantly improved adherence to medications, physical activity, salt intake restriction, and lifestyle modifications, resulting in improved TTR rates and HTN management. To the best of our knowledge, no research in Saudi Arabia has investigated the impact of digital technology on TTR for BP levels and subsequent clinical outcomes. Therefore, future studies should prioritize investigating the effectiveness of digital tools in improving BP control, not only in Saudi Arabia but globally. This approach is optimal for encouraging multidisciplinary care involving physicians, pharmacists, nurses, dietitians, and patients, thereby promoting HTN management through ensuring medication adherence and proper monitoring of BP control.

The present study is the first to investigate the TTR values in assessing BP control in Saudi Arabia. Our study's strengths include the large sample size (exceeding 30,000 hypertensive patients) and the collection of patient data from primary care centers and hospitals across multiple regions in the country. Furthermore, our study's utilization of the TTR to examine HTN management effectiveness offers valuable insights into current practice and points out factors requiring attention for improved HTN management within similar patient cohorts.

Limitations

Several limitations in our study should be acknowledged. Firstly, the precise history of anti-hypertensive medication classes prescribing and the pattern of their combination were not feasible. This could create uncertainty in assessing the relationship between specific drug classes and TTR values as data were collected retrospectively. This limitation restricted our ability to evaluate the appropriateness of anti-hypertensive medications usage and interpret their effectiveness truthfully. Secondly, since follow-up data is unavailable, longer-term treatment outcomes associated with antihypertensive medications, including efficacy and adverse drug reactions, were not obtained. Finally, it was not possible to describe the trajectory of antihypertensive medication used over time and its correlation with changes in the disease progression or management courses.

Conclusions

The TTR monitoring approach, which relies on measuring BP over long-term follow-up, affords objective and unbiased information to healthcare providers to assess BP control better, manage, and predict outcomes for HTN patients. The extremely low TTR values noticed in the majority of hypertensive patients in our study are alarming and emphasize the need for intensified efforts from clinicians to monitor and manage patients. They need to follow the latest treatment guidelines suggested by ACC/AHA and closely monitor the patient's adherence to their treatment plans. This is essential to achieve and maintain BP within the target TTR values, which is expected to improve disease outcomes and minimize its complications and burden among Saudi patients.

Conflict of Interest
The authors declare no conflict of interest to report.

Authors' Contributions
M. Alshabeeb and R. Alajlan conceptualized the study, prepared the study proposal, and planned and collected data. M. Alshabeeb, R. Alajlan, and S. Abohelaika analyzed patients' profile data. S. Abohelaika, A. Alqurain, and M. Alshabeeb performed data analyses, while F. Alomar, R. Alajlan, and F. Alherz supported data analysis. M. Alshabeeb, R. Alajlan, S. Abohelaika, and A. Alqurain wrote the introduction, methods, and results sections. All authors participated in preparing the discussion section, and F. Alomar and F. Alherz edited the manuscript. All authors have read and agreed to the final version of the manuscript.

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Informed Consent
The data were collected from chart reviews devoid of direct interaction with patients or presentation of identifiable images or data. Thus, informed consent from patients was not required for this study according to the national legislation and institutional policy.

Ethics Approval
This observational retrospective cohort study was reviewed and approved by the Institutional Review Board (IRB) at King Abdullah International Medical Research Centre (KAIMRC), Riyadh, Kingdom of Saudi Arabia (approval reference number: NRC21R/464/11; date: 28 November 2021).

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Availability of Data and Materials
The data supporting the findings of this study are available upon reasonable request from the corresponding author.

AI Disclosure
No artificial intelligence tools were used for writing or conducting the research.

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