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Knowledge Representation and Reasoning

Dr.Google in Patient-Physician Interactions: Pros and Cons

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ABSTRACT

Dr Google has evolved with time from being a medical infopedia to an artificial intelligence (AI) powered provider capable of interacting with patients in real-time due to the involvement of social media and AI chatbots. Dr Google is not only consulted as a pre-visiting health information searching tool but also provides health monitoring and treatment plans. With the help of social media, people can connect and share medical information through health forums and YouTube videos and seek help. However, it can create new challenges for medical providers through rapport building, challenging preconceived notions, and managing unnecessary patient demands. The involvement of Google can have advantages and disadvantages from patients' and doctors' viewpoints and can affect the physician scoring system and insurance reimbursement. Hence, it is critical to review the pros and cons of Google's involvement in medicine and understand the possible future implications.

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INTRODUCTION

Dr Google is considered a widely accessible medical information platform on the internet, providing website articles, videos, blogs, discussion forums, and recently available AI chatbots, such as ChatGPT. These platforms can provide information on health and disease, including the natural history of a disease, the presumptive diagnosis, and treatment options.[1] In the modern era, Dr. Google has evolved to encompass emerging platforms, such as data-based AI models and social media networks like Twitter, Facebook, YouTube, and Reddit forums, which are faster and more interactive. Individuals can interact and share information with the help of direct messages, webinars, online promotions, and collaborations.[2] People using the internet are more likely to report reassurance (regression coefficient=0.18; $p<0.0001$)[3], though there is not enough data on the quality of this information. The information on Dr Google could be of high quality and evidence-based through medical journals and official websites, or it could be suboptimal and biased in the form of medical blogs, discussion forums, YouTube videos, and health promotions on social media, and the information obtained through modern AI chatbots is questionable.[4,5] Google is the most popular search engine worldwide and is extensively used to access medical information by individuals before visiting their general practitioner (GP) to search for their symptoms and try to self-diagnose.[6,7] Instead of investigating what they might be experiencing and whether or not more testing is necessary, people use the information offered by Dr Google to schedule appointments with their general practitioners to explore the possibilities available online. The findings may impact the doctor-patient relationship with Dr Google, which may or may not align with the doctor's diagnosis and recommended course of treatment. Patients may request additional diagnostic testing.[8] It is also likely from such an interaction that patients may seek multiple opinions, change or negatively rate their physician or self-medicate, which lands the physicians in a situation where they may agree to fulfil a patient's demand.[9] It is feared that prescribing based on patient demand can lead to over-utilization of medical resources and affect the quality of care.[10]

The focus of this review article is to research how the internet-seeking behaviour of patients has changed with the introduction of social media and modern AI tools, laying down its advantages and disadvantages. It is crucial to review how Dr Google has affected the physician scoring system, insurance reimbursement, and future implications on the physician-patient relationship.

Pros and Cons of Dr Google

Patient's perspective

Doctors perceive the Internet as challenging current medical practice and therapeutic relationships. However, there are advantages and disadvantages to using the internet when looking from the patient's perspective. Since consultation with a doctor is time-limited, the Internet can be a supplementary guide to make patients more aware of their condition and educate them about available treatment options.[11] A study carried out by Al Ghamdi and Moussa[12] highlighted that 45% of the patients presenting to the physician had searched the internet for information before their appointment, 72.5% of them discussed the information with their doctors, and 71.7% of the patients who discussed the information believed that it had a positive impact on the physician-patient relationship.[12] On the other hand, bringing up and discussing the information searched for on the internet also led to conflicts between the patients and physicians. This stemmed from different interpretations of the online information, leading to a difference in opinion, often leading to patients ignoring the physician's expertise.[13,14] Some patients use the Internet as a replacement for healthcare services instead of a supplement, which can lead them to self-diagnose, seek information on alternative treatments and medicine, or engage in healthcare strategies inconsistent with medical recommendations.[15] The ease with which medical information is available on the internet causes patients to have cyberchondria, defined as increased distress and health anxiety due to repeated online searching, which persists despite interference with functioning and negative consequences.[16] The risk factors for the development of cyberchondria are poor coping with information overload, erroneous expectations of the internet, and confusion about the trustworthiness of the sources of online health information.[17]

Physician's perspective

Internet use by patients can serve as a big advantage to the physician in cases where patients use the abundant information available on the internet concerning wellness and disease prevention.[18] The internet can prove an effective channel for primary health promotion, encouraging people to scour the internet for health information and maintain a healthy lifestyle. This internet-based lifestyle intervention can overcome barriers to preventive counselling. It can help incorporate evidence-based lifestyle interventions into primary care, providing moti-

vation and methods for behaviour change.[19] The internet has benefited patients seeking cancer care since self-aggregating patient groups online helps find new research options and thus ensures faster enrollment in clinical trials.[20] There is increased medical content available online, which precludes the possibility of any health practitioner having information about everything that can be helpful to the patient.[21]

Patient-Physician Relationship

The physician-patient relationship is thought to depend on multiple factors, which include, but are not limited to, the prior relationship of the physician to the patient, patient demographics, etc.

Most patients in multiple studies reported that internet health information seeking did not adversely affect the physician-patient relationship.[11,18] A study by Newnham et al.[22] reported that 40% of patients felt that the physician-patient relationship was unaffected by internet searching, 24% felt that it improved the relationship, and only 8% felt that it affected the relationship adversely. The patients who perceived their relationship with the physicians had improved saw the internet as an additional source supporting the doctors' advice.[11]

In addition, a study by Murray et al. also highlighted the impact of physicians' reactions to patients sharing their online findings in determining the positive or negative effect on the relationship's quality.[9] In situations where the patients felt that the physicians were threatened by their bringing up online information, 49% of the patients were seriously dissatisfied with the consultation, and 4% believed that their relationship had worsened. Positive effects were observed when the physician was not challenged by the online information.[23]

Patient Satisfaction score

The involvement of Dr Google can introduce new challenges for physicians, such as elaborate debates with Google-informed patients and the dilemma of prescribing services at the patient's demand.[10] This can adversely affect patient satisfaction scores and may lead physicians to agree with the patient's needs in scenarios where high-value care may not align with patient satisfaction. For example, not suggesting early imaging for lower back pain or not prescribing antibiotics for upper respiratory infections can be considered low-value care.[24] This may lead to physicians being rated low by the patients, adversely affecting insurance reimbursement. Physicians may agree to such requests if they face penalties due to low patient satisfaction scores.[10] Moreover, a study found that higher patient satisfaction was associated with greater healthcare expenditure and greater mortality.[25] This may highlight the negative impact of Dr Google on the healthcare system. However, further research is needed to critically analyse the effects of Google-informed patients seeking healthcare services and physician rating systems.

Future Perspective

As Dr Google's influence continues to grow in the healthcare sector, there are various potential future perspectives on physician management and patient education. While acknowledging the constraints and challenges of using internet health information, it is crucial to investigate the possible benefits and opportunities Dr Google can provide.

Facilitating Patient-Physician Collaboration

In the future, healthcare practitioners should actively encourage patients to conduct online research by directing them to credible sources and giving tools for important information evaluation. By acknowledging and incorporating patients ' web research into consultations, physicians can establish a shared understanding and collaborate with patients to generate individualised treatment programmes. This collaborative approach can improve the doctor-patient relationship, patient satisfaction, and healthcare results.[26,27] It is crucial to understand that sometimes symptoms may be non-specific and not always indicate a specific disease. Sometimes, more than one symptom may confuse the diagnosis, especially in systemic diseases. In addition, the diagnosis of a severe disease may be delayed if the internet source misinterprets the patient's symptoms and findings, delaying the doctor's visit or directing the patient to the wrong specialist. Hence, the person who makes the final decision regarding examination, diagnosis, and treatment is a physician.

Leveraging Artificial Intelligence for Predicting Future Risk

Large amounts of medical information can be aggregated and analysed by online search engines from various sources, including academic publications, clinical studies, and health databases. This data can be analysed to determine certain illnesses' patterns, trends, and risk factors. Online resources can provide information on various symptoms and their possible causes. People can learn about potential health hazards by comparing their symptoms to the information offered. On the oth-

er hand, self-diagnosis should be treated cautiously, and it's always best to visit a healthcare expert for an appropriate assessment.[28,29] Recently, Google has made major advances in using artificial intelligence (AI) to forecast cardiovascular risk and strokes by utilising retail scans to screen patients for diabetic retinopathy. Google's AI technology has shown encouraging results in finding minor signs and patterns indicative of cardiovascular health by applying deep learning algorithms to an extensive collection of retinal images. AI algorithms may accurately forecast an individual's risk of developing cardiovascular illnesses and stroke using this novel approach, even before clinical symptoms appear. This technology has the potential to transform preventive healthcare by enabling early interventions, personalised risk assessments, and tailored treatment strategies based on non-invasive screenings that are easily accessible.[30]

Personalized Medicine and Precision Healthcare

In collaboration with upcoming technologies like genomics and wearable devices like smartphones and watches, Dr Google has the potential to pave the path for personalised medicine and precision healthcare. Patients may have access to internet platforms in the future that combine their health data, genetic information, and lifestyle factors to provide personalised health insights and suggestions. Physicians can use this detailed patient profile and their medical skills to provide precise, patient-centered care. By merging online health information and self-reported data, healthcare practitioners can better understand each patient's unique healthcare needs, resulting in more effective interventions and improved outcomes.[31,32]

Online Intellectual Property Rights Infringement of Scientific Work

A recent issue in the era of AI-powered Dr Google is the violation of the intellectual property rights of the authors of scientific sources, research papers and books. Questions concerning unlicensed content in training data, rights of use and infringement, ownership of AI-generated works, and whether or not users should be able to prompt these tools with direct references to other creators' copyrighted and trademarked works by name without their consent are all raised by these upcoming developments.33 It is also essential to consider the risk of Dr Google users being accused of intellectual rights violations by indirectly being able to access protected information. This issue is on the agenda in many countries, including the USA and China, and it is clear that current laws and regulations are inadequate and need updating.

CONCLUSIONS

The use of the internet for seeking health information, commonly known as Dr Google, has developed into a complex information-sharing and AI-generated aid. Dr Google can have pros and cons, requiring consideration of multiple factors. The impact of Dr Google on patient satisfaction scores is an emerging challenge that needs further research. Moreover, the future implications of Dr Google have promising benefits. However, the impact of such consequences can be better observed as Dr Google unfolds further.

Authors' Contribution

Study Conception: BS, PS, FA, GK, VG, RJ; Study Design: BS, PS, FA, GK, VG, RJ; Literature Review: BS, PS, FA, GK, VG, RJ; Critical Review: GK, VG, RJ; Manuscript preparing: BS, PS, FA.

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Cardiovascular Medicine and Haematology

Physical therapy and the arrhythmias: The potential benefits and challenges of their kinship

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ABSTRACT

Cardiovascular disease is the primary cause of mortality in the United States, and cardiac arrhythmias are a common cause of hospital admission with significant mortality and morbidity. Cardiovascular diseases significantly burden the healthcare system, with high costs associated with hospitalization, medication, and ongoing management. By finding cost-effective methods to prevent and treat cardiovascular diseases, healthcare resources can be allocated more efficiently, ultimately improving health outcomes and reducing the burden on the healthcare system. Exercise therapy is a low-cost intervention that can be done without expensive equipment or medical procedures. Exercise therapy can help decrease risk factors for heart disease, including high blood pressure, obesity, and high cholesterol, by improving overall fitness and reducing chronic inflammation. Over time, there have been concerns about exercise-induced arrhythmia because it can reduce physical activity among patients with arrhythmia. In this review, we emphasized the beneficial effects of physical activity on arrhythmia patients.

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INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of mortality in the United States, resulting in the death of one person every 34 seconds. In 2020, it claimed the lives of almost 697,000 people, accounting for 1 in 5 fatalities.[1] An abnormality with the rate or rhythm of the heartbeat is known as arrhythmia, and common symptoms include chest pain, palpitations, dizziness, weakness, and shortness of breath. Atrial fibrillation (AF), the most common arrhythmia, affects three to six million people in the United States, and it is the primary diagnosis in more than 454,000 hospital admissions annually.[2,3] By 2030, it is projected that AF will impact around 12.1 million individuals in the United States.[3] This necessitates more effective and innovative techniques to diagnose, treat, and prevent cardiovascular disorders. Exercise therapy is crucial in preventing and treating CVD. Exercise therapy is a structured form of physical activity that is carried out to achieve certain physical benefits. These benefits may include maintaining range of motion, strengthening muscles, increasing joint flexibility, or improving cardiovascular and pulmonary function.[4] According to the Physical Activity Guidelines for Americans (PAG), physical activity can be categorised as mild, moderate, or high intensity based on specific levels of energy expenditure (Table 1). The expression of energy expenditure is done using multiples of the metabolic equivalent of task (MET), with 1 MET being the rate of energy expenditure while in a sedentary position. Non-sedentary walking behaviour that requires less than 3.0 MET is considered light-intensity activity. 3.0 to fewer than 6.0 METs are required for moderate-intensity exercise, and vigorous activity needs 6.0 or more METs. The PAG suggest engaging in a minimum of 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) of moderate-intensity aerobic exercise per week. Alternatively, one can opt for 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) of vigorous-intensity aerobic exercise per week. Another option is to combine both moderate- and vigorous-intensity aerobic activities equivalently.5 The EXPERT (Exercise Prescription in Everyday Practice and Rehabilitative Training) tool is an interactive, computerised system designed to provide healthcare practitioners with the ability to prescribe exercise training programs that are both clinically beneficial and medically safe for individuals with CVD.[6]

Physical exercise and cardiac health have a well-established association. Cardiovascular diseases can be prevented and treated through vigorous participation in physical activities, exercise, and achieving optimal cardiorespiratory fitness (CRF). CRF is the ability of the circulatory and respiratory systems to deliver oxygen to the mitochondria in skeletal muscles, which is necessary for energy production during physical activity.[7,8] Promoting regular moderate-to-vigorous physical activity in healthy individuals and most patients with cardiovascular illnesses is advisable. This is because such activity has positive benefits in reducing the burden of risk factors (such as obesity, hypertension, and hyperlipidemia), enhancing overall well-being, and decreasing mortality rates.[9]

Recent studies have explored the correlation between physical activity and AF, indicating that the most physically active individuals exhibit a reduced incidence of AF. For instance, participants with the highest physical activity levels in the Cardiovascular Health Study experienced a 46% lower incidence of AF than their sedentary counterparts.10 The analysis conducted by Ortega-Moral *et al.*[11] reported a significant improvement in resting heart rate, maximum exercise capacity, and vO_2 peak (maximum oxygen uptake) in patients with AF. A separate investigation by Malmo *et al.*[12] determined that a twelve-week aerobic interval training regimen diminishes AF duration in individuals with non-permanent AF. Furthermore, this training is linked to a notable enhancement in AF symptoms, O2 peak (peak oxygen consumption), left atrial and ventricular function, cholesterol levels, and overall quality of life.[13] Medical interventions concern disease causation and disease processes, whereas rehabilitation, which includes most aspects of physical activity, concerns disease consequences. Its goals are to improve symptoms, function, and quality of life.[13] While moderate exercise benefits cardiovascular health, long-term endurance sports practice is associated with a higher risk of symptomatic lone AF.[14] Due to their dread of exercise-induced episodes of AF, people with AF

Table 1. Light, moderate and vigorous intensity physical activities based on the MET[5]

Intensity	MET	Examples
Light	less than 3	walking at a slow pace, cooking
Moderate	3 to less than 6	walking briskly, raking the yard
Vigorous	6 or more	running, jogging

MET: Multiples of the metabolic equivalent of task.

are more likely to lead sedentary lifestyles; however, to maintain a healthy lifestyle, AF patients should engage in physical activity.[15] Physical activity can help to create a bridge between sedentary lifestyles and strenuous exercise that will enhance physical activity without raising the risk of arrhythmia.

Pathophysiology

One of the most effective ways to improve one's health is to engage in physical activity, which can take various forms, ranging from endurance to resistance training. According to the training specificity principle, multiple forms of exercise bring about a unique set of physiological adaptations in the body. In general, endurance exercises improve aerobic energy metabolism and fatigue resistance, whereas resistance training improves muscle hypertrophy and the body's capacity to generate force.[16,17]

On the other hand, interval training consists of shorter bouts of exercise interspersed with periods of rest. Interval training without body weight increases mitochondrial content and peak aerobic capacity (vO_2 max)[18], while interval training using bodyweight resistance exercise increases vO_2 max and muscular strength.[19] Long-term effects of any exercise typically result in brainstem cardiovascular activation, which modulates hemodynamic status during exercise by integrating signals originating from the brain and inducing an increase in blood volume, stroke volume, cardiac output, and vO_2 max along with a reduction in resting heart rate and blood pressure.[20]

Disruptions in the sympathetic and/or parasympathetic nervous systems of the autonomic nervous system (ANS) can cause cardiac arrhythmias. AF is thought to be caused by the simultaneous activation of both the sympathetic and parasympathetic systems. In contrast, ventricular fibrillation or ventricular tachycardia is believed to be caused by increased sympathetic stimulation. Stimulation of the sympathetic system is linked to the occurrence of ventricular tachycardia, which can cause irregular heart rhythms and, in severe instances, cardiac death in hereditary arrhythmia syndromes, including long QT and catecholaminergic polymorphic ventricular tachycardia. There is increasing evidence that altering the ANS can be a safe and effective treatment method for managing cardiac arrhythmias.[21] A delicate balance in these two limbs of the ANS is required to maintain arrhythmia. Several ANS-modulating interventions have been developed over the years to prevent and manage arrhythmias, in addition to traditional drug therapies such as beta-blockers.[22] It is well established that both endurance and resistance exercises can alter autonomic nervous system activity, increasing cardiac parasympathetic tone and decreasing sympathetic activity.[23] This has a positive effect on the prognosis of individuals who suffer from a variety of morbidities. When compared to other forms of exercise, resistance training has a more profound impact on both sympathetic and parasympathetic activities, especially among middle-aged women.[24] Researchers found that in a study using dogs as a model for sudden death, endurance exercise training enhanced the regulation of the parasympathetic nervous system in the heart, normalised the balance of beta-adrenoceptors (specifically, reducing sensitivity and expression of beta(2)-adrenoceptors), and provided protection against ventricular fibrillation resulting from acute myocardial ischemia. Exercise training may enhance cardiac electrical stability in individuals identified as having a heightened risk of sudden cardiac death.[22]

The complex interaction between the sympathetic and parasympathetic (vagal) limbs of the ANS regulates Ca2+ ion release and reuptake by the sarcoplasmic reticulum, leading to rhythmic contraction and heart relaxation.[25] Sympathetic stimulation causes depolarisation of the surface membrane and transverse tubule, which opens the L-type Ca channels located in them. A little amount of Ca2+ is thus introduced, and this causes a significant rise in [Ca2+] in the dyadic space (the region bounded by the t-tubule and sarcoplasmic reticulum [SR]), which makes the SR Ca2+ release channel (ryanodine receptors [RyR]) open up, causing the influx of a more significant amount of calcium from the SR in a process called calcium-induced calcium release. This calcium now binds to the troponin, which causes the sliding of thick and thin filaments, causing the cell to shorten, which causes the heart to contract. Activation of the parasympathetic nervous system causes Ca2+ to withdraw from the cytoplasm. To achieve this, RyRs close and Ca2+ is pushed back into the SR by the SR Ca-ATPase and pushed out of the cell, mostly via sodium-calcium exchange (NCX). Abnormalities in this intracellular Ca2+ handling are another mechanism that can lead to contractile dysfunction and/or trigger tachyarrhythmias. Several diseases, including heart failure and myocardial infarction, are known to cause dysregulated SR Ca2+ release, which can lead to malignant arrhythmias.[26,27]

Regular physical exercise normalises repolarisation and calcium-handling abnormalities that contribute to the onset of cardiac arrhythmias through changes in the expression of calcium-handling genes.[28] This results in a lower incidence of arrhythmia among exercise-perform-

ing individuals.

Aside from the positive effects, some studies have discovered that exercise has a negative impact on the heart, predisposing healthy individuals to arrhythmia. Exercise training causes significant changes in cardiac physiology and structure, which are referred to collectively as the "athlete's heart."[29] Exercise has been shown to increase parasympathetic tone, and parasympathetic tone shortens the atrial refractory period, allowing for easier re-entry formation and AF formation, contributing to exercise-induced arrhythmia.[30] Long-term exercise and physical activity cause a variety of structural changes. Atrial structural remodelling includes atrial dilatation as well as modifications in tissue properties and ultrastructure. Atrial enlargement is a recognised consequence of endurance exercise training that predisposes to AF. Despite evidence linking endurance exercise to AF, current guidelines do not recommend routine AF screening in athletes.[31] Therefore, patients with exercise-induced arrhythmias must be evaluated and handled appropriately before starting any physical activity.

DISCUSSION

Regular physical activity and high CRF contribute to lower AF incidence. There are some small but significant monitors for the benefits of exercise. Although the risk of cardiovascular disease has reduced and life expectancy has improved with the recommended guidelines[32], the risk of sudden cardiac death may be transiently increased during and just after exercise[33], specifically in patients with unidentified cardiovascular risk factors or so-called "silent" coronary artery disease. Progressive right ventricular remodelling may be another cause of exercise-induced ventricular arrhythmia in a small subset of athletes.[34-36] According to Guasch *et al.*[37], regular endurance exercise over a long period seems to elevate the risk of atrial arrhythmias despite indications of lower mortality in the same cohort. Despite a reduction in cardiovascular disease incidence overall, exercise-induced changes in autonomic tone, as well as the development of an arrhythmogenic atrial substrate, appear to contribute to an excess of AF among athletes.[37]

Exercise-based cardiac rehabilitation aims to improve the health of people who have arrhythmia or have been treated for it by getting them to exercise regularly.[38] Patients with exercise-induced arrhythmias should be evaluated and treated as needed.[31] It is generally advisable to gradually and progressively increase exercise intensity while avoiding intense sessions that could immediately activate the sympathetic system and suppress vagal activity. This helps reduce the risk of ventricular fibrillation. On the contrary, habitual vigorous exercise leads to the dominance of the parasympathetic system, which enhances cardiac electrical stability and consequent protection against life-threatening ventricular arrhythmias and modifies the cardiovascular risk by positively affecting lipid levels or reducing the hemodynamic stress on underlying ischemic heart disease.[29] Exercise intolerance and poor quality of life are two hallmarks of AF, particularly when comorbid with conditions like heart failure, diabetes, or valvular heart disease. To this purpose, and considering that regular exercise improves functioning capacity and reduces fatigue, it is generally beneficial to inculcate exercise training in treating AF patients whose HR is appropriately controlled. First, we note that limited prospective randomised controlled trials explain the effects of exercise rehabilitation on individuals with AF. AF is a readily diagnosable condition with well-established treatment guidelines. Even though AF is common among patients involved in rehabilitation programs, few controlled trials employ conventional laboratory procedures and endpoints to assess the usability and efficacy of exercise testing and training in these patients.[39] To evaluate the effectiveness of exercise-based therapies, additional randomised clinical studies with minimal risks of bias and chance must be done in a larger patient group with AF.[38]

CONCLUSIONS

Physical activity and exercise have been widely recognised as beneficial for cardiac health. Despite individuals with AF being potentially more capable of engaging in vigorous physical activity, their arrhythmias frequently disrupt such activities, leading to reduced physical exertion. Paradoxically, this diminished physical activity also contributes to their cardiovascular health benefits. Physical activity and exercise can help maintain a delicate balance in the autonomic nervous system, reducing the risk of cardiac arrhythmias and improving cardiovascular health. Through its effect on the ANS, exercise training can help patients with cardiac arrhythmia, and it may improve the electrical stability of the heart by normalis-

ing the repolarisation and Ca-handling abnormalities that can lead to arrhythmia. More research is needed to fully understand the effect of physical activity on cardiac arrhythmia and help patients with this condition.

Future Perspectives

- With advances in technology and data analysis, exercise regimens can be customised to each individual's specific needs and health conditions. This will help decrease the risk of exercise-induced arrhythmias and optimise the preventive effects of physical activity.
- Further research will explore the effect of different exercise modes (high-intensity interval training and resistance training) and the optimal exercise dose, leading to more effective preventive exercise regimens for arrhythmia.
- In the future, exercise may be incorporated as a critical component of an integrated approach to arrhythmia management, along with medical treatments and modifications to risk factors such as diet and stress management. This comprehensive approach will help control arrhythmias more effectively and reduce the burden on individuals and healthcare systems.

Authors' Contribution

Study Conception: FA, VM, SS, KP, SGK, SG, NG, RJ; Study Design: FA, VM, SS, KP, SGK, SG, NG, RJ; Literature Review: FA, VM, SS, KP, SGK, SG, NG, RJ; Supervision: NG, RJ; Critical Review: SGK, SG, NG, RJ; Manuscript preparing: FA, VM, SS, KP.

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Comparison of the effects of apheresis and pooled platelet transfusions on platelet count

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ABSTRACT

Background: To compare the increase in platelet count after the transfusion of apheresis and pooled platelet suspensions among patients in the internal medicine intensive care unit.

Methods Patients who received platelet suspension transfusions and were followed up at the internal medicine intensive care unit at Mehmet Akif Inan Training and Research Hospital were evaluated. The patient's platelet counts were administered apheresis, and pooled platelet suspensions were recorded before and after transfusion. The increase in platelet count was calculated. The two groups were statistically compared.

Results: A total of 4,701 platelet suspension transfusions were performed at our hospital between January 1, 2020, and December 31, 2023. Of these transfusions, 2,990 belonged to pooled platelet suspensions and 1,711 to apheresis platelet suspensions.

Conclusion: Platelet suspension transfusion is frequently used in patients receiving internal medicine intensive care. However, there is an ongoing debate concerning whether apheresis or pooled platelet transfusion is more effective in increasing platelet count. In this study, we found a significantly higher increase in platelet count among patients in the internal medicine intensive care unit after apheresis platelet suspension transfusion than pooled platelet suspension transfusion.

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INTRODUCTION

Currently, platelet suspension is frequently used in patients receiving intensive care in internal medicine. Platelet suspension transfusion is commonly performed on patients admitted to the internal medicine intensive care unit due to haematological malignancies, solid tumours, and gastrointestinal bleeding. Platelet suspension is obtained through three methods: apheresis platelet transfusion, random platelet suspension derived from whole blood, and pooled platelet suspension.[1]

Platelet transfusion was initially performed using a random platelet suspension obtained from whole blood. Subsequently, pooled platelet suspensions began to be applied by combining these random platelet suspensions. In the 1970s, with the advancement of technology, apheresis platelet suspension started to be obtained from donor plasma using special techniques and devices through a procedure called apheresis.[2,3] During this procedure, blood is extracted from one arm, and platelets are separated using a cell separation device and collected in a bag. The remaining blood components are returned to the donor through the opposite arm. Thus, donors can donate more frequently than whole blood donations.

In recent years, single donor apheresis-derived platelets have steadily increased compared to random donor platelets.[4] However, implementing stringent exclusion criteria for platelet donation has posed challenges in recruiting and retaining donors.[5,6] Technical advances in automated cell sorters have improved the quality and efficiency of apheresis platelet collection.[7]

Several factors must be considered before selecting the method of platelet suspension. Alloimmunisation refers to the potential for infection, transfusion reaction risk, bone marrow suppression, and platelet value increase. Some adverse reactions may also develop with platelet suspension transfusion. Immunologically, febrile reactions, graft-versus-host disease, anaphylaxis, hemolysis, hypotension, and transfusion-related acute lung injury can be cited as such reactions.[8]

Platelet suspension also poses a risk of infection. In particular, immunodeficiency virus, hepatitis B virus, and hepatitis C virus infections were of great concern as transfusion-transmitted infections in the past. However, the wider adoption of additional nucleic acid tests in donors and the careful selection of donors have significantly reduced the risk of these viral transmissions through transfusion. Nevertheless, sepsis due to the bacterial contamination of platelets remains a significant threat to recipient safety.[8] This study aimed to compare the platelet increase in patients who received pooled and apheresis platelet suspensions.

MATERIAL AND METHODS

From January 1, 2020, through December 31, 2023, 160 adult patients aged ≥18 years were followed up at the tertiary step internal medicine intensive care unit at our hospital. Of these patients, 80 received apheresis platelet suspension, and 80 received pooled platelet suspension.

The hemogram examinations of patients who received a platelet suspension transfusion were performed before and 24 hours after the transfusion. Venous blood from the patient of 2 mL was taken into an EDTA tube. Patients with a history of coagulation disorders or anticoagulant drug use were excluded from the study. Additionally, patients with active bleeding, using medications that would affect platelet count, and patients whose platelet count could not be measured before and 24 hours after transfusion were excluded from the study. Data was collected from the hospital's information system. Pooled platelet suspensions were obtained from the regional blood centre of the Turkish Red Crescent. Pooled platelet suspensions were created by combining four random platelet suspensions. Apheresis platelet suspension was created using the centrifugation method with the Trima Accel® v7 (Terumo BCT, Inc., USA) device in the blood transfusion unit of our hospital. Platelet values were measured fully automatically using the laser technique on the Cell-Dyn Ruby (Abbott Laboratories, USA) device.

Patients who received platelet transfusions were divided into two groups: those who received apheresis platelet suspension and those who received pooled platelet suspension. The increase in platelet values was calculated and statistically compared between these two groups.

Before starting the study, approval was obtained from the Ethics Committee of the Harran University Faculty of Medicine (date: December 11, 2023, and approval number: H.R.U./23.23.21).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as

Table 1. The most frequent comorbid diseases and the most frequently used drugs in patients undergoing platelet transfusion

Medication use	n (%)	Comorbidities	n (%)
Antihypertensive	56 (35%)	Respiratory diseases	83 (52%)
Antidiabetic	53 (33%)	Diabetes mellitus	53 (33%)
Diuretic	59 (37%)	Cancer	43 (27%)
Antibiotic	115 (72%)	Dyslipidemia	59 (37%)
Antiviral	72 (45%)	Hypertension	56 (35%)
Inhalation drugs	101 (63%)	Stroke	8 (5%)
Chemotherapeutics	40 (25%)	Cardiovascular diseases	54 (34%)
Antiarrhythmic	27 (17%)	Hematological diseases	43 (27%)
Antifungal	22 (14%)	Liver diseases	35 (22%)
Steroid	77 (48%)	COVID-19 infection	19 (12%)
Proton pump inhibitor	138 (86%)	Other diseases	8 (5%)

numbers and percentages for categorical variables and mean ± standard deviation and median (interquartile range) values for continuous variables. Continuous variables were examined regarding the normality assumptions using the Kolmogorov-Smirnov test, and the p-value was <0.05. Therefore, the Mann-Whitney U test, a non-parametric method, was used in pairwise group comparisons. Pearson's chi-square and Fisher's exact tests were conducted to compare categorical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 4,701 units of platelet suspension were transfused in our hospital over the three-year study period. Of these transfusions, 1,711 (36.40%) belonged to apheresis platelet suspensions and 2,990 (63.60%) to pooled platelet suspensions. Among the pooled platelet suspensions, 0 Rh(+) (33.42%) was the most common blood group. The least common was AB Rh(–) (0.27%); 147 (92%) of the patients were intubated, 102 (64%) of the patients had infections and patients who received platelet transfusion received an average of 3.25±3.04 (mean ± SD) blood product transfusions. Comorbidities and used medication in patients were presented in Table 1.

The most common reason for the destruction of suspensions was the expiration of the products in both groups. In the pooled platelet suspension group, 183 products were destroyed, and the destruction rate (number of products destroyed/total number of products × 100) was calculated to be 5.76%. In the apheresis platelet suspension group, the number of destroyed products was 227, and the destruction rate was 3.80%. When evaluated by year, the highest rate of platelet suspension was observed in 2021 and the lowest in 2023, while pooled platelet suspension was most performed in 2021 and least performed in 2022. The apheresis unit in our hospital was established in 2021. Therefore, apheresis platelet suspension transfu-

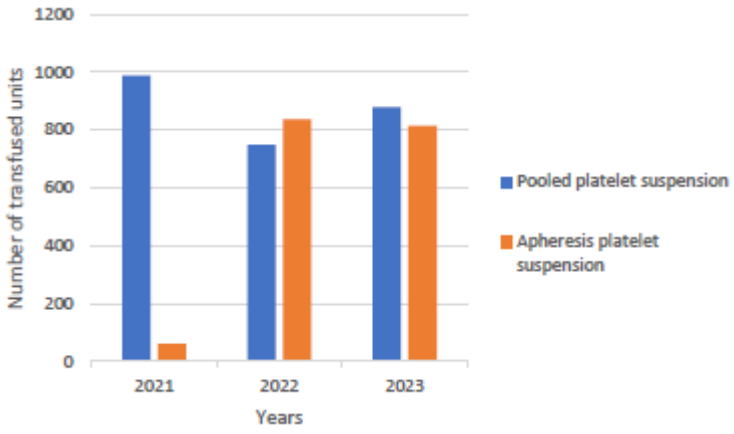

Figure 1. Number of platelet suspensions transfused by year.

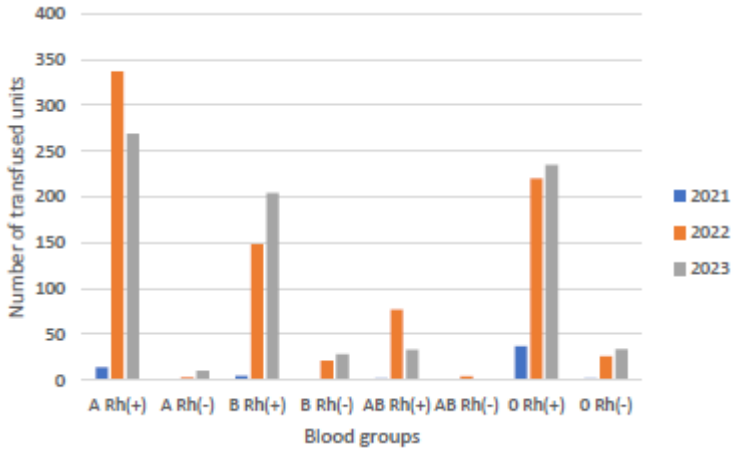

Figure 2. Number of apheresis suspensions transfused by year and blood group.

sion in 2021 is lower than pooled platelet suspension transfusion (Figure 1). The use of apheresis platelet suspension was observed to increase over the years. Throughout the three years, the highest percentage of platelet suspension transfusions was seen in the blood group A Rh(+) (36.23%) and the lowest rate in the blood group AB Rh(–) (0.29%) (Figure 2). In the pooled platelet suspension group, the highest number of platelet suspensions belonged to the blood group 0 Rh(+) (36.09%) and the lowest number to the blood group AB Rh(–) (0.26%) (Figure 3).

Among the 160 patients evaluated in the internal medicine intensive care unit, 53.7% of the total platelet suspension transfusions were administered to male patients. The mean age of patients who underwent platelet suspension was 54.35 years. The mean platelet count change in one suspension unit was 18.77 in the pooled platelet suspension group and 22.67 in the apheresis platelet suspension group (Table 2). No adverse events or transfusion reactions were observed in either group.

As shown in Table 2, the platelet count change showed a significant difference between the groups (p=0.048), significantly higher in the apheresis platelet suspension group. However, when the platelet count change was evaluated according to age (p=0.977) and gender (p=0.501), no significant difference was observed between the groups.

DISCUSSION

The utilisation of blood product separation and platelet suspension transfusion commenced in the 1950s.[9] Pooled platelet suspension was obtained by combining four to six units of these products. In the following years, apheresis platelet suspension emerged as an alternative. However, there is still no consensus on whether pooled or apheresis platelet suspension will be more beneficial in patients, and both suspension methods are used at varying rates. There is a growing trend in our hospital toward the use of apheresis platelet suspension. According to our study, among the patients in the internal medicine

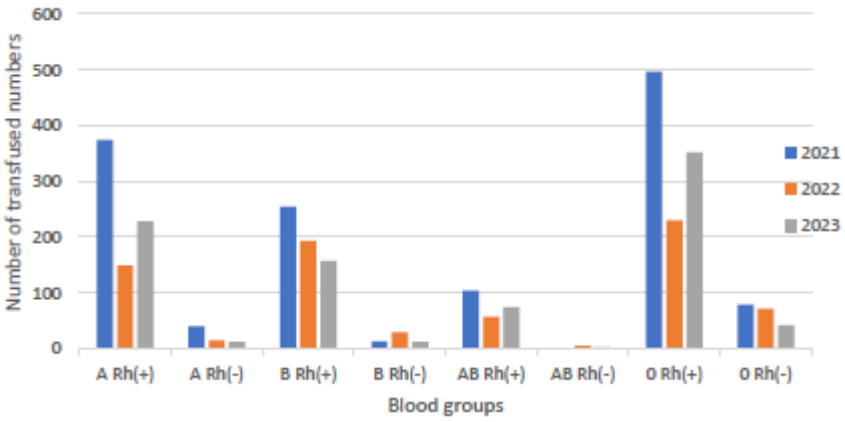

Figure 3. Number of pooled suspensions used by year and blood group.

Table 2. Comparison of the sociodemographic and clinical characteristics of the groups

Variables	Total group (n: 160)	Pooled platelet group (n: 80)	Apheresis platelet group (n: 80)	*P*-value
Age (years) mean±SD	54.35±23.98	54.65±25.86	54.05±22.27	0.977[a]
Gender n (%)				0.501[b]
Female	74 (46.3)	40 (50.0)	34 (42.5)	
Male	86 (53.7)	40 (50.0)	46 (57.5)	
Blood groups n (%)				
0 (–)	4 (2.5)	4 (5.0)	0	
0 (+)	52 (32.5)	24 (30.0)	28 (35.0)	
A (+)	52 (32.5)	12 (15.0)	40 (50.0)	
AB (–)	2 (1.3)	2 (2.5)	0	
AB (+)	12 (7.5)	8 (10.0)	4 (5.0)	
B (–)	4 (2.5)	4 (5.0)	0	
B (+)	34 (21.3)	26 (32.5)	8 (10.0)	
Platelet count change				0.048[a]
mean±SD	20.72±13.16	18.77±13.55	22.67±12.61	
median (IQR)	16.0 (16.00)	14.50 (14.75)	20.0 (16.75)	

SD: standard deviation, IQR: interquartile range. [a] Mann-Whitney U test, [b] Pearson chi-square test.

intensive care unit, the rate of apheresis platelet suspension transfusions was 36.40%, and that of pooled platelet suspension transfusions was 63.60%. A 2015 study conducted in the USA reported that 93.9% of the platelet suspension transfusions belonged to apheresis suspensions, and the remaining portion consisted of pooled platelet suspensions separated from whole blood.[10]

Several factors influence the supply of pooled and apheresis platelet suspensions in healthcare institutions. These factors include expenses, difficulty in finding donors, and the absence of apheresis units in every centre. Physicians' preference for apheresis or pooled platelet suspension is affected by the expected numerical increase in platelet count, the risk of contagious infection or unwanted reactions, such as febrile reactions, and the possibility of forming alloantibodies. Furthermore, physicians may be limited to pooled platelet suspension due to the lack of an apheresis unit in certain healthcare centres.

Our study found that apheresis platelet suspension transfusion increased platelet count more than pooled platelet transfusion among the patients in the internal medicine intensive care unit (p=0.048). Similarly, Rahman *et al.*[11] found that the increase in platelet count after apheresis platelet suspension transfusion was higher than pooled platelet transfusion. In another study, Agarwal *et al.*[12] determined that apheresis platelet suspension increased blood pressure more than pooled platelet suspension. The authors also noted that the apheresis suspension was of better quality according to criteria such as the pH of the platelet suspension and the number of platelets per unit in the suspension. Furthermore, in our study, the lower destruction rate in apheresis platelet suspension showed that this method produced more efficient results.

Ness *et al.*[13] stated that apheresis platelet suspension increased platelet value more but was not preferred due to its higher cost. Upon performing a cost analysis at our hospital, we similarly found that apheresis platelet suspension was more expensive than pooled apheresis suspension.

One of the most critical factors in platelet suspension preferences is the reactions resulting from the transfused product. However, in our study, no reaction developed in either group. Additionally, one of the risks of platelet transfusion is the risk of infection. The risk of infection is higher in hospitalised patients and patients who receive platelet transfusions than those who do not.[14] In our study, no platelet transfusion-related infection developed in either group.

The data included in this paper was sourced exclusively from a single centre. To enhance the efficacy of our study, it would be advantageous to incorporate data from many centres and include pediatric patients. In addition, conducting a comparison of the increase in platelet count according to patient diagnoses will yield more comprehensive data.

CONCLUSIONS

Platelet suspension is a blood product commonly used in healthcare. It is an indispensable blood product with no substitute; therefore, its use is of vital importance. According to our study, apheresis platelet suspension transfusion increased the platelet count more. However, it is a more expensive product. We consider that the use of apheresis platelet suspension in healthcare centres where there is no difficulty in finding a donor, and there are no financial constraints will improve the platelet levels of patients better.

Conflict of Interest

The author(s) declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

Ethical Approval

The Medical Ethics Committee of Harran University, Şanlıurfa, Turkey, approved the study protocol (decision number: HRÜ/23.23.21, date: 11.12.2023).

Authors' Contribution

Study Conception: İHD., EC., İI.; Study Design: İHD., EC.; Literature Review: İHD.; Critical Review: İHD.; Data Collection and/or Processing: EC.; Analysis and/or Data Interpretation: İHD., EC.; Manuscript preparing: İHD., EC.

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Effects of multimorbidity and polypharmacy on blood pressure target attainment in patients with hypertension

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ABSTRACT

Background Hypertension prevalence increases with age, as well as polypharmacy and multimorbidity (P&M), which are the use of multiple medications and the presence of multiple chronic diseases, respectively. Whether P&M affects attaining blood pressure (BP) goals is not clear.

Methods Hypertensive patients in the general internal medicine outpatient clinic were evaluated retrospectively. Data regarding age, gender, comorbidities, medications, office BP (OBP), home BP (HBP), and ambulatory BP (ABP) were obtained. Having two or more diseases was classified as multimorbidity, whereas using five or more drugs was classified as polypharmacy. OBP <140/90 mmHg, HBP <135/85 mmHg, and ABP <130/80 mmHg were considered BP targets. Differences in BP and attaining targets were analyzed according to P&M. Correlation analysis was also performed between BP, age, comorbidities, and medications.

Results Of the 147 patients, 124 (84.4%) had multimorbidity, and 56 (38.1%) had polypharmacy. While systolic BP in OBP and HBP did not differ in the P&M groups (all $p>0.05$), diastolic BP was lower in patients with both (all $p<0.05$). Age, total number of medications, anti-hypertensive tablets, and active substance numbers showed a negative correlation with diastolic BP in both OBP and HBP (all $p<0.05$). There was no difference between BP goal attainments in P&M groups ($p>0.05$).

Conclusion P&M does not affect the achievement of office and home BP targets. Lower diastolic BP with P&M does not reflect better control but reflects the effect of age on diastolic BP.

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INTRODUCTION

Hypertension is one of the most common chronic diseases, with wide adverse implications for cardiovascular, cerebrovascular, and renal outcomes.[1,2] Thanks to anti-hypertensive medications' effect on lowering all-cause mortality, many elderly patients are now continuing their lives without experiencing hypertension-related adverse outcomes.[3,4] However, hypertensive patients generally need two to three medications for their blood pressure (BP) to reach BP goals that prevent adverse outcomes.[5] Besides, patients with hypertension usually have one or more accompanying diseases, such as diabetes, dyslipidemia, chronic kidney disease, and cardiovascular disease, which necessitate multiple medications as well.[6-11] This translates into the fact that patients with hypertension have significant rates of multimorbidity and polypharmacy, two interrelated global challenges with substantial impact on both patients and societies. In Europe, a 2018 study found that the prevalence of polypharmacy ranged from 25 to 40%.[12] Polypharmacy has various imprecise definitions and is subject to debate. The study above defined polypharmacy as "concurrent use of five or more medications per day." However, many other definitions exist as well.[13] Similar to polypharmacy, multimorbidity has multiple definitions, but "having two or more co-existing conditions in an individual" is the most adapted definition by the World Health Organization.[14] Similar to polypharmacy, multimorbidity has a high prevalence and is reported to range from 15 to 43%.[15] It has been demonstrated that patients with multimorbidity and polypharmacy have increased healthcare utilisation, have more frequent hospital admissions, experience longer hospital stays, and have higher rates of falls, cognitive impairment, and mortality.[15,16]

It has been shown that medication non-adherence among patients with hypertension is common and associated with the number of medications prescribed.[17] The recent European Society of Hypertension addresses this issue and recommends single pill combinations to improve adherence.[5] Also, the BP goals of patients with hypertension up to 80 years old are similar to younger patients' goals.[5] However, whether the presence of polypharmacy or multimorbidity impacts BP levels and reaching BP targets. A higher number of medications does not necessarily translate into lower adherence to anti-hypertensive medications. A meta-analysis demonstrated that medication regimen complexity was associated with medication non-adherence in only 2 of 6 observational studies.[18] Moreover, one study in this meta-analysis found that participants with less complex medication regimens were more likely to stop medications when feeling worse.[19] In the context of the current ambiguous literature data, we aimed to investigate whether having multimorbidity or polypharmacy is associated with worse BP control and lower BP goal attainment rates.

MATERIAL AND METHODS

This study was designed as a retrospective case-control study in the Başkent University Ankara Hospital General Internal Medicine outpatient clinic. We evaluated the eligibility of patients with a primary hypertension diagnosis (ICD-10 code: I10) admitted to the clinic between June 2023 and January 2024. Electronic medical records were used for data gathering.

The study included patients with BP readings obtained from either office, home, or ambulatory settings. Age, gender, chronic diseases (grouped as follows: diabetes mellitus, cardiovascular diseases, metabolic diseases, pulmonary diseases, malignancy, rheumatological diseases, neuropsychiatric diseases, and others), number of comorbidities, number of total medications (including over-the-counter pills, vitamins, pain medications, etc.), anti-hypertensive medication's active substance numbers and pill numbers, and systolic and diastolic BP readings of office, home, or ambulatory BPs were acquired. Having multimorbidity was defined as having two or more diseases apart from hypertension, and having polypharmacy was defined as using five or more medications, including anti-hypertensive pills.

The study assigned an anonymous serial number to the patients to ensure confidentiality. The data processing did not require informed consent, and written informed consent was not obtained due to the study's retrospective design. The study complies with the principles outlined in the Declaration of Helsinki, and the study was approved by the Başkent University Review Board (decision number: KA23/454).

Statistical analysis

Continuous variables (i.e., age, BP, number of comorbidities, and medications) were presented by median (interquartile range). In contrast, categorical variables (i.e., gender, comorbidities, multimorbidity, polypharmacy, and BP target attainment) were presented as numbers (percentages). Between-group dif-

ferences were analysed using Pearson's chi-squared test (χ^2 test) or Fisher's exact test for categorical variables. The Mann-Whitney U test was used for continuous variables between two groups and continuous variables between more. Relationships between continuous variables were tested using Spearman's correlation test. Statistics were provided according topatients' multimorbidity and polypharmacy presence. IBM SPSS Software version 23.0 (SPSS Inc., Chicago, IL) was used for analyses. We performed two-sided significance testing and considered p-values less than 0.05 as significant.

Table 1. Demographic, clinical and blood pressure values of the patients

Variables	Values
Age (years) median (IQR)	67 (21)
Gender (Female/Male) n (%)	104 (70.7)/43 (29.3)
Comorbidities n (%)	
Diabetes mellitus	60 (40.8)
Cardiovascular disease	30 (20.4)
Metabolic	68 (46.3)
Pulmonary	17 (11.6)
Malignancy	9 (6.1)
Rheumatological	14 (9.5)
Neuropsychiatric	33 (22.4)
Number of chronic diseases n (%)	
0	3 (2)
1	20 (13.6)
2	33 (22.4)
3	32 (21.8)
4	31 (21.1)
5	20 (13.6)
6 and above	8 (5.5)
Multimorbidity n (%)	124 (84.4)
Number of total medications n (%)	
0	16 (10.9)
1-5	85 (57.8)
6-10	34 (23.1)
11 and above	12 (8.1)
Polypharmacy n (%)	56 (38.1)
Number of anti-hypertensive pills n (%)	35 (23.8)
0	55 (37.4)
1	45 (30.6)
2	10 (6.8)
3	2 (1.4)
4	
Number of anti-hypertensive active substances n (%)	
0	35 (23.8)
1	28 (19)
2	41 (27.9)
3	29 (19.7)
4	12 (8.2)
5	2 (1.4)
Blood pressure (mmHg) median (IQR)	
Office (n: 124)	150 (27) / 87 (15)
Home (n: 69)	130 (15) / 75 (13)
Ambulatory (n: 16)	127 (17) / 77 (17)

RESULTS

One hundred and forty-seven patients were included in the study. Of those, the majority were women (70.7%), and the median age was 67 years (21). Metabolic diseases, including diabetes mellitus, constituted the most common co-morbidity (46.3%), followed by neuropsychiatric conditions (22.4%) and cardiovascular diseases (20.4%). One hundred twenty-four patients (84.4%) had multimorbidity. While 16 patients did not use any medications, 85 patients (57.8%) used 1 to 5 medications, 34 (23.1%) used 6 to 10 medications, and 12 (8.1%) used 11 or more medications. Fifty-six patients (38.1%) had polypharmacy. While 55 (37.4%) patients were using one anti-hypertensive medication pill and 45 (30.6%) were on two anti-hypertensive pills, 35 (23.8%) patients were not using anti-hypertensive medications. Regarding the number of anti-hypertensive active substances, 28 (19%) patients were on one medication, 41 (27.9%) were on two medications, and 29 (19.7%) were on three medications. Of the 147 patients, 124 had office BP readings, 69 had home BP readings, and only 16 had ambulatory BP readings. Median systolic and diastolic BP of office, home, and ambulatory readings were 150/87, 130/75, and 127/77 mmHg, respectively. The baseline clinical features of the patients were detailed in Table 1.

The age of patients with multimorbidity was significantly higher (69 vs. 51 years, $p<0.001$) compared to those who did not have multimorbidity. The median number of total medications, the number of anti-hypertensive pills, and active substances were also significantly higher among patients with multimorbidity (4 vs. 1, 1 vs. 0, and 2 vs. 0, respectively, all $p<0.001$). Considering office BP readings, systolic BP was not different (155 vs. 145 mmHg, $p=0.21$); however, diastolic BP was lower among patients with multimorbidity (85 vs. 95 mmHg, $p=0.016$). Regarding home and ambulatory BP readings, both systolic and diastolic BPs did not differ between multimorbidity groups (all $p>0.05$). Goal BP attainment rates using different office, home, or ambulatory BP readings were not

Table 2. Clinical and blood pressure values of the patients according to multimorbidity and polypharmacy

Variables	Multimorbidity			Polypharmacy		
	Absent n: 23	Present n: 124	*P*-value	Absent n: 91	Present n: 56	*P*-value
Age (years) median (IQR)	51 (19)	69 (15)	<0.001	64 (20)	72.5 (15)	<0.001
Number of medications n (%)						
Total medications	1 (2)	4 (6)	<0.001	2 (2)	8 (4)	<0.001
Anti-hypertensive pills	0 (1)	1 (1)	<0.001	1 (1)	2 (1)	<0.001
Anti-hypertensive active substance	0 (1)	2 (2)	<0.001	1 (2)	2.5 (1)	<0.001
Office BP (mmHg) median (IQR)	n: 20	n: 104		n: 77	n: 47	
Systolic	145 (25)	155 (25)	0.21	150 (25)	155 (35)	0.92
Diastolic	95 (15)	85 (15)	0.016	90 (15)	85 (20)	0.015
Office BP target attainment n (%)	7 (35)	33 (31.7)	0.77	24 (31.2)	16 (34)	0.74
Home BP (mmHg) median (IQR)	n: 12	n: 57		n: 41	n: 28	
Systolic	125 (20)	130 (14)	0.4	131.5 (18)	127 (12)	0.13
Diastolic	80 (16)	75 (11)	0.3	80 (15)	70.5 (12)	0.02
Home BP target attainment n (%)	8 (66.7)	40 (70.2)	0.81	25 (61)	23 (82.1)	0.06
Ambulatory BP (mmHg) median (IQR)	n: 2	n: 14		n: 11	n: 5	
Systolic	133.5 (NA)	127 (17)	0.41	128 (12)	121 (36)	0.74
Diastolic	77 (NA)	74 (18)	0.93	78 (15)	68 (14)	0.14
Ambulatory BP target attainment n (%)	1 (50)	8 (57.1)	0.84	6 (54.5)	3 (60)	0.83

BP: blood pressure, NA: not applicable.

among multimorbidity groups (all p>0.05). Table 2 showed the characteristics of patients with multimorbidity in detail.

Patients with polypharmacy had significantly higher ages (72.5 vs. 64 years, p<0.001) as well. The median number of anti-hypertensive pills and active substances was significantly higher among patients with polypharmacy (2 vs. 1 and 2.5 vs. 1, respectively, all p<0.001). Considering office BP readings, systolic BP was not different (150 vs. 155 mmHg, p=0.92); however, diastolic BP was lower among patients with polypharmacy (85 vs. 90 mmHg, p=0.015). Regarding home BP readings, systolic BP was not different (127 vs. 131.5 mmHg, p=0.13); however, diastolic BP was lower among patients with polypharmacy (70.5 vs. 80 mmHg, p=0.02). Regarding ambulatory BP readings, both systolic and diastolic BPs did not differ between polypharmacy groups (all p>0.05). Goal BP attainment rates using different office, home, or ambulatory BP readings were not among the polypharmacy groups (all p>0.05). Table 2 demonstrated the characteristics of patients with polypharmacy in detail.

Systolic BP, whether it is attained via office or home readings, is not correlated with age, number of comorbidities, number of total medications, number of anti-hypertensive pills, or active substances. How-

Table 3. Correlations between blood pressures and clinical features

Variables	Office blood pressure		Home blood pressure		Ambulatory blood pressure	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Age	r=0.17	r= –0.401	r=0.08	r= –0.35	r= –0.19	r= –0.29
	p=0.05	p<0.001	p=0.48	p=0.003	p=0.48	p=0.27
Number of comorbidities	r=0.16	r= –0.19	r= –0.07	r= –0.39	r= –0.23	r= –0.22
	p=0.07	p=0.020	p=0.56	p=0.001	p=0.38	p=0.40
Total medications	r=0.05	r= –0.30	r= –0.13	r= –0.40	r= –0.12	r= –0.33
	p=0.53	p<0.001	p=0.27	p=0.001	p=0.63	p=0.2
Anti-hypertensive pill number	r=0.05	r= –0.29	r= –0.11	r= –0.32	r=0.15	r= –0.25
	p=0.54	p=0.001	p=0.36	p=0.007	p=0.55	p=0.33
Anti-hypertensive active substance number	r=0.007	r= –0.34	r= –0.08	r= –0.33	r= –0.02	r= –0.19
	p=0.94	p<0.001	p=0.46	p=0.005	p=0.91	p=0.47

ever, diastolic BP readings significantly negatively correlated with all these factors. Ambulatory readings of systolic or diastolic BPs are not associated with the characteristics above. Table 3 illustrated the correlations between BPs and clinical features in detail.

DISCUSSION

This study demonstrated that although polypharmacy and multimorbidity are common among patients with hypertension, BP levels and goal BP attainment rates do not differ according to their presence. Moreover, diastolic BP levels are even lower in patients with multimorbidity and polypharmacy. However, this finding is attributable to the age-related diastolic BP drop rather than better BP control.

Patients with hypertension usually need more than one medication to control their BP, as also reflected by our study. Besides, accompanying diseases necessitate further medication. Regarding our patient cohort, 40.8% had diabetes mellitus, which requires at least one medication, and 20.4% had cardiovascular disease, which necessitated more than one medication. The resulting multimorbidity and polypharmacy are associated with adverse health outcomes.[15,16]; however, it is not clear whether worse outcomes are caused by loss of BP control due to an increasing number of pills or whether increased disease and pill burden result in loss of BP control. The HYVET study demonstrated that patients over 80 years old benefit from lowering their BP lowering.[20] Moreover, subgroup analysis of the SPRINT trial illustrated that the benefit of intensive BP control was observed independently of their frailty level.[21] These two studies prove that BP control should not be loosely based on age among elderly patients. Despite these findings, the latest European guideline suggests consideration of monotherapy among hypertensive elderly patients with polypharmacy.[5] Gupta *et al*.'s[17] study found supporting evidence that polypharmacy was an important risk factor for non-adherence to anti-hypertensive medication, a study performed by measuring BP medications or metabolites in blood or urine samples. The results of our study may seem contradictory to Gupta's study at first glance. Polypharmacy has an impact on medication adherence and causes partial non-adherence. However, it is likely that lower adherence-caused reductions of medications' blood levels are not of clinical importance and do not necessarily translate into loss of BP control.

Patients in our cohort with multimorbidity and polypharmacy had significantly lower diastolic BP. The most likely explanation for this finding is that patients with multimorbidity and polypharmacy were significantly older than those without (69 vs. 51 mmHg, $p<0.001$ and 72.5 vs. 64 mmHg, $p<0.001$). Since age itself is associated with diastolic BP fall, this finding is expected.[22]

The level of goal BP attainment in office BP measurements was fairly low compared to attainment rates in home BP measurements. The difference between office and home BP widens as BP rises, yet our findings differ more than expected. Among systolic BP, the highest difference was observed among patients with multimorbidity (155 vs. 130 mmHg), around 20 mmHg. Regarding diastolic BP, the highest differences were observed among patients with polypharmacy and without multimorbidity (85 vs. 70.5 mmHg and 95 vs. 80 mmHg), around 10 to 15 mmHg. Although BP targets derived from randomised controlled trials are mostly based on office BP measurements, office BP measurement does not have the highest concordance with end-organ damage prediction. A recent study demonstrated that home BP measurements were superior to office and ambulatory BP measurements in predicting target organ damage.[23] We demonstrated that multimorbidity and polypharmacy did not affect the gap between office and home BP measurements.

We acknowledge our study's limitations. Firstly, this study was a single-centre retrospective study; thus, findings cannot be confidently generalised. Secondly, the number of patients with office, home, and ambulatory BP readings was not equal, which caused improper comparisons between different BP measurement methods. Thirdly, we defined BP targets roughly but did not define precise targets according to age, frailty, and underlying comorbidities.

CONCLUSIONS

Multimorbidity and polypharmacy are common in the elderly and are important issues to address; however, achieving BP goals does not seem to be affected by the presence of multimorbidity or polypharmacy.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or

publication of this article.

Ethical Approval

The study complies with the principles outlined in the Declaration of Helsinki, and the study was approved by the Başkent University Review Board (Decision Number: KA23/454).

Authors' Contribution

Study Conception: ATG, NH, AEA, CK, TÇ, YAA, EÖ, SK, ZŞ; Study Design: ATG, NH, AEA, CK, TÇ, YAA, EÖ, SK, ZŞ; Literature Review: ATG; Critical Review: ATG; Data Collection and/or Processing: NH, AEA, CK, TÇ, YAA, EÖ, SK, ZŞ,; Analysis and/or Data Interpretation: ATG, NH, AEA; Manuscript preparing: ATG, NH, AEA, CK, TÇ, YAA, EÖ, SK, ZŞ.

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