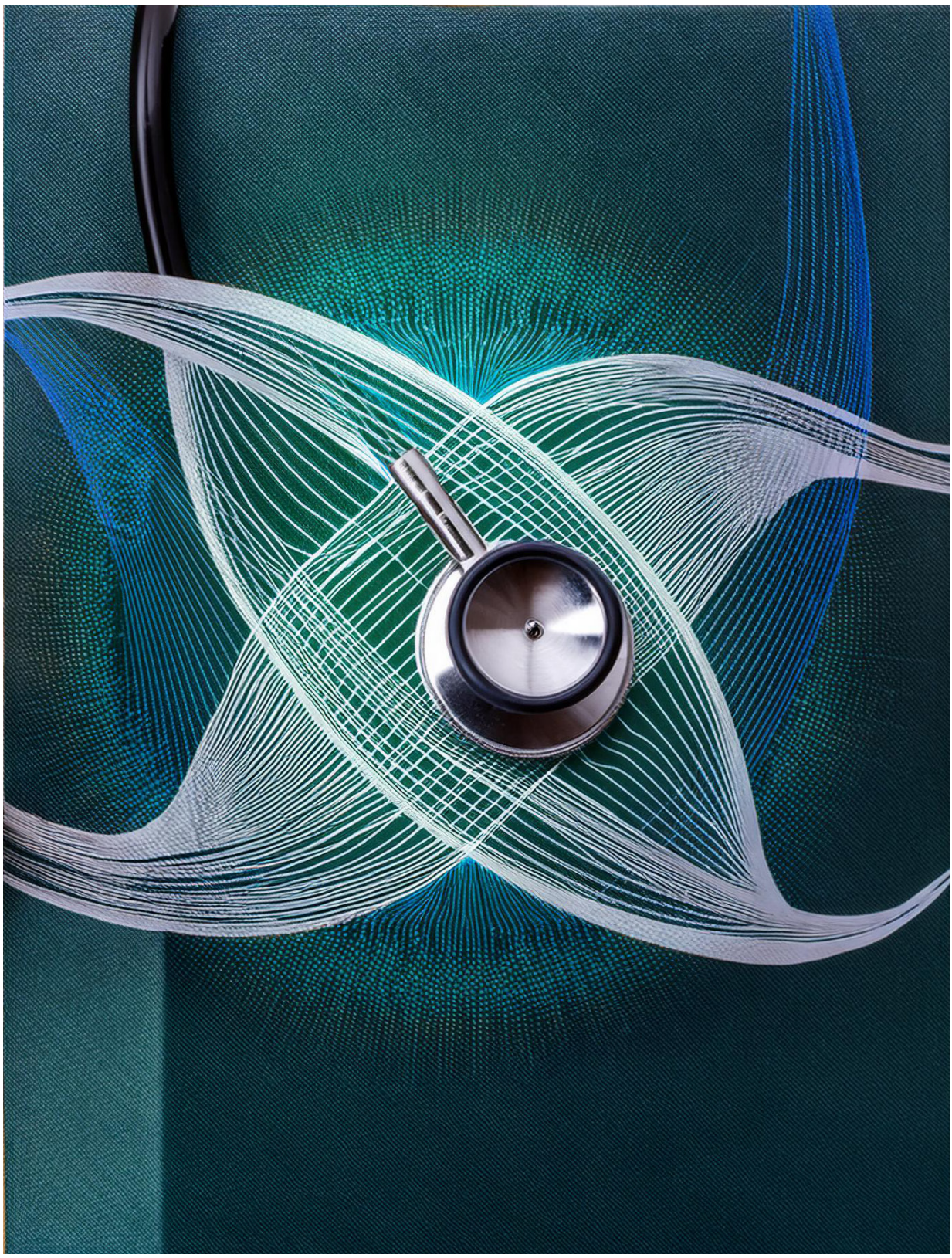
January 2025

Turkish Journal of Internal Medicine

e-ISSN: 2687-4245

Volume 7, Issue 1



Turkish Journal of Internal Medicine

http://www.tjim.org

e-ISSN:2687-4245

Aim and Scope

Turkish Journal of Internal Medicine (TJIM) is an international peer-reviewed scientific journal that publishes manuscripts describing both clinical and basic science research in medicine. Manuscripts must describe original data that has not been published previously nor submitted for publication elsewhere. Manuscripts that adhere to the TJIM submission guidelines and are deemed appropriate for the scope of the journal are sent to two reviewers who are specialists in the field. The reviewers' comments are then considered by the members of the TJIM Executive Editorial Board who discuss the suitability of each submission. The final decision for all submitted manuscripts rests with the Editor-in-Chief.

The journal publishes in the field of original research, case report, reviews, short report, short communication and letters to the editor are published only in English.

Editorial Board of TJIM complies with the criteria of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME) , and Committee on Publication Ethics (COPE).

The journal is published quarterly (January, April, July and October).

No fee is required for publishing the manuscipt.

All articles are detected for similarity.

Abstracting & Indexing

The journal is abstracted and indexed with the following: DOAJ (Directory of Open Access Journals), EBSCO Publishing, Google Scholar, Index Copernicus (Under Evaluation), ResearchGate, SciLit, CrossRef, ResearchBib, Asos Index, WorldCat, ROAD, Türkiye Atıf Dizini (Turkish Citation Index), TURK MEDLINE, DRJI (Directory of Research Journals Indexing).

Publisher

Turkish Journal of Internal Medicine

Nizameddin KOCA

SBU Bursa Şehir SUAM

Nilüfer/BURSA-TURKEY

https://dergipark.org.tr/en/pub/tjim

EDITORIAL BOARD MEMBERS
(In alphabetical order)

Turkish Journal of Internal Medicine

Table of Content

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Review Article

Exploring the silent connection between sleep disorders and cardiovascular diseases: Pathophysiology and insights

Mayank Dhalani[1], Mounika Tunuguntla[2], Priyanka Aggarwal[3], FNU Anamika[4], Dharti Dua[5], Bhupinder Singh[6].

[1.] MBBS, GMERS Medical College, Gotri, Vadodara, India
[2.] Internal Medicine, Guntur Medical College, Guntur, India
[3.] Internal Medicine, Maharishi Markandeshwar Institute of Medical Sciences & Research, Ambala, India
[4.] Internal Medicine, University College of Medical Sciences, India
[5.] Internal Medicine, The Ohio State University College of Medicine, Columbus, Ohio, United States.
[6.] Internal Medicine, Government Medical College, Amritsar, India

ABSTRACT

Sleep is a complex physiological phenomenon crucial for health. Despite this, millions suffer from sleep disorders, contributing to a range of health issues, particularly cardiovascular diseases (CVD). The pathophysiological mechanisms linking sleep disorders, such as insomnia and obstructive sleep apnea (OSA), to cardiovascular risk factors include disruptions in inflammatory, autonomic, and metabolic pathways. Increased sympathetic nervous system activity, chronic inflammation, and metabolic dysregulation stemming from poor sleep can lead to conditions like hypertension, obesity, and insulin resistance, significantly elevating the risk for CVD.

This article reviews the connection between sleep quality and cardiovascular disease risks. Sleep disorders (i.e., insomnia and OSA) have been found to impact cardiovascular risk factors adversely. Studies have found an association between abnormal sleep and increased cardiovascular morbidity and mortality by higher risks of hypertension, diabetes, obesity, and dyslipidemia.

The review also discusses non-pharmacological interventions, such as relaxation training, Cognitive behavioural therapy for insomnia (CBT-I), and red light therapy, which have shown efficacy in improving sleep quality and reducing cardiovascular risks. Dual orexin receptor antagonists and Ashwagandha promise to enhance sleep quality and cardiovascular health, but further research is needed. Addressing sleep disorders and promoting healthy sleep practices are essential for mitigating the global burden of cardiovascular diseases, underscoring the need for continued research and effective public health interventions.

Turk J Int Med 2025;7(1):1-11
DOI: 10.46310/tjim.1491486

Keywords: *Cardiovascular diseases, obstructive sleep apnea, insomnia*

Received: *May 29, 2024* ***Accepted:*** *September 16, 2024* ***Published Online:*** *January 29, 2025*

How to cite this article: *Dhalani M, Tunuguntla M, Aggarwal P, Anamika F, Dua D, Singh B. Exploring the silent connection between sleep disorders and cardiovascular diseases: Pathophysiology and insights Turk J Int Med 2025;7(1):1-11. DOI: 10.46310/tjim.1491486*

Address for Correspondence:
Mayank Dhalani, GMERS MEDICAL COLLEGE, Gotri, Vadodara, India
E-mail: mayankdhalani1999@gmail.com

INTRODUCTION

Sleep is a multifaceted physiological phenomenon wherein the body and mind enter a state of rest for a duration.[1] The World Health Organization has acknowledged sleep as a crucial health state and activity; however, millions worldwide suffer from insufficient sleep, and approximately 50 to 70 million adults in the US experience a sleep disorder or report inadequate sleep.[2,3] People in various age groups need varying amounts of sleep depending on their physiological requirements. Infants can sleep up to 12-15 hours daily, which may benefit their growth and development. In contrast, children and teenagers should sleep an average of 9-11 hours and 8-10 hours per night, respectively. Meanwhile, the typical adult requires between 7-9 hours of sleep each night, but around sixty, the average night's sleep tends to be shorter, lighter, and more frequently interrupted by awakenings.[4] There are two main stages of sleep: REM (rapid eye movement) and NREM (non-rapid eye movement), which are divided into three stages (N1–N3) (Table 1). Each phase and stage of sleep involves changes in muscle tone, brain wave patterns, and eye movements, and the body cycles through these stages approximately 4 to 6 times each night, with an average cycle length of ninety minutes.[5] Several factors contribute to optimal sleep, including enough duration, excellent quality, appropriate scheduling, and the absence of sleep-related problems. Individuals' health and well-being are negatively impacted by sleep deprivation.[4] Getting adequate sleep is critical for maintaining good physical and mental health. Medical disorders such as obstructive sleep apnea, obesity, diabetes mellitus, insulin resistance, hypertension, depression, and anxiety are all significantly correlated with sleep deprivation.[6]

Cardiovascular disease (CVD) risk factors include non-modifiable factors such as age, sex, race, and family history, as well as modifiable factors such as hypertension, hyperlipidemia, diabetes, obesity, smoking, poor nutrition, stress, a sedentary lifestyle, all of which are also associated with sleep disorders.[7,8] In addition, studies have shown reduced sleep duration to seven out of the top 15 US causes of death, such as high blood pressure, diabetes, blood toxicity, cancer, heart disease, and stroke.[7] Studies show that inadequate sleep length and poor sleep quality are linked to a higher risk of CVD. Sleep has been related to cardiovascular health. CVD stands as a prominent global cause of mortality and impairment, and projections anticipate the number of cardiovascular-related deaths to surpass 24 million by 2030, imposing a substantial burden of disease.[9] Therefore, addressing risk factors such as obstructive sleep apnea (OSA) and insomnia is crucial in managing and preventing morbidity and mortality associated with CVD.[10]

In addition to short sleep, defined as less than seven hours, long sleep, or more than nine hours, is associated with a higher risk of CVD mortality, particularly in older adults and Asian populations.[10] For people with irregular sleep patterns, a one-hour reduction in sleep length per day is associated with a 3-11% increase in the risk of stroke, osteoporosis, coronary heart disease, and type 2 diabetes mellitus. On the other hand, those who are lengthy sleepers have a 7-17% increased risk of stroke mortality, coronary heart disease, stroke, and type 2 diabetes mellitus for every hour they sleep longer.[11] Studies reveal that people with sleep disorders or OSA are significantly more susceptible to metabolic disorders like obesity, type 2 diabetes mellitus, and dyslipidemia, as well as CVDs and cerebrovascular conditions like arrhythmias, atherosclerosis, coronary heart disease, heart failure, hypertension, and stroke.[3] This article aims to review the link between sleep quality and CVD risk.

PATHOPHYSIOLOGY

Sleep disorders are known to affect the development of CVDs by impacting various physiological pathways such as inflammatory, autonomic, and metabolism. These pathways collectively contribute to the development of high blood pressure, glucose intolerance, visceral adiposity, dyslipidemia, and endothelial dysfunction, which can ultimately lead to cardiovascular problems.[12,13] These physiological mechanisms are used to illustrate links between sleep and CVD.

Blood pressure

Chronic insomnia has been linked to increased plasma and urine noradrenaline, which leads to increased sympathetic activation. Excess sympathetic nervous system activity causes peripheral vasoconstriction, activating the renin-angiotensin-aldosterone system.[14] Insomnia also causes stress dysregulation, which increases pulsatile cortisol release and causes hypothalamic-pituitary-adrenal (HPA) axis dysfunction. This dysregulation of the HPA axis raises ACTH (adrenocorticotropic hormone).[15] The activation of the renin-angiotensin-

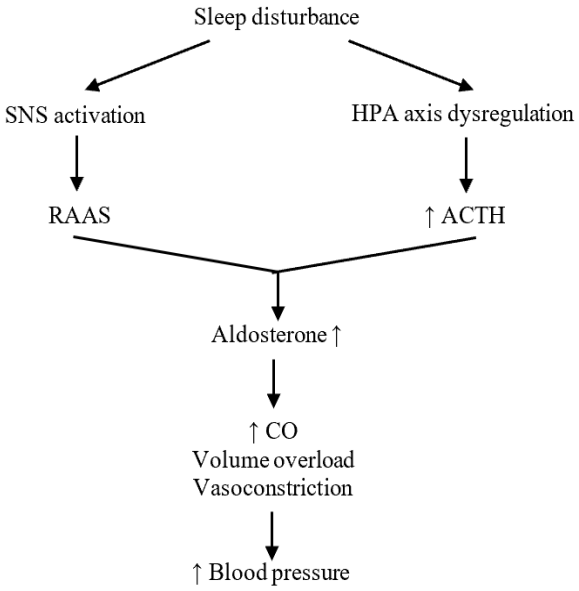


Figure 1. Pathway for sleep disturbances and blood pressure.
SNS: sympathetic nervous system, HPA: hypothalamic-pituitary-adrenal, RAAS: renin-angiotensin-aldosterone system, ACTH: adrenocorticotropic hormone, CO: cardiac output.

aldosterone system and ACTH release both increase the release of the aldosterone hormone.[14,15] This raised aldosterone hormone acts via the aldosterone receptor, which causes sodium retention and reabsorption, high cardiac output, volume overload, vasoconstriction, arterial stiffness, and vascular remodeling.[16] All of these effects result in elevated blood pressure (Figure-1). This increased blood pressure can damage arteries by making them less elastic, which decreases blood and oxygen flow to the heart and may lead to heart diseases.[17]

Inflammation

Inflammation has a major impact on the initiation and progression of CVD.[18] The hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system are also in charge of preserving the inflammatory cells.[19,20] The sympathetic nervous system regulates pro-inflammatory cytokine production by releasing the neurotransmitter norepinephrine into peripheral tissues, primary and secondary lymphoid organs, and all other major organ systems, including the vasculature and perivascular tissues. Once released, norepinephrine modulates immune response gene transcription by stimulating β-adrenergic receptors.[19] This adrenergic signalling cascade also suppresses the transcription of antiviral type I interferon (IFN) genes and up-regulates transcription of the pro-inflammatory immune response genes IL (interleukin)-1, tumour necrosis factor (TNF), and IL6, leading to increases in systemic inflammatory activity.[20] The HPA axis, via glucocorticoids, regulates gene expression in practically every body cell. Hormone-induced glucocorticoid receptor activation in leukocytes results in a significant downregulation of proviral gene programs (e.g., transcription of type I IFN genes, e.g., IFNA and IFNB, mediated by interferon regulatory factors [IRF]) and pro-inflammatory gene networks (e.g., NF-κB-mediated transcription of pro-inflammatory cytokine genes, such as IL1B, IL6, and TNF).[19] This mechanism triggers pro-inflammatory cascades in sleep deprivation that promote pro-inflammatory markers (such as TNFα, IL-1, IL-6, and IL-17, C-reactive protein [CRP], cellular adhesion molecules, and visfatin) and the development of atherosclerotic plaques.[21]

Metabolic dysregulation

Sleep deprivation has also been associated with hormonal changes that affect appetite, including increased hunger due to higher ghrelin levels and decreased satiety due to lower leptin levels.[22] The imbalance of leptin and ghrelin can impact glucose metabolism, cortisol levels, and growth hormone secretion.[23] Lack of sleep also raises cortisol levels because of dysregulation of the HPA axis and activation of the sympathetic nervous system. These

processes raise catecholamines and growth hormone levels, which reduces hepatic and peripheral insulin sensitivity and increases lipolysis.[24] The activation of lipolysis results in increased levels of non-esterified fatty acids and free fatty acids, further decreasing the hepatic insulin sensitivity and peripheral glucose uptake.[24,25] These high-free fatty acid and insulin resistance increase the risk of diabetes and obesity.[26] Chronic metabolic dysfunction in the form of insulin resistance and impaired glucose tolerance is a leading risk factor for CVD morbidity and mortality.[27]

Cardiovascular Diseases

Sleep disturbance leads to high blood pressure, insulin resistance, and a pro-inflammatory state. Increased visceral adiposity, blood pressure, glucose intolerance, and dyslipidemia characterise metabolic syndrome. Individually, these comorbidities induce endothelial dysfunction by increasing reactive oxygen species (ROS) and an imbalance between endothelium-derived relaxing (e.g., nitric oxide, prostaglandin [PG]-I2, endothelium-derived relaxing factor downregulation [EDRF]) and contracting factors (e.g., thromboxane [Tx]-A2, endothelin [ET]-1 upregulation).[12]

Endothelial dysfunction has several adverse impacts. Firstly, it could cause blood vessels to constrict, which would raise blood pressure; this may lead to inflammation within the arterial wall, which may contribute to the development of atherosclerosis (Figure-2). Moreover, it can stimulate an increase in platelet production, promoting the formation of blood clots. Lastly, it can compromise the integrity of blood vessel walls, making them leaky and exposing surrounding tissues to harmful lipoproteins and other toxic substances. It poses a multifaceted risk to cardiovascular health, leading to CVD.[28]

Arrhythmia

Poor sleep is an atrial fibrillation (AF) risk factor, directly affecting AF pathogenesis and other established risk factors.[29] Conditions like OSA, central sleep apnea (SLA), and restless legs syndrome (RLS) diminish sleep quality and harm the cardiovascular system.[30] Patients with OSA experience recurrent episodic airway obstruction resulting in negative intrathoracic pressure, hypoxemia, pulmonary hypertension, disturbances of autonomic tone, and sleep fragmentation.[31] These result in structural (increased left atrium [LA] volume, left ventricle [LV]) diastolic dysfunction, increased LV afterload, increased LA wall stress) and electrical disturbances (increased P wave duration and dispersion, disturbance in automatic tone, pro-inflammatory state may alter atrial electrical properties) that promote atrial arrhythmogenesis.[32]

INTERVENTIONS FOR PATIENTS WITH SLEEP DISORDERS AND THEIR ROLE IN THE MANAGEMENT OF CARDIOVASCULAR DISEASES

Non-pharmacological interventions

Cognitive behavioural therapy for insomnia

According to the American Academy of Sleep

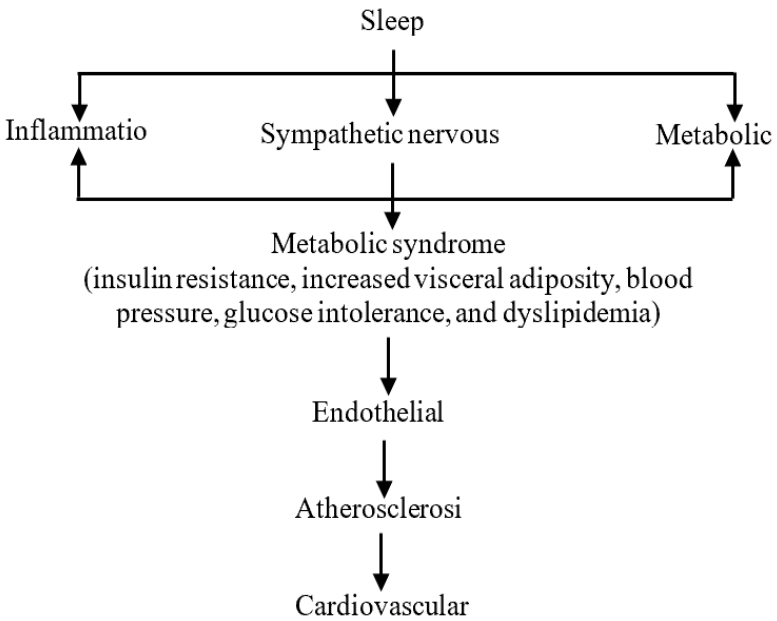


Figure 2. Flow diagram representing pathways and mechanisms for sleep disturbances leading to cardiovascular disease.

Medicine (AASM), cognitive behavioural therapy for insomnia (CBT-I) is recommended if insomnia has been determined due to intrusive thoughts or excessive worry, where a professional therapist helps manage the intrusive thoughts and behaviours that might be interfering with the sleep.[33] CBT-I comprises five components: sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relaxation training (RT). Sleep restriction techniques limit the amount of time spent in bed and delay the sleep until the patient's sleep drive builds up, making them fall asleep easily. Stimulus control breaks the conditioning of using the bed for general activities like eating, drinking, and using a laptop and reserves the bed for sleep and sex. Cognitive restructuring targets the intrusive thinking patterns which restrict a person from falling asleep. Sleep hygiene, on the other hand, includes a set of guidelines that promote a healthy lifestyle, like daily exercise and avoiding alcohol and caffeine in the evening. Trauer et al.[34], in their meta-analysis, showed that CBT-I is an effective treatment for people with chronic insomnia. The application of CBT-I resulted in notable increases in overall sleep duration and efficiency and significant decreases in sleep latency.[34]

Relaxation training

Another non-pharmacological treatment option includes relaxation therapy, where progressive muscle relaxation starts at the feet and works one way up. It has been described as a useful technique for managing insomnia.[35] In a pilot study by Garcia et al.[36], evaluating the effect of RT on insomnia and quality of life in postmenopausal women, RT showed significant differences between the intervention and control groups with improvements in sleep quality, reduction in the severity of insomnia and vasomotor symptoms. RT has also been shown effective in the recovery of ischemic heart disease, as a therapy for secondary prevention, and in improving psychological and physical health in older patients with heart failure.[37]

Red light therapy

Many recent studies have shown a significant association of red light therapy in improving sleep quality and cognition.[38] In a cohort study involving female basketball players, whole-body irradiation with a red light over 14 days significantly improved the quality of sleep, serum melatonin levels, and endurance performance of the athletes. The Pittsburgh Sleep Quality Index questionnaire measured sleep quality, and the post-intervention analysis demonstrated a greater improvement in the Pittsburgh Sleep Quality Index score in the intervention group compared to the controls ($p<0.001$).[39] Therefore, red light therapy may improve outcomes in patients with co-morbid CVDs, possibly by improvement in overall sleep quality.[40] Some other trials have also shown the role of red-light therapy in mitigating cardiovascular ageing with significant results in its favour.[41]

Recent pharmacological advancements

Dual orexin receptor antagonists

Orexin A and B are neuropeptides demonstrated to induce sympathetic dysregulation and hypertension in animal and human studies.[42] Dual orexin receptor antagonists represent a novel class of drugs utilised for insomnia treatment, exhibiting superior efficacy compared to placebo, as evidenced in a systematic review conducted by Rocha in 2023.[43] Although the effects of Dual orexin receptor antagonists on the cardiovascular system are yet unknown, in animal models, their capacity to inhibit orexin receptors has demonstrated promise in lowering risk factors related to cardiovascular illnesses, such as hypertension.[44]

Ashwagandha

Ashwagandha, also known as Indian Ginseng, is a shrub shown to improve sleep disorders in recent clinical trials. In a randomised controlled trial comprising 150 men and women aged 18 to 65 with insomnia, they were randomised to take Ashwagandha root and leaf extracts and a placebo. The study concluded with improvements in sleep in both groups; however, improvements were significantly higher in the Ashwagandha group (72%) than in the control group (29%).45 Similarly, many other studies have shown significant results for Ashwagandha in improving sleep efficiency, overall sleep time, and sleep latency through mechanisms involving increased expressions of gamma-aminobutyric acid A (GABAA), gamma-aminobutyric acid B1 (GABAB1), and serotonin receptors in the brain.[46,47] Ashwagandha has also been reported to demonstrate beneficial effects on the cardiovascular system by enhancing overall cardio-respiratory endurance (CRE). For instance, a trial by Tiwari et al.[48] found

that Ashwagandha significantly improved athletes' maximum aerobic capacity (a measure of CRE) (p=0.0074) over 8 weeks. The mouse models of myocardial infarction have also demonstrated cardio-protective properties of Ashwagandha through mechanisms involving upregulation of anti-apoptotic pathways and reduction of lipid peroxidation.[49] However, there is no data on actual human subjects being treated with Ashwagandha alone or as an adjunct to standard therapy for CVD like myocardial infarction or heart failure. Although Ashwagandha has shown physiological enhancements in healthy subjects, its use in patients with cardiovascular comorbidities is questionable. In terms of safety, trials have demonstrated that Ashwagandha has been well tolerated over several weeks of consumption, however, few case reports of hepatic adverse effects have raised concerns. Other studies have also claimed Ashwagandha may affect thyroid functions, but no specific dose has been studied. There is also a possibility of interactions with other drugs, which is scope for further research.[50]

DISCUSSION

Sleep disturbances associated with poor sleep, including quantity, quality, and associated sleep disorders, have been shown to negatively impact the risk factors for CVDs like diabetes, hypertension, obesity, and dyslipidemia, leading to increased cardiovascular morbidity and mortality.[50] In a systematic review conducted by Laksono et al.[51], short sleep was significantly and consistently associated with an increased incidence of hypertension and a high risk of developing heart failure. In contrast, both short and long sleep have been shown to increase the risk of AF and coronary heart disease, where short sleep duration was defined as sleep less than or equal to 4.9 hours to less than 7 hours, while long sleep duration was defined as sleep more than or equal to 7.5 hours to more than or equal to 10 hours in the study.[51] In a large-scale cross-section study conducted by the National Health Interview Survey (NHIS), people with both extremes of sleep duration have shown a higher prevalence of hypertension (<6 hours/night, prevalence of 32.4%; ≥10 hours/night, prevalence of 32.5%) compared to the referent category (8 hours/night, prevalence of 23.2%).[52] The sleep heart health study, another cross-sectional study, suggests similar findings. According to the findings, people who sleep less than 6 hours or more than 7 hours a day had adjusted odds ratios for hypertension of 1.66 (95% confidence interval [CI]: 1.35-2.04) and 1.19 (1.02-1.39), respectively; those who sleep between 8 and 9 hours a night and those who sleep for 9 hours or more had adjusted odds ratios of 1.19 (1.04-1.37) and 1.30 (1.04-1.62), respectively (p<0.0001 for the association between sleep duration and hypertension).[53] Although cross-sectional studies have proven the association of both short and long duration of sleep with hypertension, observational studies have only been able to prove the temporal association of short sleep but not long sleep with hypertension.[54] Multiple studies have shown an association between abnormal sleep duration and the prevalence of coronary heart disease. The NHIS discovered that the multivariate odds ratio of CVD was 2.20 (with a 95% CI of 1.78-2.71), 1.33 (1.13-1.57), 1.23 (1.06-1.41), and 1.57 (1.31-1.89) for sleep durations of <5 h, 6 h, 8 h, and ≥9 h when compared to a referent's 7 h of sleep.[55]

Intima media thickness (IMT) indicates the thickness of the inner layers of arteries, specifically the intima and media. It is utilised as a surrogate marker for atherosclerosis, as outlined in research conducted by Kastelein in 2003.[56] Moreover, a study by Zhang et al. in 201457 revealed a subtle connection between carotid IMT (CIMT) and the likelihood of developing coronary artery disease. In the Study of Health in Pomerania (SHIP), individuals who averaged 7-8 hours of sleep showed the lowest IMT values (0.76±0.15 and 0.79±0.16 mm, respectively). Conversely, IMT increased with both shorter and longer sleep durations. For instance, subjects sleeping only 5 hours displayed age- and sex-adjusted differences of 0.042 mm IMT (95% CI 0.008-0.076 compared to those sleeping 8 hours). Similarly, individuals with 11-12 hours of sleep showed increased IMT values (adjusted differences vs 8 hours of sleep: 0.084 mm [0.040-0.128] IMT).[58]

A greater incidence of AF has also been linked to sleeplessness, as per a meta-analysis of prospective cohort studies. It is found to increase the risk of AF by a standardised rate ratio (SRR) of 1.30 (95% confidence interval of 1.26 to 1.35), CVDs by 1.45 (1.29 to 1.64), coronary heart disease by 1.28 (1.10 to 1.50) and myocardial infarction by 1.42 (1.17 to 1.72).59 According to another meta-analysis by Sofi et al.[60], those with insomnia were more likely to experience CVD-related complications or death (relative risk

[RR]1.45, 95% CI: 1.29-1.62, p<0.00001).

The symptoms of OSA include repeated hypoxia caused by episodes of hypopnea or apnea during sleep. It has been shown to cause numerous cardiovascular complications, including hypertension, AF and other arrhythmias, heart failure, coronary artery disease, stroke, pulmonary hypertension, metabolic syndrome, diabetes, and increased cardiovascular mortality.[61] OSA has been shown to increase the odds of hypertension by 1.184 (95% CI: 1.093-1.274, p<0.05) for mild OSA, 1.316 (95% CI: 1.197-1.433, p<0.05) for moderate OSA and 1.561 (95% CI: 1.287-1.835, p<0.05) for severe OSA[62], the severity of OSA being graded by the apnea-hypopnea index (AHI) (AHI 5-15 being mild OSA, 15-30 being moderate OSA and more than 30 being severe OSA). Subjects with OSA compared to those without OSA had greater rates of AF, non-sustained ventricular tachycardia, and complex ventricular ectopy (non-sustained ventricular tachycardia or bigeminy, trigeminy, or quadrigeminy): 4.8 vs 0.9% (p=0.003) for AF; 5.3 vs 1.2% (p=0.004) for non-sustained ventricular tachycardia; and 25.0 vs 14.5% (p=0.002) for complex ventricular ectopy.[63] A grouping of many cardiovascular risk factors, such as diabetes, hypertension, dyslipidemia, and abdominal obesity, characterises metabolic syndrome.[64] Sleep duration has been suggested to play a role in the development of metabolic syndrome. A systematic review has shown that both short and long sleep was associated with metabolic syndrome (RR=1.15, 95% CI: 1.09-1.22, p<0.001) and (RR=1.19, 95% CI: 1.05-1.35, p<0.001).[65]

CONCLUSIONS

Getting enough sleep is crucial for preserving both mental and physical health. Sleep disorders like insomnia and OSA can affect inflammatory, autonomic, and metabolic pathways, potentially impacting cardiovascular health. Research also suggests that abnormal sleep duration, both short and long, is associated with an increased risk of hypertension, diabetes, obesity, and dyslipidemia, leading to elevated cardiovascular morbidity and mortality. Non-pharmacological interventions like CBT-I, RT, and red-light therapy have shown promise in improving sleep quality and mitigating cardiovascular risk factors. Dual orexin receptor antagonists have been suggested to enhance sleep quality and reduce cardiovascular morbidity, but only animal studies are supporting this. Ashwagandha also promises to improve sleep quality and cardiovascular health, but further research is needed. By addressing sleep disorders and promoting healthy sleep habits, the burden of CVDs can be significantly reduced worldwide.

Conflict of Interest

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

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MD; MT; PA;FA; DD; BS; Study Design: MD; MT; PA;FA; DD; BS; Literature Review: FA, DD; Critical Review: BS; Manuscript preparing: MD, MT, PA.

REFERENCES

1. Jawabri KH, Raja A. Physiology, sleep patterns. 2023 May 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. Available at: https://www.ncbi.nlm.nih.gov/books/NBK551680/.
2. Huang BH, Del Pozo Cruz B, Teixeira-Pinto A, Cistulli PA, Stamatakis E. Influence of poor sleep on cardiovascular disease-free life expectancy: a multi-resource-based population cohort study. BMC Med. 2023 Mar 2;21(1):75. doi: 10.1186/s12916-023-02732-x.
3. St-Onge MP, Grandner MA, Brown D, Conroy MB, Jean-Louis G, Coons M, Bhatt DL; American Heart Association Obesity, Behavior Change, Diabetes, and Nutrition Committees of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council. Sleep duration and quality: Impact on lifestyle behaviors and cardiometabolic health: A scientific statement from the American Heart Association. Circulation. 2016 Nov 1;134(18):e367-e386. doi: 10.1161/CIR.0000000000000444.
4. Chaput JP, Dutil C, Sampasa-Kanyinga H.

Sleeping hours: what is the ideal number and how does age impact this? Nat Sci Sleep. 2018 Nov 27:10:421-30. doi: 10.2147/NSS.S163071.
5. Patel AK, Reddy V, Shumway KR, Araujo JF. Physiology, sleep stages. 2024 Jan 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. Available at: https://www.ncbi.nlm.nih.gov/books/NBK526132/.
6. Hanson JA, Huecker MR. Sleep deprivation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jun 12. Available at: https://www.ncbi.nlm.nih.gov/books/NBK547676/.
7. Kaur IP, Arora K, Dhalani M, Patel M, Nishkamni, Kaur G, Jain R. The synergy of percutaneous coronary intervention and lifestyle modification in reducing mortality and blockage prevention. Cardiol Rev. 2024 Feb 1. doi:10.1097/CRD.0000000000000658.
8. Chattu VK, Manzar MD, Kumary S, Burman D, Spence DW, Pandi-Perumal SR. The global problem of insufficient sleep and its serious public health implications. Healthcare (Basel). 2018 Dec 20;7(1):1. doi: 10.3390/healthcare7010001.
9. Lao XQ, Liu X, Deng HB, Chan TC, Ho KF, Wang F, Vermeulen R, Tam T, Wong MCS, Tse LA, Chang LY, Yeoh EK. Sleep quality, sleep duration, and the risk of coronary heart disease: A prospective cohort study with 60,586 adults. J Clin Sleep Med. 2018 Jan 15;14(1):109-17. doi: 10.5664/jcsm.6894.
10. Krittanawong C, Tunhasiriwet A, Wang Z, Zhang H, Farrell AM, Chirapongsathorn S, Sun T, Kitai T, Argulian E. Association between short and long sleep durations and cardiovascular outcomes: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care. 2019 Dec;8(8):762-70. doi: 10.1177/2048872617741733.
11. Li J, Cao D, Huang Y, Chen Z, Wang R, Dong Q, Wei Q, Liu L. Sleep duration and health outcomes: an umbrella review. Sleep Breath. 2022 Sep;26(3):1479-501. doi: 10.1007/s11325-021-02458-1.
12. Tran V, De Silva TM, Sobey CG, Lim K, Drummond GR, Vinh A, Jelinic M. The vascular consequences of metabolic syndrome: rodent models, endothelial dysfunction, and current therapies. Front Pharmacol. 2020 Mar 4;11:148. doi: 10.3389/fphar.2020.00148.
13. Khan MS, Aouad R. The effects of insomnia and sleep loss on cardiovascular disease. Sleep Med Clin. 2017 Jun;12(2):167-77. doi: 10.1016/j.jsmc.2017.01.005.
14. Murck H, Schüssler P, Steiger A. Renin-angiotensin-aldosterone system: the forgotten stress hormone system: relationship to depression and sleep. Pharmacopsychiatry. 2012 May;45(3):83-95. doi: 10.1055/s-0031-1291346.
15. Seravalle G, Mancia G, Grassi G. Sympathetic nervous system, sleep, and hypertension. Curr Hypertens Rep. 2018 Jul 6;20(9):74. doi: 10.1007/s11906-018-0874-y.
16. Jarrin DC, Alvaro PK, Bouchard MA, Jarrin SD, Drake CL, Morin CM. Insomnia and hypertension: A systematic review. Sleep Med Rev. 2018 Oct;41:3-38. doi: 10.1016/j.smrv.2018.02.003.
17. About high blood pressure. Potential problems having high blood pressure could cause: Heart attack and heart disease. Centers for Disease Control and Prevention. May 15, 2024. Available at: https://www.cdc.gov/high-blood-pressure/about/index.html.
18. Willeit P, Thompson SG, Agewall S, Bergström G, Bickel H, Catapano AL, Chien KL, de Groot E, Empana JP, Etgen T, Franco OH, Iglseder B, Johnsen SH, Kavousi M, Lind L, Liu J, Mathiesen EB, Norata GD, Olsen MH, Papagianni A, Poppert H, Price JF, Sacco RL, Yanez DN, Zhao D, Schminke U, Bülbül A, Polak JF, Sitzer M, Hofman A, Grigore L, Dörr M, Su TC, Ducimetière P, Xie W, Ronkainen K, Kiechl S, Rundek T, Robertson C, Fagerberg B, Bokemark L, Steinmetz H, Ikram MA, Völzke H, Lin HJ, Plichart M, Tuomainen TP, Desvarieux M, McLachlan S, Schmidt C, Kauhanen J, Willeit J, Lorenz MW, Sander D; PROG-IMT study group. Inflammatory markers and extent and progression of early atherosclerosis: Meta-analysis of individual-participant-data from 20 prospective studies of the PROG-IMT collaboration. Eur J Prev Cardiol. 2016 Jan;23(2):194-205. doi: 10.1177/2047487314560664.
19. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol. 2011 Aug 5;11(9):625-32. doi: 10.1038/nri3042.
20. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014 May;140(3):774-815. doi:

10.1037/a0035302.
21. Grandner MA, Sands-Lincoln MR, Pak VM, Garland SN. Sleep duration, cardiovascular disease, and proinflammatory biomarkers. Nat Sci Sleep. 2013 Jul 22;5:93-107. doi: 10.2147/NSS.S31063.
22. Miller MA, Kruisbrink M, Wallace J, Ji C, Cappuccio FP. Sleep duration and incidence of obesity in infants, children, and adolescents: a systematic review and meta-analysis of prospective studies. Sleep. 2018 Apr 1;41(4). doi: 10.1093/sleep/zsy018.
23. Ruan H, Xun P, Cai W, He K, Tang Q. Habitual sleep duration and risk of childhood obesity: systematic review and dose-response meta-analysis of prospective cohort studies. Sci Rep. 2015 Nov 5;5:16160. doi: 10.1038/srep16160.
24. Broussard JL, Chapotot F, Abraham V, Day A, Delebecque F, Whitmore HR, Tasali E. Sleep restriction increases free fatty acids in healthy men. Diabetologia. 2015 Apr;58(4):791-8. doi: 10.1007/s00125-015-3500-4.
25. Karpe F, Dickmann JR, Frayn KN. Fatty acids, obesity, and insulin resistance: time for a reevaluation. Diabetes. 2011 Oct;60(10):2441-9. doi: 10.2337/db11-0425.
26. Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. Nat Rev Endocrinol. 2009 May;5(5):253-61. doi: 10.1038/nrendo.2009.23.
27. Huang Y, Cai X, Chen P, Mai W, Tang H, Huang Y, Hu Y. Associations of prediabetes with all-cause and cardiovascular mortality: a meta-analysis. Ann Med. 2014 Dec;46(8):684-92. doi: 10.3109/07853890.2014.955051.
28. Endothelial Dysfunction. Cleveland Clinic. Dec 5, 2022. Available at: https://my.clevelandclinic.org/health/diseases/23230-endothelial-dysfunction.
29. Groh CA, Faulkner M, Getabecha S, Taffe V, Nah G, Sigona K, McCall D, Hills MT, Sciarappa K, Pletcher MJ, Olgin JE, Marcus GM. Patient-reported triggers of paroxysmal atrial fibrillation. Heart Rhythm. 2019 Jul;16(7):996-1002. doi: 10.1016/j.hrthm.2019.01.027.
30. May AM, Van Wagoner DR, Mehra R. OSA and cardiac arrhythmogenesis: Mechanistic insights. Chest. 2017 Jan;151(1):225-41. doi: 10.1016/j.chest.2016.09.014.
31. Maan A, Mansour M, Anter E, Patel VV, Cheng A, Refaat MM, Ruskin JN, Heist EK. Obstructive sleep apnea and atrial fibrillation: Pathophysiology and implications for treatment. Crit Pathw Cardiol. 2015 Jun;14(2):81-5. doi: 10.1097/HPC.0000000000000044.
32. Mannakkara N. The impact of poor sleep on atrial fibrillation. British Cardiac Society. Nov, 2021. Available at: https://bcs-web.squiz.cloud/resources/editorials/articles/the-impact-of-poor-sleep-on-atrial-fibrillation.
33. Rossman J. Cognitive-behavioral therapy for insomnia: An effective and underutilized treatment for insomnia. Am J Lifestyle Med. 2019 Aug 12;13(6):544-7. doi: 10.1177/1559827619867677.
34. Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive behavioral therapy for chronic insomnia: A systematic review and meta-analysis. Ann Intern Med. 2015 Aug 4;163(3):191-204. doi: 10.7326/M14-2841.
35. Kılıç N, Parlar Kılıç S. The effect of progressive muscle relaxation on sleep quality and fatigue in patients with rheumatoid arthritis: A randomized controlled trial. Int J Nurs Pract. 2023 Jun;29(3):e13015. doi: 10.1111/ijn.13015.
36. Garcia MC, Kozasa EH, Tufik S, Mello LEAM, Hachul H. The effects of mindfulness and relaxation training for insomnia (MRTI) on postmenopausal women: a pilot study. Menopause. 2018 Sep;25(9):992-1003. doi: 10.1097/GME.0000000000001118.
37. van Dixhoorn J, White A. Relaxation therapy for rehabilitation and prevention in ischaemic heart disease: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2005 Jun;12(3):193-202. doi: 10.1097/00149831-200506000-00002.
38. Zang L, Liu X, Li Y, Liu J, Lu Q, Zhang Y, Meng Q. The effect of light therapy on sleep disorders and psychobehavioral symptoms in patients with Alzheimer's disease: A meta-analysis. PLoS One. 2023 Dec 6;18(12):e0293977. doi: 10.1371/journal.pone.0293977.
39. Zhao J, Tian Y, Nie J, Xu J, Liu D. Red light and the sleep quality and endurance performance of Chinese female basketball players. Athl Train. 2012 Nov-Dec;47(6):673-8. doi: 10.4085/1062-6050-47.6.08.
40. Zhang W, Gao X, Wang X, Li D, Zhao Y, Zhang T, Ne J, Xu B, Li S, Jiang Z, Sun H, Ma W, Yang F, Cai B, Yang B. Light emitting diodes photobiomodulation improves cardiac function

by promoting ATP synthesis in mice with heart failure. Front Cardiovasc Med. 2021 Dec 2;8:753664. doi: 10.3389/fcvm.2021.753664.
41. Syed SB, Ahmet I, Chakir K, Morrell CH, Arany PR, Lakatta EG. Photobiomodulation therapy mitigates cardiovascular aging and improves survival. Lasers Surg Med. 2023 Mar;55(3):278-93. doi: 10.1002/lsm.23644.
42. Bigalke JA, Shan Z, Carter JR. Orexin, sleep, sympathetic neural activity, and cardiovascular function. Hypertension. 2022 Dec;79(12):2643-55. doi: 10.1161/HYPERTENSIONAHA.122.19796.
43. Rocha RB, Bomtempo FF, Nager GB, Cenci GI, Telles JPM. Dual orexin receptor antagonists for the treatment of insomnia: systematic review and network meta-analysis. Arq Neuropsiquiatr. 2023 May;81(5):475-83. doi: 10.1055/s-0043-1768667.
44. Huber MJ, Chen QH, Shan Z. The orexin system and hypertension. Cell Mol Neurobiol. 2018 Mar;38(2):385-91. doi: 10.1007/s10571-017-0487-z.
45. Deshpande A, Irani N, Balkrishnan R, Benny IR. A randomized, double blind, placebo controlled study to evaluate the effects of ashwagandha (Withania somnifera) extract on sleep quality in healthy adults. Sleep Med. 2020 Aug:72:28-36. doi: 10.1016/j.sleep.2020.03.012.
46. Park CW, Hong KB, Suh HJ, Ahn Y. Sleep-promoting activity of amylase-treated Ashwagandha (Withania somnifera L. Dunal) root extract via GABA receptors. J Food Drug Anal. 2023 Jun 15;31(2):278-88. doi: 10.38212/2224-6614.3456.
47. Langade D, Thakare V, Kanchi S, Kelgane S. Clinical evaluation of the pharmacological impact of ashwagandha root extract on sleep in healthy volunteers and insomnia patients: A double-blind, randomized, parallel-group, placebo-controlled study. J Ethnopharmacol. 2021 Jan 10:264:113276. doi: 10.1016/j.jep.2020.113276.
48. Tiwari S, Gupta SK, Pathak AK. A double-blind, randomized, placebo-controlled trial on the effect of Ashwagandha (Withania somnifera dunal.) root extract in improving cardiorespiratory endurance and recovery in healthy athletic adults. J Ethnopharmacol. 2021 May 23:272:113929. doi: 10.1016/j.jep.2021.113929.
49. Mikulska P, Malinowska M, Ignacyk M, Szustowski P, Nowak J, Pesta K, Szeląg M, Szklanny D, Judasz E, Kaczmarek G, Ejiohuo OP, Paczkowska-Walendowska M, Gościniak A, Cielecka-Piontek J. Ashwagandha (Withania somnifera)-Current research on the health-promoting activities: A narrative review. Pharmaceutics. 2023 Mar 24;15(4):1057. doi: 10.3390/pharmaceutics15041057.
50. Ravichandran R, Gupta L, Singh M, Nag A, Thomas J, Panjiyar BK. The interplay between sleep disorders and cardiovascular diseases: A systematic review. Cureus. 2023 Sep 25;15(9):e45898. doi: 10.7759/cureus.45898.
51. Laksono S, Yanni M, Iqbal M, Prawara AS. Abnormal sleep duration as predictor for cardiovascular diseases: a systematic review of prospective studies. Sleep Disord. 2022 Feb 7:2022:9969107. doi: 10.1155/2022/9969107.
52. Fang J, Wheaton AG, Keenan NL, Greenlund KJ, Perry GS, Croft JB. Association of sleep duration and hypertension among US adults varies by age and sex. Am J Hypertens. 2012 Mar;25(3):335-41. doi: 10.1038/ajh.2011.201.
53. Gottlieb DJ, Redline S, Nieto FJ, Baldwin CM, Newman AB, Resnick HE, Punjabi NM. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. Sleep. 2006 Aug;29(8):1009-14. doi: 10.1093/sleep/29.8.1009.
54. Covassin N, Singh P. Sleep duration and cardiovascular disease risk: epidemiologic and experimental evidence. Sleep Med Clin. 2016 Mar;11(1):81-9. doi: 10.1016/j.jsmc.2015.10.007.
55. Sabanayagam C, Shankar A. Sleep duration and cardiovascular disease: results from the National Health Interview Survey. Sleep. 2010 Aug;33(8):1037-42. doi: 10.1093/sleep/33.8.1037.
56. Kastelein JJ, Wiegman A, de Groot E. Surrogate markers of atherosclerosis: impact of statins. Atheroscler Suppl. 2003 Mar;4(1):31-6. doi: 10.1016/s1567-5688(03)00007-2.
57. Zhang Y, Guallar E, Qiao Y, Wasserman BA. Is carotid intima-media thickness as predictive as other noninvasive techniques for the detection of coronary artery disease? Arterioscler Thromb Vasc Biol. 2014 Jul;34(7):1341-5. doi: 10.1161/ATVBAHA.113.302075.
58. Wolff B, Völzke H, Schwahn C, Robinson D, Kessler C, John U. Relation of self-reported sleep duration with carotid intima-media thickness in a general population sample. Atherosclerosis. 2008 Feb;196(2):727-32. doi: 10.1016/j.atherosclerosis.2006.12.023.

59. Wu TT, Zou YL, Xu KD, Jiang XR, Zhou MM, Zhang SB, Song CH. Insomnia and multiple health outcomes: umbrella review of meta-analyses of prospective cohort studies. Public Health. 2023 Feb;215:66-74. doi: 10.1016/j.puhe.2022.11.021.
60. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. Eur J Prev Cardiol. 2014 Jan;21(1):57-64. doi: 10.1177/2047487312460020.
61. Li YE, Ren J. Association between obstructive sleep apnea and cardiovascular diseases. Acta Biochim Biophys Sin (Shanghai). 2022 Jul 25;54(7):882-892. doi: 10.3724/abbs.2022084.
62. Hou H, Zhao Y, Yu W, Dong H, Xue X, Ding J, Xing W, Wang W. Association of obstructive sleep apnea with hypertension: A systematic review and meta-analysis. J Glob Health. 2018 Jun;8(1):010405. doi: 10.7189/jogh.08.010405.
63. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S; Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med. 2006 Apr 15;173(8):910-6. doi: 10.1164/rccm.200509-1442OC.
64. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009 May-Jun;2(5-6):231-7. doi: 10.1242/dmm.001180.
65. Che T, Yan C, Tian D, Zhang X, Liu X, Wu Z. The association between sleep and metabolic syndrome: A systematic review and meta-analysis. Front Endocrinol (Lausanne). 2021 Nov 19;12:773646. doi: 10.3389/fendo.2021.773646.

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Evaluation of antifungal treatment strategies in febrile neutropenic episodes of high-risk hematologic malignancies: A single center retrospective study

Aycan Acet[1], **Vildan Ozkocaman**[2], **Fahir Ozkalemkas**[3]

[1] Department of Internal Medicine, Kütahya Health Sciences University, Faculty of Medicine, Kütahya, Türkiye

[2] Department of Internal Medicine, Division of Hematology, Uludağ University Faculty of Medicine, Bursa, Türkiye

ABSTRACT

Background Febrile neutropenic patients are at high risk for developing invasive fungal infection (IFI). Currently, two treatment strategies, empiric and preemptive, are used in febrile neutropenic patients with IFI. This study aimed to evaluate empirical and preemptive treatment strategies in patients with high-risk hematologic malignancies.

Methods We retrospectively analyzed 402 febrile neutropenic attacks in 281 patients with hematological malignancies hospitalized in a university hospital hematology clinic. Between June 2006 and January 2009, 154 febrile neutropenic episodes of 104 patients who met the study eligibility criteria were included. Patients who received antibiotic and antifungal treatment for febrile neutropenia were retrospectively recorded. Patients treated with empiric and preemptive approaches were identified and compared with statistical methods.

Results Antifungal treatment was initiated as empiric treatment in 62 (40%), preemptive therapy in 55 (36%) (subgroups; 45 [29%] possible-IFI and 10 [7%] probable-IFI), and 37 (24%) for secondary prophylaxis. In terms of length of hospitalization and all-cause mortality, no statistically significant results were found when patients receiving empiric and preemptive treatment were compared. ($p>0.05$).

Conclusion In patients with high-risk hematologic malignancies, even if empiric treatment is initiated, a dynamic approach that can be summarized as persistently trying to obtain evidence by using ancillary diagnostic tools and early termination of therapy in unnecessary cases seems appropriate.

Turk J Int Med 2025;7(1):12-21
DOI: 10.46310/tjim.1602618

Keywords: *High-risk hematologic malignancy, febrile neutropenia, invasive fungal infections, empiric-preemptive therapy*

Received: *December 16, 2024* ***Accepted:*** *January 25, 2025* ***Published Online:*** *January 29, 2025*

How to cite this article: *Acet A, Ozkocaman V, Ozkalemkas F. Evaluation of antifungal treatment strategies in febrile neutropenic episodes of high-risk hematologic malignancies: A single center retrospective study. Turk J Int Med 2025;7(1):12-21. DOI: 10.46310/tjim.1602618*

Address for Correspondence:
Aycan ACET, Department of Internal Medicine, Kütahya Health Sciences University, Kütahya, Türkiye
E-mail: aycanacet80@icloud.com

INTRODUCTION

In recent decades, the frequency of invasive fungal infection (IFI) has increased in patients with hematologic malignancy.[1] While empirical treatment approaches based on fever were at the forefront in the past, in recent years, the high cost of empirical treatment, the side effect profile of amphotericin B, which increases morbidity and cost, and the development of computed tomography and serologic methods for detecting fungal cell wall antigens in body fluids have led to the discussion of preemptive treatment approaches to start antifungal treatment with more evidence. Patients with high-risk hematologic malignancies with fever refractory to broad-spectrum antibacterial therapy and new infiltration with unexplained causes on radiologic imaging are candidates for fungal infections. One of the most critical problems faced by clinicians is the decision to initiate antifungal drugs in a neutropenic patient with prolonged fever, which is costly and may have high side effects. The high risk of invasive pulmonary aspergillosis (IPA), especially in patients with hematologic malignancies or those undergoing stem cell transplantation, emphasizes the importance of decision-making in this situation. However, delay in diagnosis is the most important problem in invasive aspergillosis.[2] Aspergillosis rarely grows in blood cultures; its growth is generally considered contamination. The sensitivity of cultures obtained from respiratory tract secretions is low. Growth occurs in only 8-34% of sputum samples and 45-62% of bronchoalveolar lavage (BAL) samples of patients with invasive aspergillosis. Histopathology is required for diagnosis but marked pancytopenia, respiratory distress, and bleeding risk are inhibiting factors for diagnosis.[3] Empirical antifungal treatment is a common approach. Only 20-25% of those receiving empirical antifungal treatment in the USA and Europe are IFIs. Another known fact is that while the frequency of aspergillosis is around 2-10% with empirical treatment, this rate approaches 30% in patients without empirical treatment and with prolonged neutropenia.[4,5] To move away from the empirical approach, providing evidence of fungal infection through tissue diagnosis or culture results is essential.

MATERIAL AND METHODS

Patient selection and study design

We retrospectively analyzed 402 febrile neutropenic episodes of 281 patients with hematologic malignancies who received inpatient treatment during the 2.5-year period between June 2006 and January 2009 in the department of hematology, Uludağ University Faculty of Medicine. Among these, 154 FEN of 104 patients who received antifungal drugs were analyzed.

Patients aged 18 years or older, patients who received chemotherapy for hematologic malignancy and had a febrile neutropenic episodes, patients diagnosed with IFI (possible, probable, proven) according to the guidelines and/or patients who received systemic (oral or parenteral) antifungal therapy for treatment were included in the study. Only patients with a diagnosis of mucosal (oropharyngeal, vaginal) candidiasis and patients younger than 18 years of age were excluded. Patient files were reviewed and age, sex, comorbidity, underlying hematologic malignant disease, duration of hospitalization, number and duration of febrile neutropenic episodes, antifungal treatment strategies, reasons for use, side effects, reasons for change, duration and doses of antifungal drugs used, Blood, catheter, BAL, sputum cultures, blood and BAL galactomannan (GM) antigen, infections that developed under treatment, radiology and laboratory findings, data about the operation if an operation was performed, and data about the patient and disease status at the end of the febrile neutropenic episode were recorded.

The use of computerized tomography and bronchoalveolar lavage in FEN episodes

Computed tomography (CT) was performed if fever did not respond to broad-spectrum antibacterial treatment within 96 hours and signs of lower respiratory tract infection or new infiltrates were detected on chest radiography. Bronchoscopy and BAL were performed in patients with CT findings compatible with IFI (nodules, halo sign, air-crescent sign, cavitation); BAL fluid was examined microbiologically and serologically. Serum samples were collected twice a week, and GM antigen testing was performed; BAL GM antigen testing was also performed.

Invasive fungal infection criteria and antifungal treatment strategies

Invasive fungal infection was defined according to EORTC/MSG criteria[6], and patients were classified as possible, probable and proven. Antifungal treatment strategies were empiric and preemptive; initial treatment was usually amphotericin B deoxycholate, and other antifungals were switched to in case of

severe side effects, intolerance or non-response.

Statistical analysis

Statistical analysis of the obtained data was performed with the SPSS 13.0 computer program. In the study, temporal variables were presented as minimum, maximum and median values and categorical variables were presented as frequency (%) when necessary. Pearson chi-square test was used to compare the empiric and preemptive groups. In the study, $p<0.05$ was considered statistically significant.

RESULTS

Of the 104 patients who met the inclusion criteria, 65 (63%) were male and 39 (37%) were female. Of the patients, 60 (57.6%) were acute myeloid leukemia (AML), 21 (20.1%) acute lymphoid leukemia (ALL), 7 (6.73%) non-Hodgkin's lymphoma (NHL), and 2 (1.92%) Hodgkin's lymphoma, 2 were biphenotypic leukemia, 2 (1.94%) myelodysplastic syndrome, 3 (2.88%) multiple myeloma (MM), 4 (3.84%) aplastic anemia and 3 (2.88%) chronic lymphocytic leukemia. Regarding primary hematologic disease, 52 episodes of febrile neutropenia (34%) were newly diagnosed. Forty-three (28%) of the episodes were in complete response to treatment, 41 (27%) were recurrent disease, 10 (6%) were resistant disease, and 8 (5%) were in other groups. Twenty-seven (26%) of the patients had a concomitant chronic disease. The hospitalization duration range was 8-151 (median: 37.5) days. All patients had neutropenic fever. The total duration of antifungal use was 2-77 (median: 18) days. The number of patients who died at the end of all episodes was 40. Patient and episode characteristics are summarized in Table 1. When the group of patients receiving treatment for secondary prophylaxis was excluded from all episodes of febrile neutropenia, 62 (53%) of the remaining 117 episodes of febrile neutropenia were empiric, and 55 (47%) were preemptive antifungal treatment. The distribution of antifungal treatment according to febrile neutropenia episodes is shown in Table 2. In the empirical treatment group, CT findings included ground-glass opacities in 28 (56%), nodular infiltrates in 9 (18%), consolidation in 11 (22%), a mass appearance in 1 (2%), and six attacks. Pleural fluid appearance was detected in 6 (12%) patients, while the findings were normal in 8 (16%). Characteristic findings for IPA included a halo sign in 14 (28%) and cavitation and air-crescent sign in 2 (4%) attacks.

Table 1. Characteristics of 154 febrile neutropenia episodes in 104 patients

Gender (male/female) (n)	65/39
Age (years)	41 (18-79)
Hematological disease (n)	
Acute myeloid leukemia	60
Acute lymphocytic leukemia	21
Non-Hodgkin lymphoma	7
Hodgkin lymphoma	2
Biphenotypic leukemia	2
Myelodysplastic syndrome	2
Multiple myeloma	3
Aplastic anemia	4
Chronic lymphocytic leukemia	3
Hematological disease status n (%)	
New Diagnosis	52 (34%)
Complete response	43 (28%)
Relapse	41 (27%)
Refractory	10 (6%)
Other	8 (5%)
Total duration of antifungal use (days)	18 (2-77)
Total hospitalization duration (days)	37.5 (8-151)
Discharged/died (n)	114/40

The data were given as median (min: max).

Table 2. Distribution of antifungal treatment according to febrile neutropenia episodes

Antifungal treatment	Episodes n (%)
Empiric	62 (40%)
Preemptive (total)	55 (36%)
Possible-IFI	45 (29%)
Probable-IFI	10 (7%)
Secondary prophylaxis	37 (24%)

In the preemptive treatment group, CT findings

Table 3. Chest computerized tomography findings of patient attacks

Reason for antifungal use	Empirical	Preemptive	Secondary prophylaxis	Total
Attack/patient (n)	49/46	52/49	25/19	126/114
Findings n (%)				
Ground-glass opacity	28 (56%)	43 (78%)	11 (52%)	82 (65%)
Nodular infiltrates	9 (18%)	23 (42%)	2 (9%)	34 (27%)
Consolidation	11 (22%)	25 (45%)	5 (24%)	41 (33%)
Cavitation/air-crescent sign	2 (4%)	9 (16%)	2 (9%)	13 (11%)
Halo sign	14 (28%)	21 (38%)	3 (14%)	38 (30%)
Mass	1 (2%)	-	-	1 (1%)
Pleural effusion	6 (12%)	4 (7%)	2 (9%)	12 (9%)
Normal	8 (16%)	-	3 (14%)	11 (8%)

consisted of ground-glass opacities in 43 (78%) attacks, nodular infiltrates in 23 (42%), consolidation in 25 (45%), and pleural fluid appearance in 4 (7%) attacks. Specific findings for IPA included a halo sign detected in 21 (38%) and cavitation and air-crescent sign in 9 (16%) attacks.

In the group receiving secondary prophylaxis, CT findings showed ground-glass opacities in 11 (52%) attacks, nodular infiltrates in 2 (9%), consolidation in 5 (24%), and pleural fluid appearance in 2 (9%) attacks. Normal findings were observed in 3 attacks (14%). Specific findings for IPA included a halo sign in 3 (14%) attacks, along with cavitation and air-crescent sign in 2 (9%).

Considering all febrile neutropenic episode attacks, CT findings revealed ground-glass opacities in 82 (65%), nodular infiltrates in 34 (27%), consolidation in 41 (33%), and pleural fluid in 12 (9%) attacks. Normal findings were noted in 11 (8%) patients. The specific findings for IPA included a halo sign in 38 attacks (30%) and an air-crescent sign and cavity in 13 attacks (11%). The CT findings related to patient attacks are summarized in Table 3.

Table 4 presented the characteristics of patients with hematologic malignancies who underwent BAL. Among the 38 patients, the most common diagnosis was AML (68.4%), followed by ALL (23.6%), with fewer cases of NHL (2.6%), MM (2.6%), and aplastic anaemia (2.6%). All patients had neutropenia and fever during hospitalization, with a median hospitalization duration of 39 days (range: 22–101). BAL GM antigen was positive in 47% of patients, while serum GM positivity was observed in 26%. Non-specific chest CT findings were the most common (63.1%), with the halo sign (23.6%) and air-crescent sign or cavity (13.1%) detected in fewer cases.

A total of 62 febrile neutropenia episodes of patients who received antifungal treatment with an

Table 4. Characteristics of patients undergoing bronchoscopy-guided bronchoalveolar lavage

Reason for antifungal administration	Empirical	HP-IPA	LP-IPA	Secondary prophylaxis	Total
Attack/patient (n)	8/8	12/12	11/11	7/7	38/38
Gender (male/female)	5/3	12/0	9/2	4/2	25/6
Age (years)	44.5 (24-57)	52.5 (29-70)	38 (24-63)	38 (24-57)	48 (24-70)
Diagnosis (n)					
AML	7	8	6	5	26 (68.4%)
ALL	1	3	3	2	9 (23.6%)
NHL	-	1	-	-	1 (2.6%)
MM	-	-	1	-	1 (2.6%)
AA	-	-	1	-	1 (2.6%)
Hematological disease status (n)					
New Diagnosis	5	8	6	3	22 (57.8%)
Remission	2	4	4	1	11 (28.9%)
Relapse	1	-	1	2	4 (10.5%)
Resistance	-	-	-	1	1 (2.6%)
Hospitalization duration (days)	42.5 (23-89)	38 (27-82)	39 (26-82)	39 (22-101)	39 (22-101)
Patient factors					
Neutropenia	8	12	11	7	38 (100%)
Fever	8	12	11	7	38 (100%)
Steroid usage	-	-	-	-	-
Duration of antifungal therapy (days)	20.5 (9-50)	15 (5-26)	19 (5-47)	29 (11-48)	18 (5-50)
CT findings					
Halo sign	1	6	2	-	9 (23.6%)
Air-crescent sign/cavity	1	3	-	1	5(13.1%)
Non-specific	6	3	9	6	24 (63.1%)
BAL GM					
Positive	2	5	9	2	18 (47%)
Negative	6	7	2	5	20 (53%)
Serum GM					
Positive	2	1	6	1	10 (26%)
Negative	6	11	5	6	28 (74%)
Number of serum GM evaluated (per attack)	12 (9-25)	11 (8-23)	15 (7-23)	11 (6-29)	11 (6-29)
Discharged/died (n)	7/1	9/3	9/2	7/0	32/6

The data were n, n (%), or median (min: max).

HP-IPA: highly probable invasive pulmonary aspergillosis, LP-IPA: low probable invasive pulmonary aspergillosis, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, NHL: non-Hodgkin lymphoma, AA: aplastic anemia, CT: computerized tomography, BAL GM: bronchoalveolar lavage galactomannan antigen, GM: galactomannan antigen.

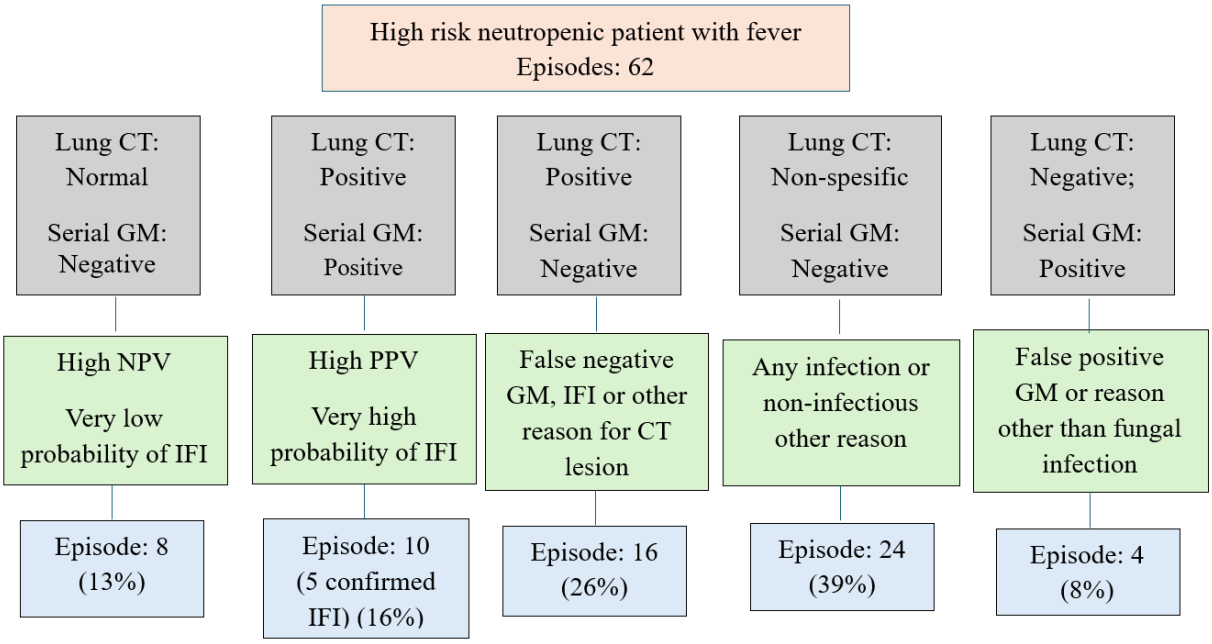


Figure 1. Re-evaluation of febrile neutropenia attacks in patients who received antifungal treatment with empirical approach in line with preemptive approach
NPV: negative predictive value, PPV: positive predictive value, GM: galactomannan, CT: computerized tomography, IFI: invazive fungal infection.

empirical approach were re-evaluated after the end of the febrile neutropenia episode in line with the preemptive approach. Radiologic and laboratory findings suggestive of fungal infection were identified in 10 (16%) of these episodes, and fungal growth was detected in 5 (8%) (Figure 1). Our analysis of 55 febrile neutropenia episodes in the preemptive group found that 26 (47%) febrile neutropenia episodes had findings suggestive of fungal infection with radiologic and laboratory diagnostic methods. Of these episodes, fungal infection was proven in 11 (20%) (Figure 2). The two antifungal treatment groups were similar in terms of the compared characteristics. Since mortality due to IFI was not evaluated in our study, all-cause mortality was calculated by comparing empiric-preemptive antifungal treatment strategies. Regarding all-cause mortality, there was no statistically significant difference between the episodes of patients treated with empirical antifungal therapy and those treated with preemptive therapy ($p>0.05$). Comparative characteristics of these two treatment groups were presented in Table 5.

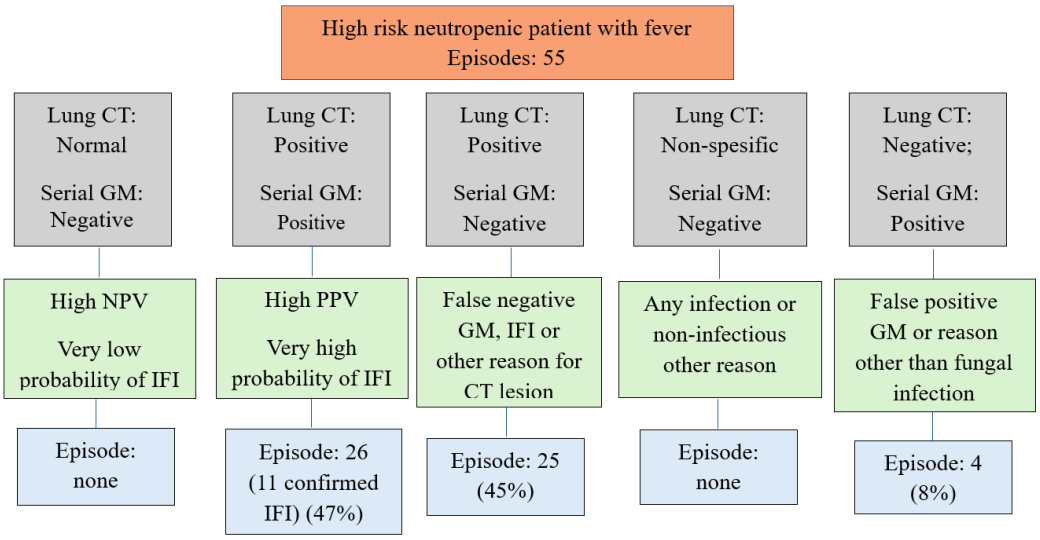


Figure 2. Evaluation of febrile neutropenia attacks in patients given antifungal therapy with a preemptive approach
NPV: negative predictive value, PPV: positive predictive value, GM: galactomannan, CT: computerized tomography, IFI: invazive fungal infection.

Table 5. Comparison of antifungal treatment strategies

Variables	Empiric (%)	Preemptive (%)
Attack/patient (n)	58/62	54/55
Gender (male/female)	39/23 (67%/33%)	36/18 (67%/33%)
Age (years)	39 (19-71)	48 (18-79)*
Diagnosis (n)		
Acute myeloid leukemia	34 (59%)	31 (58%)
Acute lymphocytic leukemia	10 (17%)	12 (22%)
Non-Hodgkin lymphoma	3	4
Hodgkin lymphoma	1	1
Biphenotypic leukemia	2	0
Myelodysplastic syndrome	2	1
Multiple myeloma	2	1
Aplastic anemia	3	2
Chronic lymphocytic leukemia	1	2
Hematological disease status (n)		
New Diagnosis	27 (44%)	23 (42%)
Remission	11 (18%)	10 (18%)
Relapse	14 (22%)	13 (24%)
Resistance	6 (10%)	4 (7%)
Other	4 (6%)	5 (9%)
Total duration of antifungal use (days)	18 (2-69)	14 (2-60)
Total hospitalization duration (days)	39 (14-151)	38 (11-91)
Discharged/died (n)	47/15	34/21

* $p<0.05$

DISCUSSION

Infections in neutropenic patients are an important cause of morbidity and mortality. In this patient group, signs of inflammation are faint due to neutropenia. Therefore, it is often not possible to identify the focus of infection. However, the initiation of antimicrobial therapy is urgent as the patient's condition may deteriorate rapidly, and the patient could die within hours. In this case, the only criterion for starting antimicrobials in neutropenic patients is the patient's fever. In national and international guidelines published on febrile neutropenia, the finding that directs treatment is high fever.[7,8] Accordingly, broad-spectrum antibiotics are started empirically in neutropenic patients with fever. If the patient's fever persists on the 3rd to 5th day of treatment, it is not easy to understand whether the reason for the patient's fever not decreasing is due to a bacterial or fungal cause. Diagnosis of fungal infections in neutropenic patients is difficult. The time spent to make the diagnosis may negatively affect the prognosis. The faster fungal infections developing in neutropenic patients are treated, the better the outcome.[9] Based on these data, guidelines recommend initiating antifungal treatment in case of persistent fever on the 3rd to 5th day of antimicrobial treatment.[7,8] This approach, which accepts the patient's fever as the main criterion, is called empirical treatment. Approximately two-thirds of febrile neutropenic patients receive antifungal treatment with this approach.[10] The aim is to ensure that patients likely to have IFI are treated early in the disease. Early initiation of treatment is thought to change the survival rate favorably.[10] Empirical antifungal treatment can be administered to up to 40-50% of the high-risk neutropenic patient population, although the actual incidence of IFI is believed to be between 10-15%. [12]

Antifungal treatment was given in 154 (38%) of the 402 febrile neutropenic episodes analyzed in our study. When the episodes in which antifungal treatment was given for secondary prophylaxis were excluded from these episodes, this rate decreased to 29%. The episodes in which empirical antifungal treatment was given only for fever constituted 12% of all febrile neutropenic episodes and 40% of all antifungal treatments. In the empiric treatment group, at least one evidence of IFI was obtained in 49% of episodes using diagnostic methods such as CT, BAL, GM measurement, and culture. In contrast, no evidence was obtained in 51%. In summary, in the empiric treatment group, no concrete evidence in favor

of IFI could be obtained in approximately half of the patients. Studies have shown that empirical therapy remains the standard of care in many institutions, with a significant percentage of chemotherapy courses employing this strategy.[13,14]

Recent advances in non-culture diagnostic methods and a better understanding of risk factors will narrow the patient population that may benefit from antifungal treatment. In this way, the concept of early treatment will not be compromised, and drug interactions, drug toxicity, and cost increases due to unnecessary drug administration will be reduced. Cost-effectiveness analyses have highlighted the economic implications of both strategies. Empirical treatment is less expensive than preemptive therapy, with one study reporting costs of $147,482 for empirical treatment compared to $147,910 for preemptive treatment.[15] This cost difference is significant, particularly in healthcare systems where resource allocation is crucial. Additionally, rapid diagnostic tests can further improve the cost-effectiveness of preemptive strategies by reducing unnecessary antifungal exposure and associated side effects.[16]

The time between the onset of IFI and clinical signs and symptoms may provide an opportunity to identify these patients through screening and achieve a better response with early treatment. Fever is not the only criterion in such a preemptive approach.[17] Currently, non-culture microbiologic methods that can be used in daily practice are serum GM measurement, serum beta-D-glucan measurement, and fungal DNA determination by polymerase chain reaction. These methods have deficiencies or superiorities compared to each other.[18] The use of biomarkers such as GM has been explored to guide preemptive therapy, allowing antifungal treatment to be initiated only when specific thresholds are met.[19,20] In preemptive treatment, diagnostic accuracy is improved when combining the diagnostic tools of CT and GM results. Our findings suggest a notable relationship between chest CT findings and BAL GM results. Among patients with positive BAL GM results, 23.6% exhibited specific chest CT findings such as the halo sign, and 13.1% demonstrated the air-crescent sign or cavitation. These characteristic CT findings for IPA were more commonly observed in the preemptive treatment group, aligning with the higher rates of BAL GM positivity. In contrast, serum GM positivity was observed in a smaller proportion of patients (26%), suggesting that serum GM may have lower diagnostic sensitivity than BAL GM. This discrepancy highlights the potential value of BAL GM in correlating with specific radiological findings, such as the halo and air-crescent signs. At the same time, serum GM appears less consistently associated with these features. These results underscore the importance of integrating BAL GM results with chest CT findings to improve diagnostic accuracy in febrile neutropenic episodes of patients with hematologic malignancies.

However, some points should be noted in the evaluation of laboratory results. False-positive results in GM testing, a critical diagnostic tool for invasive aspergillosis, can significantly complicate clinical decision-making. Various factors contribute to these false positives, particularly the influence of certain antibiotics, nutritional supplements, and underlying health conditions. One of the primary causes of false-positive GM tests is the administration of beta-lactam antibiotics, such as piperacillin-tazobactam and amoxicillin-clavulanate. These antibiotics can lead to cross-reactivity due to their structural similarities with GM, a polysaccharide found in the cell walls of certain fungi, including Aspergillus species.[21] Studies have shown that patients receiving these antibiotics often exhibit elevated GM levels, which can mislead clinicians into suspecting invasive aspergillosis when it is not present.[22]

In our study, the rate of febrile neutropenia episodes with high positive predictive value and very high probability of IFI was 16% in the empiric group and 47% in the preemptive group. In the empiric group, the rate of febrile neutropenia episodes with high negative predictive value and very low probability of IFI was 13%. In contrast, there was no such episode in the preemptive group. Since the factors that make non-culture microbiologic methods false negative or false positive are not fully known and since the number of patients with tissue diagnosis is very low and postmortem biopsy cannot be performed, it is difficult to comment on episodes with suspicious probability of IFI. Although the percentage of all-cause mortality was higher in the preemptive group than in the empiric group, there was no statistically significant difference between them.

Preemptive therapy can lead to lower overall antifungal exposure and reduced healthcare costs without increasing mortality rates compared to empirical therapy.[23,24] The efficacy of preemptive therapy is contingent upon the accuracy of diagnostic

tests and the timely identification of at-risk patients. Limitations in the sensitivity of tests such as the GM assay can delay treatment initiation, potentially allowing IFIs to progress.[19,20] The reliance on imaging studies, such as CT scans, introduces additional complexity, as these tests may not always provide definitive results.[19] Despite these challenges, some studies have reported that preemptive therapy can be as effective as empirical therapy in preventing IFIs, particularly in high-risk populations.[24,25]

A systematic review highlighted that patients receiving preemptive therapy had significantly lower antifungal exposure and clinical expenses without an increase in mortality rates.[23] Therefore, the answer to whether empirical or preemptive treatment is superior cannot be given with certainty.[26]

In our study, in 55 (36%) of the episodes in which antifungal drugs were used, antifungal treatment was initiated based on at least one CT, GM, and culture results. There were 40 episodes (26%) in which the initial treatment was empiric or secondary prophylaxis, and later evidence in favor of fungal infection was obtained by culture and non-culture diagnostic methods. Regardless of the initial treatment, 62% of all antifungal treatment episodes had varying degrees of evidence of fungal infection.

In a meta-analysis of 6 randomized controlled trials comparing patients with hematologic malignancies who received empirical antifungal therapy with those who did not, it was reported that empirical treatment did not significantly reduce mortality but significantly reduced the development of IFI.[27] In Europe and the USA, 20-25% of those receiving empirical antifungal treatment have IFI.[28]

The retrospective nature of our data, the fact that the data included patients for whom decisions were made on a case-by-case basis (not randomized, hence the high probability of unequal risk profiles). The fact that deaths directly related to fungal infection were not fully distinguished among the causes of death in the mortality rate calculation makes it difficult to finalize the conclusions reached in our study.

CONCLUSIONS

In conclusion, for an empirical and preemptive treatment approach in febrile neutropenic patients with hematologic malignancies who have fever resistant to antibacterial therapy, it may be an appropriate option for each center to evaluate the risk profile and frequency of IFIs of their patients and decide which treatment strategy is suitable for their patients. A ‘ dynamic ‘ approach seems appropriate even if empirical treatment is initiated in high-risk patients. It can be summarized as urgent and persistent efforts to obtain evidence using auxiliary diagnostic tools and early termination of therapy in unnecessary cases. On the other hand, well-designed randomized prospective studies are needed to arrive at a definitive judgment on empirical and preemptive approaches.

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 Statement

The protocol of the study was approved by the Medical Ethics Committee of Uludag University Faculty of Medicine (Decision number: 2009-3/39).

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Authors’ Contribution

Study Conception: FÖ, VÖ; Study Design: FÖ, VÖ; Literature Review: AA; Critical Review: AA; Manuscript preparing: AA.

REFERENCES

1. Ascioglu S, de Pauw BE, Meis JF. Prophylaxis and treatment of fungal infections associated with haematological malignancies. Int J Antimicrob Agents. 2000 Aug;15(3):159-68. doi: 10.1016/s0924-8579(00)00159-x.
2. von Eiff M, Roos N, Schulten R, Hesse M, Zühlsdorf M, van de Loo J. Pulmonary aspergillosis: early diagnosis improves survival. Respiration. 1995;62(6):341-7. doi: 10.1159/000196477.
3. Reichenberger F, Habicht J, Matt P, Frei R, Solèr M, Bolliger CT, Dalquen P, Gratwohl A, Tamm M. Diagnostic yield of bronchoscopy in histologically proven invasive pulmonary aspergillosis. Bone Marrow Transplant. 1999 Dec;24(11):1195-1199. doi: 10.1038/sj.bmt.1702045.
4. De Pauw BE, Deresinski SC, Feld R, Lane-

Allman EF, Donnelly JP. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. A multicenter randomized trial. The Intercontinental Antimicrobial Study Group. Ann Intern Med. 1994 May 15;120(10):834-44. doi: 10.7326/0003-4819-120-10-199405150-00004.

5. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis. 2003 May 1;36(9):1103-1110. doi: 10.1086/374339.
6. Pauw B, Walsh TJ, Donnely P, et al. Revised Definitions of İnvasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Insitute of Allergy and Infectıous Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Inf Dis 2008;46:1813-21
7. Febrile Neutropenia Study Group: Guidelines for the diagnosis and treatment of febrile neutropenic patients. Flora. 2004;9:5-28 (in Turkish).
8. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002 Mar 15;34(6):730-51. doi: 10.1086/339215.
9. Rieger CT, Ostermann H. Empiric vs. preemptive antifungal treatment: an appraisal of treatment strategies in haematological patients. Mycoses. 2008;51 Suppl 1:31-4. doi: 10.1111/j.1439-0507.2008.01526.x.
10. Wingard JR. Empirical antifungal therapy in treating febrile neutropenic patients. Clin Infect Dis. 2004 Jul 15;39 Suppl 1:S38-43. doi: 10.1086/383052.
11. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med. 1982 Jan;72(1):101-11. doi: 10.1016/0002-9343(82)90594-0.
12. Mahfouz T, Anaissie E. Prevention of fungal infections in the immunocompromised host. Curr Opin Investig Drugs. 2003 Aug;4(8):974-90.
13. Soyer N, Kiper Ünal HD, Vural F, Şahin F, Töbü M, Dönmez A, Tombuloğlu M, Arda B, Saydam G. Epidemiology and analysis of invasive fungal infections in patients withhematological malignancies: a single-center real-life experience. Turk J Med Sci. 2017 Nov 13;47(5):1535-1542. doi: 10.3906/sag-1611-90.
14. Pagano L, Caira M, Nosari A, Cattaneo C, Fanci R, Bonini A, Vianelli N, Garzia MG, Mancinelli M, Tosti ME, Tumbarello M, Viale P, Aversa F, Rossi G; HEMA e-Chart Group. The use and efficacy of empirical versus pre-emptive therapy in the management of fungal infections: the HEMA e-Chart Project. Haematologica. 2011 Sep;96(9):1366-1370. doi: 10.3324/haematol.2011.042598.
15. Walker BS, Schmidt RL, Tantravahi S, Kim K, Hanson KE. Cost-effectiveness of antifungal prophylaxis, preemptive therapy, or empiric treatment following allogeneic hematopoietic stem cell transplant. Transpl Infect Dis. 2019 Oct;21(5):e13148. doi: 10.1111/tid.13148.
16. Fung M, Kim J, Marty FM, Schwarzinger M, Koo S. Meta-analysis and cost comparison of empirical versus pre-emptive antifungal strategies in hematologic malignancy patients with high-risk febrile neutropenia. PLoS One. 2015 Nov 10;10(11):e0140930. doi: 10.1371/journal.pone.0140930.
17. Uzun Ö. Preemptive antifungal treatment. Ankem Derg. 2007;21(Suppl 2):220-3 (in Turkish).
18. Maertens J, Deeren D, Dierickx D, Theunissen K. Preemptive antifungal therapy: still a way to go. Curr Opin Infect Dis. 2006 Dec;19(6):551-6. doi: 10.1097/QCO.0b013e3280106854.
19. Yuan W, Ren J, Guo X, Guo X, Cai S. Preemptive antifungal therapy for febrile neutropenic hematological malignancy patients in China. Med Sci Monit. 2016 Nov 7;22:4226-4232. doi: 10.12659/msm.897596.
20. Cordonnier C, Robin C, Alanio A, Bretagne S. Antifungal pre-emptive strategy for high-risk neutropenic patients: why the story is still ongoing. Clin Microbiol Infect. 2014 Jun;20 Suppl 6:27-35. doi: 10.1111/1469-0691.12428.
21. Otting KA, Stover KR, Cleary JD. Drug-laboratory interaction between beta-lactam antibiotics and the galactomannan antigen test used to detect mould infections. Braz J Infect Dis. 2014;18(5):544-7. doi:10.1016/j.bjid.2014.03.009.
22. Vergidis P, Razonable RR, Wheat LJ, Estes L, Caliendo AM, Baden LR, Wingard JR, Baddley J, Assi M, Norris S, Chandrasekar P, Shields R,

Nguyen H, Freifeld A, Kohler R, Kleiman M, Walsh TJ, Hage CA. Reduction in false-positive Aspergillus serum galactomannan enzyme immunoassay results associated with use of piperacillin-tazobactam in the United States. J Clin Microbiol. 2014 Jun;52(6):2199-2201. doi: 10.1128/JCM.00285-14.

23. Salehi M, Ghaderkhani S, Sharifian RA, Dehghan Manshadi SA, Samiee Fard E, Khodavaisy S, Pourahmad R, Foroushani AR, Rodini K, Kamali Sarvestani H. The value of nasal and oral clinical examination in febrile neutropenic patients for ınitiating antifungal therapy as a preemptive method. Front Med (Lausanne). 2022 Jan 28;8:803600. doi: 10.3389/fmed.2021.803600.
24. Fung M, Kim J, Marty FM, Schwarzinger M, Koo S. Meta-Analysis and Cost Comparison of Empirical versus Pre-Emptive Antifungal Strategies in Hematologic Malignancy Patients with High-Risk Febrile Neutropenia. PLoS One. 2015 Nov 10;10(11):e0140930. doi: 10.1371/journal.pone.0140930.
25. Walker BS, Schmidt RL, Tantravahi S, Kim K, Hanson KE. Cost-effectiveness of antifungal prophylaxis, preemptive therapy, or empiric treatment following allogeneic hematopoietic stem cell transplant. Transpl Infect Dis. 2019 Oct;21(5):e13148. doi: 10.1111/tid.13148.
26. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002 Mar 15;34(6):730-51. doi: 10.1086/339215.
27. Goldberg E, Gafter-Gvili A, Robenshtok E, Leibovici L, Paul M. Empirical antifungal therapy for patients with neutropenia and persistent fever: Systematic review and meta-analysis. Eur J Cancer. 2008 Oct;44(15):2192-2203. doi: 10.1016/j.ejca.2008.06.040.
28. Akan H. EORTC definitions in fungal infections. Ankem Derg. 2009;23(Suppl.2):130-4 (in Turkish).

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Evaluation of diagnosis and treatment approaches related to iron deficiency of family physicians

Kamil Konur[1] , **Elif Akdoğan**[2]

[1.] Recep Tayyip Erdogan University Faculty of Medicine, Department of Internal Medicine, Department of General Internal Medicine, Rize, Türkiye

[2] Recep Tayyip Erdogan University Faculty of Medicine, Department of Internal Medicine, Department of Hematology, Rize, Türkiye

ABSTRACT

Background Anaemia is defined by the World Health Organization (WHO) as a hemoglobin value below 13 g/dL in men and 12 g/dL in women. It is a serious public health problem that can significantly affect the quality of life.

Methods Our study, whose universe consists of family physicians who actively work in family health centers in Rize province, was conducted in 2021. After being informed about our study, 81 family physicians who agreed to participate voluntarily were included.

Results Our research is a cross-sectional descriptive type of research. A 20-question survey prepared by scanning the literature was presented as a data collection tool. While 73 (90.1%) participants are general practitioners, 8 (8.9%) are family medicine specialists. The rate of physicians correctly knowing the ferritin value to diagnose iron deficiency anemia in a patient without acute infection was 70.4% (n: 57). After the diagnosis of iron deficiency anemia, physicians recommended gastrointestinal system screening in 39.5% (n: 32) of all men and 87.7% (n: 71) of postmenopausal women. The rate of recommending treatment for 3-6 months after the hemoglobin level returned to normal was 93.8% (n: 76).

Conclusion Based on the data we obtained, it was seen that family physicians' knowledge level about iron deficiency anemia management was insufficient, and there were deficiencies in the diagnosis and treatment processes. For this reason, interactive, applied training programs should be organized.

Turk J Int Med 2025;7(1):22-27
DOI: 10.46310/tjim.1566675

Keywords: *Iron, Family Physicians, Iron Deficiency*

Received: *October 14, 2024* ***Accepted:*** *January 2, 2025* ***Published Online:*** *January 29, 2025*

How to cite this article: *Konur K, Akdogan E. Evaluation of diagnosis and treatment approaches related to iron deficiency of family physicians. Turk J Int Med 2025;7(1):22-27. DOI: 10.46310/tjim.1566675*

Address for Correspondence:
Kamil Konur, Recep Tayyip Erdogan University Faculty of Medicine, Department of Internal Medicine, Department of General Internal Medicine, Rize, Türkiye
E-mail:kamilkonur@gmail.com

INTRODUCTION

Iron deficiency anaemia (IDA) is the most common form worldwide. The World Health Organization (WHO) defines anaemia as haemoglobin (Hb) levels below 13 g/dL in men and below 12 g/dL in women.[1] In pregnant women, anaemia is defined as Hb levels of 11 g/dL or lower. According to WHO data, the prevalence of anaemia among adults is 24.8% globally. IDA is a significant public health problem that can substantially impact the quality of life due to its clinical manifestations. The symptoms in patients with IDA are influenced by factors such as age, severity of anaemia, comorbidities and the duration of anaemia. As a result of tissue hypoxia, symptoms such as weakness, fatigue, dizziness, headache, and palpitations may occur.[2] Regardless of the presence or absence of symptoms, iron deficiency should be treated with or without anaemia because failure to replenish iron stores may worsen anaemia and lead to organ ischaemia.[3] Family physicians have observed significant differences in diagnostic and treatment approaches for anaemia management, highlighting the need for evidence-based local or national guidelines.[4,5] Therefore, we aimed to evaluate the management of anaemia by family physicians in light of existing guidelines.

MATERIAL AND METHODS

Our study was conducted between December 2020 and April 2021. Our research population consists of 101 family physicians, including general practitioners and family physician specialists, who are actively working in family health centres in Rize province. Before the study, family physicians were contacted via telephone, e-mail, and other mobile communication programmes and were given detailed information about the study. A total of 81 physicians volunteered to participate in the study. Physicians who could not be reached or did not want to participate were excluded from the study. Face-to-face interviews with participating physicians were avoided due to the COVID-19 pandemic. Our research is a cross-sectional descriptive study. A 20-question survey including sociodemographic characteristics was used as a data collection tool. The survey questions included age, gender, title, years of work experience, education level, the definition of anaemia, symptoms, and the patient groups for whom they recommend gastrointestinal system screening. Three case studies were presented, and participants were asked to respond to related questions.

Statistical analysis

Pearson's Chi-Square and Fisher's Exact test were used to evaluate categorical variables. A statistical significance level of $p<0.05$ was considered.

RESULTS

Of the family physicians who participated in the study, 73 were general practitioners, and 8 were family medicine specialists. The findings of these two groups could not be compared because the difference in numbers between these two groups was too large to find significant results in statistical tests. Of the participants in the study, 17 were female and 64 were male. When the age distribution of the participants was analysed, 22 physicians were in the 25-35 age group, 38 physicians were in the 36-45 age group, and 21 physicians were in the 45+ age group. It was observed that 91.4% of the physicians diagnosed and treated patients based on the knowledge they gained in medical school or during their specialization training. The percentage of physicians who reported attending a seminar or training session on iron deficiency after graduation or specialization was 58%. Additionally, 71.6% of physicians stated that they had read a guideline on treating iron deficiency, while 87.6% expressed a desire to receive further training on this topic (Figure 1).

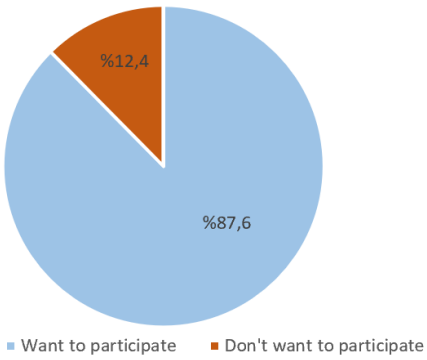


Figure 1. Willingness to participate in a training opportunity regarding the diagnosis and treatment of iron deficiency anemia

In patients without an acute infection, 70.4% of physicians correctly identified the ferritin level required to diagnose IDA. When asked about the symptoms they investigate in patients suspected of having IDA, the most frequently questioned symptom was menorrhagia, reported by 90.1% of physicians.

Table 1. Symptoms questioned by physicians when investigating the cause of iron deficiency

Symptoms	Questioned	Not questioned
Reflux symptoms	45 (55.6%)	36 (44.4%)
Weight loss	59 (72.8%)	22 (27.2%)
Melena	71 (87.7%)	10 (12.3%)
Hematochezia	59 (72.8%)	22 (27.2%)
Pica	68 (84%)	13 (16%)
Menorrhagia	73 (90.1%)	8 (9.9%)
Chest pain	22 (27.2%)	59 (72.8%)
Dyspnea	37 (45.7%)	44 (54.3%)
Hair loss	68 (84%)	13 (16%)
Restless leg symptoms	29 (35.8%)	52 (64.2%)
History of parasites	44 (54.3%)	37 (45.7%)

Other symptoms, ranked from most to least often investigated, included melena (87.7%), pica and hair loss (84%), weight loss and hematochezia (72.8%), abdominal pain and reflux symptoms (55.6%), a history of parasitic infections (54.3%), dyspnea (40.7%), restless leg syndrome symptoms (35.8%), and chest pain (27.2%) (Table 1).

After diagnosing IDA, gastrointestinal system screening was recommended by 39.5% of physicians for all male patients, while 87.7% recommended it for postmenopausal women. In the case-based questions, +2 valence iron preparations were recommended for asymptomatic IDA patients at rates of 66.7% and 24.7%, respectively. 31.8% of physicians considered high platelet levels in patients with IDA to be secondary to anaemia. In the case of asymptomatic IDA, 24.7% (n: 20) recommended +2-valent oral iron preparation treatment, 3.7% (n: 3) recommended +3-valent oral iron preparation treatment, 38.3% (n: 31) recommended parenteral iron treatment and 33.3% (n: 27) recommended erythrocyte suspension (Figure 2).

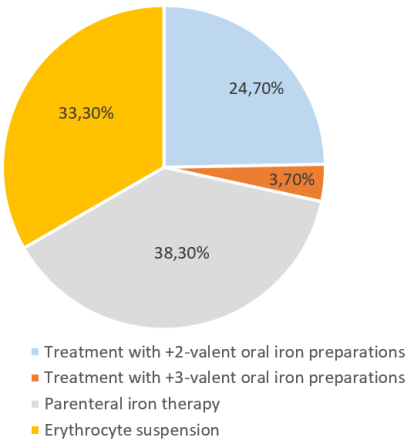


Figure 2. How should asymptomatic iron deficiency anemia be treated?

It was recommended by 93.8% of participants that iron therapy should continue for 3–6 months after Hb levels return to normal. In cases where Hb levels did not improve with oral iron therapy, participants most frequently considered bleeding (81.5%), celiac disease (59.3%), Helicobacter pylori (40.7%), or all of these factors combined (44.4%). For elderly patients with coronary artery disease and symptomatic anaemia, 53.1% of physicians recommended oral iron therapy following erythrocyte suspension transfusion.

DISCUSSION

As a result of the literature review, we concluded that our study is the first in our country to evaluate family physicians' diagnosis and treatment approaches regarding IDA. In other countries, there are studies on physicians' knowledge, attitudes, and perceptions of iron deficiency. Examples of these include a cross-sectional study among physicians on transfusion practice in patients with anaemia without bleeding by von Babo et al., a cross-sectional study by Al Sulayyim et al. on the management of diagnostic and treatment modalities by physicians in paediatric IDA patients, and a study by Desai et al. on anaemia in the elderly conducted on lecturers and resident physicians in the departments of family medicine and internal medicine at Rhode Island Memorial Hospital.[2,4,5]

The topic of education on iron deficiency after graduation or specialization was evaluated. More than half of the physicians had attended such a training session. As the years of professional experience of physicians increased, their desire for training also grew, and this difference was statistically significant (p=0.031). Additionally, it was found that most family physicians were willing to participate if a new

educational opportunity was offered.

When analyzing responses to questions regarding the symptoms physicians investigate in patients suspected of having IDA, menorrhagia was found to be the most frequently queried symptom, at a rate of 90.1%. The responses showed significant variability. Symptoms of IDA vary depending on the severity and progression of anaemia, its aetiology and any accompanying conditions.[6] Symptoms and findings related to the underlying aetiology may also be present; a patient presenting with hematochezia or weight loss could potentially have colon cancer.[7] A comprehensive inquiry into patients' symptoms suspected of IDA may be more beneficial, enabling accurate diagnosis and effective treatment. A thorough evaluation of symptoms of IDA may be helpful, and an effective treatment can be provided to patients with the correct diagnosis.

Gastrointestinal system screening is one of the investigations required when exploring the aetiology of IDA. According to the 2019 Turkish Hematology Association Guidelines for the Diagnosis and Treatment of Iron Deficiency in Adults, gastrointestinal system screening should be performed in all male and postmenopausal women unless there is an apparent non-gastrointestinal system source of bleeding.[8] Similarly, the American Gastroenterological Association and several other guidelines recommend gastrointestinal system screening for all male patients and postmenopausal women.[9,10] In our study, participants demonstrated an appropriate approach to gastrointestinal system screening in 39.5% of male cases and 87.7% of female cases. While the management of female patients was satisfactory, the same cannot be said for the management of male patients. Family physicians would benefit from educational programs to enhance their knowledge and skills.

In an asymptomatic iron deficiency case with a reported platelet count of 800,000/μL (reference range: 140-450×10³/μL), participants were asked about their approach to management. IDA is a common cause of secondary thrombocytosis.[11,12] Fewer than half of the participants adopted the correct approach by attributing the condition to secondary thrombocytosis caused by iron deficiency. When monitoring is sufficient, recommending participant referrals will likely incur additional costs to patients and the healthcare system.

Participants were presented with three different cases and asked to provide their responses. The results showed that Fe^{+2} preparations were preferred at varying rates. While we consider Fe^{+2} therapy an appropriate approach, it is insufficient and requires improvement. Iron replacement therapy is essential to improve quality of life and reduce the risk of anaemia-related complications. Oral iron supplementation is typically the first-line treatment; however, this method often proves challenging to tolerate due to side effects such as nausea, abdominal pain, and constipation.[13] Additionally, some physicians recommended parenteral iron and erythrocyte suspension as treatment options. Considering that these treatments were not indicated in our cases, such recommendations are quite concerning. The off-label use of parenteral iron and erythrocyte suspension treatments poses significant risks, including patient complications, increased costs, and added burdens on the healthcare system.[14,15] In another case, a symptomatic IDA patient aged 70 with coronary artery disease and a Hb level of 7.5 g/dL was recommended erythrocyte suspension in 87.7% (n: 71) of responses, and erythrocyte suspension followed by oral iron therapy in 53.1% (n: 43) of responses. In symptomatic IDA cases, blood transfusion provides an acute correction of anaemia, but this remains a temporary solution without subsequent iron therapy. Blood transfusion is one of the primary treatment options for patients with anaemia.[16]

When the results were analyzed, it was concluded that improvements should be made in health policies. Enhancing education and awareness in primary healthcare services, disseminating diagnostic and treatment guidelines, increasing awareness about symptom assessment, promoting the broader and more effective use of laboratory tests, creating informational materials and screening programs for the diagnosis and treatment of IDA, and adopting a proactive approach in health services are expected to contribute positively to public health.

This study has certain limitations. The sample size was limited because not all physicians in the province participated, which may affect the generalizability of the findings. The study was confined to the province of Rize and may not reflect physicians' knowledge, attitudes, and practices in other regions. Due to the COVID-19 pandemic, face-to-face interviews were avoided, and alternative methods were used. This may have increased the risk of misinterpretation or misunderstanding of the questions and potentially

affected the accuracy of the survey responses. The predominance of general practitioners among physicians serving as family doctors may have contributed to the inability to achieve the targeted outcomes.

CONCLUSIONS

Based on the data we obtained, it was seen that family physicians' knowledge level about IDA management was insufficient, and there were deficiencies in the diagnosis and treatment processes. For this reason, interactive, applied training programs should be organized. In addition, local and national guidelines should be created and used practically in IDA diagnosis and treatment management. Programs and models that will increase the communication of family physicians with internal medicine clinics should be planned. There is a need to create national guidelines and programs based on the data obtained by conducting further studies covering larger regions.

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 Statement

The study was planned by the Declaration of Helsinki and ethical rules. Written informed consent was obtained from the participants. The study was approved by Recep Tayyip Erdoğan University Faculty of Medicine Ethics Committee on 18 February 2021 with protocol number 32.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: KK, EA; Study Design: KK, EA; Literature Review: KK, EA; Critical Review: KK, EA; Manuscript preparing: KK, EA;

REFERENCES

1. de Benoist B, McLean E, Egli I, Cogswell M, eds. Worldwide prevalence of anaemia 1993–2005. WHO Global Database on Anaemia. World Health Organization 2008. Available at: https://www.who.int/publications/i/item/9789241596657. Accessed September 9, 2024.
2. Desai A, Guerrero T. Anemia in the elderly: Knowledge, Attitudes, and Perception of Primary Care Physicians. MGM J Med Sci. 2019;6(1):1-5. doi: 10.5005/JP-JOURNALS-10036-1220.
3. Yıldız A, Albayrak M. Treatment of iron deficiency anemia in adults. Turkiye Klinikleri J Hematol-Special Topics. 2017;10(3):182-7 (in Turkish).
4. von Babo M, Chmiel C, Müggler SA, Rakusa J, Schuppli C, Meier P, Fischler M, Urner M.Transfusion practice in anemic, non-bleeding patients: Cross-sectional survey of physicians working in general internal medicine teaching hospitals in Switzerland. PLoS One. 2018 Jan 30;13(1):e0191752. doi: 10.1371/journal.pone.0191752.
5. Al Sulayyim HJ, Al Omari A, Badri M.An assessment for diagnostic and therapeutic modalities for management of pediatric Iron defficiency Anemia in Saudi Arabia: a crossectional study. BMC Pediatr. 2019 Sep 5;19(1):314. doi: 10.1186/s12887-019-1704-3.
6. Iolascon A, Andolfo I, Russo R, Sanchez M, Busti F, Swinkels D, Aguilar Martinez P, Bou-Fakhredin R, Muckenthaler MU, Unal S, Porto G, Ganz T, Kattamis A, De Franceschi L, Cappellini MD, Munro MG, Taher A; from EHA-SWG Red Cell and Iron. Recommendations for diagnosis, treatment, and prevention of iron deficiency and iron deficiency anemia. Hemasphere. 2024 Jul 15;8(7):e108. doi: 10.1002/hem3.108.
7. Skorupski CP, Cheung MC, Hallet J, Kaliwal Y, Nguyen L, Pavenski K, Zuckerman JS, Lin Y. Preoperative anemia and iron deficiency in elective gastrointestinal cancer surgery patients. J Surg Oncol. 2024 Nov 12. doi: 10.1002/jso.27970. Epub ahead of print. PMID: 39530211.
8. Oymak Y, Ilhan G, Eritrosit hastalıkları ve hemoglobin bozuklukları. Tanı ve tedavi kılavuzu. Türk Hematol Derneği. Sürüm 1.1 - Eylül 2019. Available at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://thd.org.tr/thdData/userfiles/file/Ertitrosit-Tani-ve-tedavi-Kilavuzu-2019.pdf.
9. American Gastroenterological Association medical position statement: evaluation and management of occult and obscure gastrointestinal

bleeding. Gastroenterology. 2000 Jan;118(1):197-201. doi: 10.1016/s0016-5085(00)70429-x.
10. Goddard AF, James MW, McIntyre AS, Scott BB; British Society of Gastroenterology.Guidelines for the management of iron deficiency anaemia. Gut. 2011 Oct;60(10):1309-16. doi: 10.1136/gut.2010.228874.
11. Almanaseer A, Chin-Yee B, Ho J, Lazo-Langner A, Schenkel L, Bhai P, Sadikovic B, Chin-Yee IH, Hsia CC. An approach to the investigation of thrombocytosis: Differentiating between essential thrombocythemia and secondary thrombocytosis. Adv Hematol. 2024 Feb 12:2024:3056216. doi: 10.1155/2024/3056216.
12. Tefferi A. Approach to the patient with thrombocytosis. Feb 2021. Wolters Kluwer, UpToDate. Sep 26, 2024. Available at: https://www.uptodate.com/contents/approach-to-the-patient-with-thrombocytosis?search=Approach+to+the+patient+with+thrombocytosis&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1.
13. DeLoughery TG, Jackson CS, Ko CW, Rockey DC. AGA Clinical Practice Update on Management of Iron Deficiency Anemia: Expert Review. Clin Gastroenterol Hepatol. 2024 Aug;22(8):1575-1583. doi: 10.1016/j.cgh.2024.03.046.
14. Rampton D, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, Patni S, Szebeni J, Weiss G. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. Haematologica. 2014 Nov;99(11):1671-6. doi: 10.3324/haematol.2014.111492.
15. Barton JC, Barton EH, Bertoli LF, Gothard CH, Sherrer JS. Intravenous iron dextran therapy in patients with iron deficiency and normal renal function who failed to respond to or did not tolerate oral iron supplementation. Am J Med. 2000 Jul;109(1):27-32. doi: 10.1016/s0002-9343(00)00396-x.
16. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. Ann Intern Med. 1992 Mar 1;116(5):393-402. doi: 10.7326/0003-4819-116-5-393.

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Case Report

Immune thrombocytopenic purpura as a rare extra-intestinal manifestation in ulcerative colitis: A case report

Muzaffar Maqbool[1], Asma Rafi[1], Basharat Kassana[1], Sheikh Bilal[2]

[1] Department of Medicine, Government Medical College, Srinagar Kashmir, India.
[2] Department of Pathology, Government Medical College, Srinagar Kashmir, India.

ABSTRACT

Immune thrombocytopenic purpura (ITP) is characterized by immune-mediated platelet destruction of platelets. The condition involves the presence of autoantibodies targeting platelet membrane antigens. ITP has been documented in the literature as a rare extra-intestinal manifestation of inflammatory bowel disease (IBD). This case report aims to describe the rare association of ITP as an extra-intestinal manifestation of ulcerative colitis (UC), accompanied by a literature review.

We report the case of a 21-year-old male presenting with acute bloody diarrhea refractory to broad-spectrum antibiotic therapy. Given the patient's significant history of intermittent persistent diarrhea, hematochezia, hematuria, and thrombocytopenia, an evaluation for relapsing IBD was undertaken. Colonoscopic biopsy findings were consistent, with UC showing mild activity, while bone marrow aspiration revealed features indicative of chronic ITP. The patient was managed with oral corticosteroids for the IBD flare and oral mesalamine, resulting in a significant improvement in platelet count. Upon follow-up, with remission of UC, it was accompanied by a complete normalization of the patient's platelet count. ITP has been reported as a rare extra-intestinal manifestation of IBD (UC). This report emphasizes the importance of suspecting IBD in cases of unexplained thrombocytopenia, particularly in compatible clinical settings, to enable timely diagnosis and management of both conditions, ultimately improving patient outcomes.

Turk J Int Med 2025;7(1):28-32
DOI: 10.46310/tjim.1592139

Keywords: *Thrombocytopenia, inflammatory bowel disease, hematochezia*

Received: *December 4, 2024* ***Accepted:*** *January 21, 2025* ***Published Online:*** *January 29, 2025*

How to cite this article: *Maqbool M, Rafi A, Kassana B, Bilal S. Immune thrombocytopenic purpura as a rare extra-intestinal manifestation in ulcerative colitis: A case report.. Turk J Int Med 2025;7(1):28-32. DOI: 10.46310/tjim.1592139*

Address for Correspondence:
Muzaffar Maqbool, Department of Medicine, Government Medical College, Srinagar Kashmir, India.
E-mail:Muzaffarmaqbool75@gmail.com

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease resulting in inflammation and colon and rectum ulcers.[1] The primary symptoms of active disease are abdominal pain and diarrhoea mixed with blood. Other symptoms may include weight loss, fever and anaemia.[2] UC is characterized by remission and recurrence; several extra-intestinal manifestations have been reported. The main extra-intestinal manifestations are arthritis and arthropathy, primary sclerosing cholangitis, metabolic bone disease, uveitis and rarely venous thromboembolism.[3] Immune thrombocytopenic purpura (ITP) is a rare extra-intestinal manifestation of inflammatory bowel disease (IBD) and is more commonly associated with UC.[4] It is an immune-mediated destruction of platelets.[5] Molecular mimicry between the luminal mucosa and platelet membrane antigens leads to immune activation and subsequent platelet destruction in the spleen.[6]

IBD patients are at an increased risk of having another autoimmune disease, and therefore, it becomes even more challenging to distinguish between extra-intestinal manifestation and concomitant autoimmune disease. The association between IBD and ITP is rare, but it offers a therapeutic advantage as medications effective against both conditions can be used simultaneously to benefit the patient. Given the rarity of this association, we aim to describe a young patient of UC who presented with ITP as a rare extra-intestinal manifestation.

CASE REPORT

A 21-year-old male, working as a local driver and residing in a rural area of Kashmir, India, presented with a one-month history of fever and three days of loose stools, accompanied by hematochezia. The fever was low-grade, continuous, and associated with sweating. The stools were consistently loose, suggestive of large bowel involvement, mixed with fresh blood. They were associated with diffuse abdominal pain and tenesmus. A short course of intravenous antibiotics was prescribed to him at a peripheral health center before reporting to our hospital, but they did not relieve his symptoms much. The patient had a significant history of intermittent persistent diarrhea, bleeding per rectum, and hematuria on-off for the last 4 years. He was evaluated for the same on an outpatient department basis previously. Labs showed thrombocytopenia with giant platelets on PBF (peripheral blood film). PR proctoscopy revealed multiple small erythematous ulcers with friability, a biopsy showing partially ulcerated rectal mucosa with underlying normal mucosal glands and lamina propria revealing dense, chronic inflammatory cell infiltrate forming lymphoid follicles along with edema and congestion. He had previously received symptomatic treatment without a definitive diagnosis. During this admission to the ER, the patient was dehydrated and febrile to touch. He had tachycardia (110/min, regular) with BP of 100/70 mmHg and S02 of 97% on ambient air. The abdomen had diffuse tenderness on deep palpation without any definite signs of peritonitis. Labs showed thrombocytopenia, high CRP/ESR, and mild transaminases (Table 1).

PBF showed giant platelets with a manual platelet count of 60,000 per microliter. Normal gut flora was isolated from stool culture. ANA by Hep-2 cell lines was negative. Triple serology was negative. Ultrasonography of the abdomen showed mild splenomegaly (12 cm), and the rest was unremarkable. An initial impression of acute infectious enterocolitis (vs a flare of IBD) was made, and the patient was started on broad-spectrum intravenous antibiotics using ceftriaxone 1 g twice a day and metronidazole 500 mg thrice a day. The patient's clinical status, as assessed by the Truelove-Wittz severity index

Table 1. Laboratory parameters

Variables	Nov 2019	Feb 2020	Aug 06, 2023 (Admission)	Aug 11, 2023 (Discharge)
Hemoglobin (g/dL)	14.9	14.2	13.0	13.4
Platelets (per microliter)	22,000	50,000	34,000	60,000 - 100,000
ESR (mm/hour)	65	50	45	20
C-reactive protein	+	-	+	-
AST/ALT (IU/L)	N/A	N/A	82/52	42/20

ESR: erythrocyte sedimentation rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

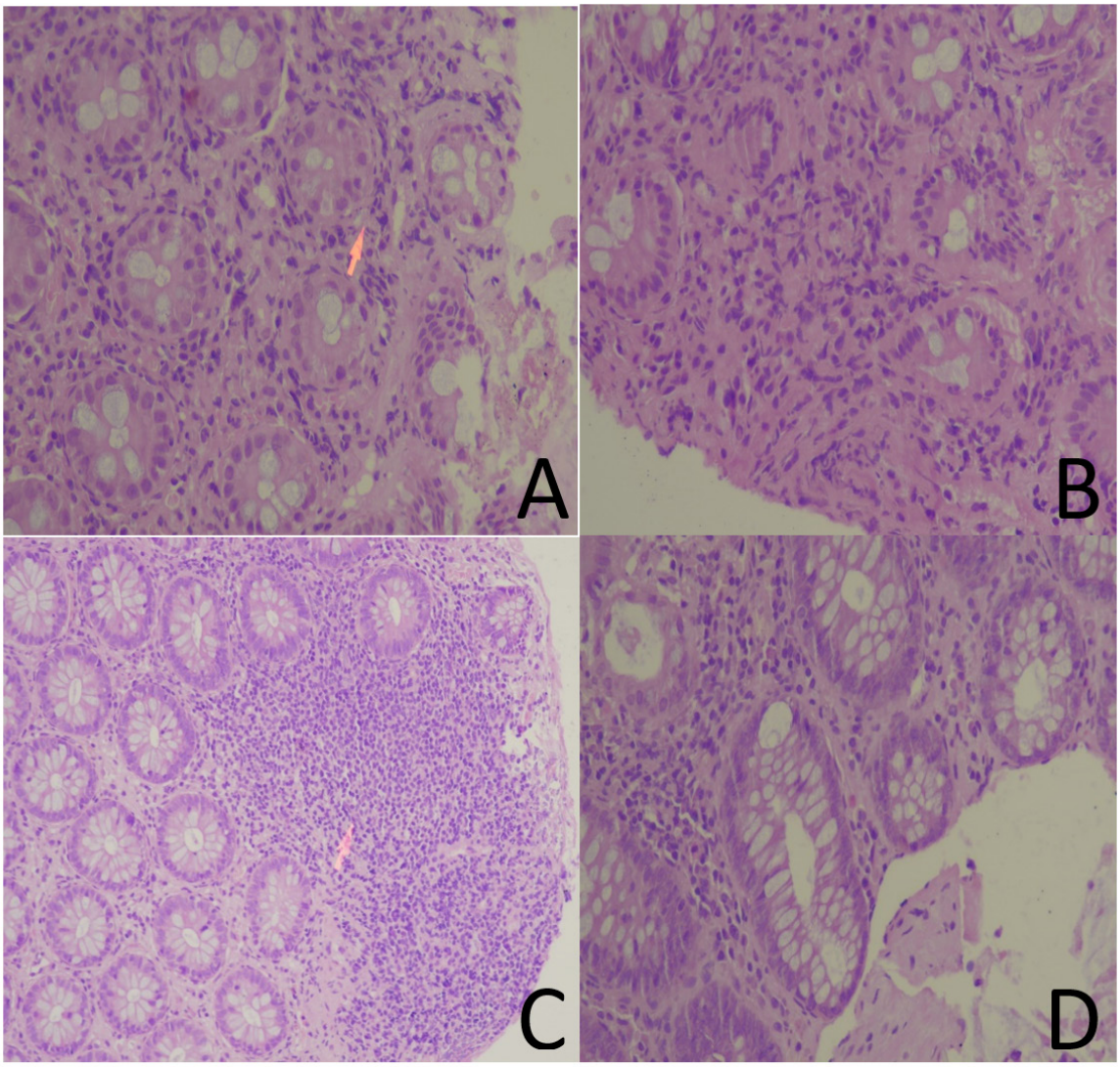


Figure 1. Colonoscopic biopsy showing A: cryptitis; B: crypt atrophy mucodepletion; C: lymphoid aggregate; D: basal plasma cell gradient

for UC, improved from severe to moderate during hospitalization. However, considering the patient's persistent symptoms along with a significant history, he was subjected to a colonoscopy. There was evidence of multiple small erosions and aphthous ulcers with background erythema from the caecum to the sigmoid colon. Severity was higher on the left side with normal vascularity and absent granularity, consistent with a Mayo endoscopic score of 3. Based on colonoscopy findings, an initial diagnosis of pancolitis with normal ileum and rectal sparing was made, and biopsies were taken for histopathological examination. The latter revealed edematous and congested lamina propria infiltrated by mixed inflammatory infiltrate and predominantly chronic mononuclear eosinophils with occasional cryptitis and crypt distortion foci. Additional pathological findings were found regarding basal plasma cell gradient, focal muco-depletion, and Paneth cell metaplasia. These findings, including focal mucodepletion and Paneth cell metaplasia, suggest chronic inflammation and disease activity in UC (Figure 1). A final impression of chronic UC with mild activity was made on this biopsy report. The same was reviewed with a gastroenterologist who started the patient on tapering doses of oral steroids and oral mesalamine 1.2 g twice a day. A hematology consultation was made because of long-standing thrombocytopenia. However, considering the patient's whole presentation, bone marrow findings ruled out cytotoxic causes of thrombocytopenia, supporting a diagnosis of peripheral platelet destruction consistent with ITP. Table 1 summarizes the laboratory findings upon admission.

The patient was discharged in a stable condition

after five days of hospitalization, with a platelet cunt of 100,000/µL. He continues to be monitored by gastroenterology and haematology specialists to ensure sustained remission and prevent complications.

DISCUSSION

As previously discussed, IBD is associated with numerous extra-intestinal manifestations. Patients with IBD also face an increased risk of developing other autoimmune diseases as well due to their overlapping pathogenic mechanisms.[7,8] ITP is considered a rare extra-intestinal manifestation of IBD.[9] Approximately 40 cases of this rare association have been documented in the literature. In such cases, treatment options include biologicals such as rituximab and infliximab and immunosuppressants like azathioprine.[10] Azathioprine is commonly employed as maintenance therapy in IBD. However, its use is associated with significant adverse effects such as myelosuppression, hepatotoxicity, and pancreatitis. These biologics target specific immune pathways, such as TNF-α inhibition (infliximab) or B-cell depletion (rituximab), to control IBD and ITP.

The coexistence of ITP as an extra-intestinal manifestation of IBD is exceedingly rare, making its recognition crucial for timely diagnosis and treatment. This case highlights the rare association of ITP as an extra-intestinal manifestation of IBD, emphasizing the need for clinicians to maintain a high index of suspicion of this association. Further studies and case reports are needed to elucidate the underlying mechanisms and optimize treatment strategies for patients with IBD and ITP.

CONCLUSIONS

ITP is a rare extra-intestinal manifestation in patients with UC. In a relevant clinical setting, thrombocytopenia should prompt physicians to consider this rare association, enabling timely diagnosis of both conditions and initiating treatments that can address both diseases concurrently.

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 Statement

No Approval is required letter from the Institutional Ethical Committee of Government Medical College Srinagar, Kashmir, India vide Ref. No. IRBGMC-SGR/MED/860dated 21/11/2024

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MM, AR, BK, SB; Study Design: MM, AR, BK, SB; Literature Review: MM, AR, BK, SB; Critical Review: MM, AR, BK, SB; Manuscript preparing: MM, AR, BK, SB;

REFERENCES

1. Ford AC, Moayyedi P, Hanauer SB. Ulcerative colitis. BMJ. 2013 Feb 5;346:f432. doi: 10.1136/bmj.f432.
2. Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, Burisch J, De Vos M, De Vries AM, Dick AD, Juillerat P, Karlsen TH, Koutroubakis I, Lakatos PL, Orchard T, Papay P, Raine T, Reinshagen M, Thaci D, Tilg H, Carbonnel F; European Crohn's and Colitis Organisation. The first european evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis. 2016 Mar;10(3):239-54. doi: 10.1093/ecco-jcc/jjv213.
3. Queliza K, Ihekweazu FD, Ali A, Kellermayer R. Inflammatory bowel disease and immune thrombocytopenic purpura: Combined immune dysregulation in an adolescent. Ann Clin Lab Sci. 2017 Mar;47(2):226-8.
4. Epistola R, Do T, Vankina R, Wu D, Yeh J, Fleischman MW, Lee JM. Immune thrombocytopenic purpura (ITP) as an uncommon extraintestinal complication of Crohn's disease: Case vignette and systematic literature review. Case Rep Hematol. 2020 Mar 26;2020:4785759. doi: 10.1155/2020/4785759.
5. Chandra S, Finn S, Obah E. Immune thrombocytopenic purpura in ulcerative colitis: a case report and systematic review. J Community Hosp Intern Med Perspect. 2014 Apr 14;4(2). doi: 10.3402/jchimp.v4.23386.

6. Cohen R, Robinson D Jr, Paramore C, Fraeman K, Renahan K, Bala M. Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001-2002. Inflamm Bowel Dis. 2008 Jun;14(6):738-43. doi: 10.1002/ibd.20406.
7. Halling ML, Kjeldsen J, Knudsen T, Nielsen J, Hansen LK. Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases. World J Gastroenterol. 2017 Sep 7;23(33):6137-6146. doi: 10.3748/wjg.v23.i33.6137.
8. Iwasa T, Nakamura K, Ihara E, Aso A, Ito T. The effective treatment with cyclosporine of a ulcerative colitis patient with concurrent idiopathic thrombocytopenic purpura who subsequently developed spontaneous pneumomediastinum. Intern Med. 2017;56(11):1331-1337. doi: 10.2169/internalmedicine.56.7909.
9. Brunet E, Martínez de Sola M, Garcia-Iglesias P, Calvet X. Immune thrombocytopenic purpura associated with Crohn's disease with complete response to infliximab. Gastroenterol Hepatol. 2019 Jan;42(1):37-8. doi: 10.1016/j.gastrohep.2018.01.011.
10. Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organisation [ECCO]. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis. 2017 Jun 1;11(6):649-70. doi: 10.1093/ecco-jcc/jjx008.

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Letter to Editor

Transforming rheumatoid arthritis care with ChatGPT: A new digital companion

Shruti Suresh Suvarna[1], **Shrishti Khetan**[1]

[1] American University of Barbados, Bridgetown, Saint Michael, Barbados

Turk J Int Med 2025;7(1):33-35
DOI: 10.46310/tjim.1600138

Keywords: *Rheumatoid Arthritis, ChatGPT, Artificial Intelligence, Telemedicine, Digital Health*

Dear Editor,

Artificial intelligence (AI) is rapidly entering various sectors, including healthcare (1). Large language models (LLMs), such as ChatGPT, developed by OpenAI, show the potential to revolutionize patient care thanks to their ability to understand and respond to human language. While other LLMs exist, such as Google Bard and Microsoft Copilot, this letter focuses on ChatGPT as a prominent example of how such tools might enhance the management of chronic conditions like rheumatoid arthritis.

Benefits of ChatGPT in rheumatoid arthritis care

Rheumatoid arthritis is a complex autoimmune disease primarily affecting joints, leading to pain, inflammation, and potential joint destruction. Effective management requires a multifaceted approach involving medication, lifestyle modifications, and consistent communication between patients and healthcare providers. ChatGPT can play a complementary role in this process by providing patients with easily accessible information and support. For instance, it can offer clear explanations of medical terms, treatment options, and the importance of medication adherence.[1,2]

Beyond providing medical information, ChatGPT can also assist patients in understanding their condition better and navigating the emotional challenges associated with rheumatoid arthritis.[3] However, it is important to avoid overstating its capabilities. For example, while ChatGPT can offer general information about coping mechanisms and relaxation techniques, it cannot provide personalized mental health counseling. Similarly, while it can help patients track their symptoms, it cannot replace the nuanced assessments and clinical judgment of healthcare professionals. Table 1 highlights various ways ChatGPT can help patients.[2]

Limitations and risks of ChatGPT

It is crucial to emphasize that ChatGPT should be viewed as a complementary tool, not a replacement for qualified healthcare professionals. While it can provide general medical information, it is not equipped to offer specific medical advice or treatment recommendations. Patients should always consult with their healthcare providers for personalized guidance before making any decisions related to their health.

Transparency regarding the source of information is paramount. While ChatGPT draws from a vast dataset,

Received: *December 13, 2024* ***Accepted:*** *January 21, 2025* ***Published Online:*** *January 29, 2025*

How to cite this article: *Suvarna SS, Khetan S. Transforming rheumatoid arthritis care with ChatGPT: A new digital companion. Turk J Int Med 2025;7(1):33-35. DOI: 10.46310/tjim.1600138*

Address for Correspondence:
Shruti Suresh Suvarna, American University of Barbados, Bridgetown, Saint Michael, Barbados
E-mail:Shrutisuvarna1996@gmail.com

Table 1. Different ways ChatGPT can be utilized

Feature	Description	Example
Medication management	Reminds patients about medication schedules, explains side effects, and provides drug interaction information	A patient with multiple medications asks ChatGPT about the best time to take their pills.
Symptom tracking	Helps patients log symptoms over time, identify patterns, and share with healthcare providers	A patient with RA logs their pain levels, and ChatGPT summarizes this data for their doctor.
Diet and nutrition advice	Offers dietary recommendations based on patient's conditions, suggesting anti-inflammatory food or recipes	An RA patient asks ChatGPT for meal plans that might help reduce inflammation.
Exercise guidance	Recommends safe and beneficial exercises for specific and provides guidance and performing them	ChatGPT suggests low-impact exercises like swimming or yoga to maintain joint flexibility.
Educational resources	Provides up-to-date information on medical conditions, treatments, resources, and recent research findings	A newly diagnosed patient asked GPT for detailed information about the condition and treatments.
Appointment Preparation	Helps patients prepare for medical appointments by generating questions and summarizing health data	ChatGPT helps a patient compile symptom logs and relevant questions for the rheumatologist visit.
Lifestyle habit formation	Assists patient in developing healthy habits, such as regular exercise, adequate sleep, and smoking cessation	The patient sets goals and receives reminders and tips from ChatGPT for maintaining healthy habits.
Emergency information	Provide immediate information on what to do in case of a medical emergency or how to recognize urgent symptoms.	A patient experiencing severe RA flare-ups asks ChatGPT for initial steps before contacting a doctor.
Support group connections	Helps patients find and connect with support groups of communities for specific conditions	An isolated patient asked ChatGPT to locate online support groups or local community meetings.
Mental health support	Provides strategies for managing stress, anxiety, and depression and suggests mindfulness exercises.	A patient experiencing anxiety due to RA receives advice on breathing exercises and meditation.

it is essential to note that this information may not always be grounded in peer-reviewed research or established medical guidelines.[4] There is also the risk of misinformation or "hallucinations," where the AI might generate incorrect or misleading information. Users should prioritize information from reputable medical organizations and journals and always discuss any information obtained through ChatGPT with their healthcare providers.

Ethical considerations in AI adoption

Integrating AI into healthcare necessitates a thoughtful approach to data privacy and security.[3] Robust safeguards must be in place to protect sensitive patient information and ensure compliance with relevant regulations, such as the Health Insurance Portability and Accountability Act (HIPAA). Open discussions about data ownership, access, and potential risks are crucial to fostering trust and responsible AI adoption in healthcare.

The effectiveness of AI tools like ChatGPT hinges on users' health literacy levels. Patients who can ask straightforward questions with a strong understanding of their situation are more likely to obtain accurate and relevant information. Educational initiatives aimed at improving health literacy, particularly in the context of AI-driven healthcare, can empower patients to engage with these tools confidently and critically evaluate the information provided.

While ChatGPT's multilingual capabilities hold promise for bridging language barriers in healthcare, it is important to acknowledge potential variations in medical terminology accuracy across languages. Efforts to ensure linguistic sensitivity and cultural appropriateness in AI-driven healthcare are essential for equitable access to reliable information.

In conclusion, while ChatGPT holds significant potential for improving RA care, it is essential to approach its integration into healthcare with a balanced perspective. This includes acknowledging

its limitations, such as the potential for bias in its responses due to the datasets it was trained on. Prioritizing patient safety and privacy, addressing health literacy needs, and actively mitigating biases within AI algorithms are crucial steps to harness the power of AI responsibly and equitably. By doing so, we can empower patients and enhance the patient-provider relationship.

Conflict of Interest

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

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: SSS, SK; Study Design: SSS, SK; Literature Review: SSS, SK; Critical Review: SSS, SK; Manuscript preparing: SSS, SK;

REFERENCES

1. Davenport T, Kalakota R. The potential for artificial intelligence in healthcare. Future Healthc J. 2019 Jun;6(2):94-8. doi: 10.7861/futurehosp.6-2-94.
2. San Francisco: OpenAI. Available at: https://openai.com/about/.
3. Subramanian M, Wojtusciszyn A, Favre L, Boughorbel S, Shan J, Letaief KB, Pitteloud N, Chouchane L. Precision medicine in the era of artificial intelligence: implications in chronic disease management. J Transl Med. 2020 Dec 9;18(1):472. doi: 10.1186/s12967-020-02658-5.
4. Deoghare S. An interesting conversation with ChatGPT about acne vulgaris. Indian Dermatol Online J. 2023 Nov 7;15(1):137-40. doi: 10.4103/idoj.idoj_77_23.