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ADDRESSING THE ESCALATING HIV EPIDEMIC IN ALBANIA: POLICY EFFICACY, IMPLEMENTATION CHALLENGES, AND STRATEGIC PATHWAYS FOR IMPROVEMENT

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Abstract: Albania, despite its historically low HIV prevalence, is experiencing a concerning and continuous rise in new infections, with reported cases doubling over the past decade. This trend necessitates a critical examination of the nation's public health response to HIV/AIDS within its unique socio-cultural and economic context.

This section outlines the methodological approach for reviewing grey literature. Due to its complexity and limited indexing, a structured search plan based on a systematic review protocol was developed, using four strategies: grey literature databases, customized Google searches, targeted websites, and expert consultation. Grey literature, including government, NGO, and institutional reports, which were assessed. This study conducted a qualitative policy analysis using national reports, global agency data (e.g., UNAIDS, WHO), and academic literature It critically examined the implementation and impact of Albania's core legal frameworks: the "Prevention and Control of HIV/AIDS Law" (2008) and the "National Action Plan 2020–2025."

Results indicate that 60–72% of new HIV cases are diagnosed at late stages, exposing serious gaps in early detection and access to testing. Key populations, such as men who have sex with men, people who inject drugs, and sex workers, remain underserved due to stigma, and traditional cultural values. Additionally, the withdrawal of major international donors, including the Global Fund, has led to critical shortages in testing supplies and awareness campaigns. While ART is available, it remains centralized in Tirana, limiting rural access.

Albania's progress in controlling its HIV epidemic is substantially impeded by deeply entrenched social stigma, systemic under-reporting, and an unsustainable reliance on external funding. To meet SDG Target 3.3 by 2030, Albania must decentralize HIV services, establish sustainable national funding mechanisms, and prioritize anti-stigma strategies through multi-sectoral collaboration.

Addressing these multifaceted challenges is paramount for improving public health outcomes and ensuring equitable HIV prevention and care in Albania.

Keywords: HIV/AIDS, Public Health Policy, Stigma, Albania, Health System
Field: Medical and Public Health Sciences (HIV/AIDS Epidemiology, Health Policy, and Healthcare Management)

1. INTRODUCTION

HIV/AIDS remains a significant global public health challenge, particularly in low- and middle-income countries were access to prevention, diagnosis, and treatment service may be limited (WHO, 2023). Despite international effort to combat HIV/AIDS, reduce transmission, and improve the life of affected individuals, the epidemic continue to pressure individuals, their families, health care systems and societies (Beyrer et al., 2024). Albania, a South-Eastern European country, is classified as a low-prevalence country, however, recent epidemiological trends indicates a gradual but concerning increase in new HIV infected cases, raising questions about the effectiveness of existing national responses (UNAIDS, 2024).

According to UNAIDS reports, the number of people living with HIV in Albania has increased from approximately 671 cases in 2013 to between 1300 and 1500 cases in 2023 (UNAIDS, 2023; Institute of Public Health Albania, 2013). This upward trend suggests the need for renewed attention to prevention, early diagnoses, and treatment strategies. This situation is particularly relevant with Sustainable Developments Goals Agenda (SDG), especially SDG 3, Target 3.3 which aims to end HIV/AIDS epidemic by 2030 through universal access to prevention and treatment, alongside with elimination of stigma and discrimination (Ministry of Health and Social Protection, 2020). This global commitment is not only a health issue, but also a social, economic, and human rights issue, which needs common actions from governments, international organizations, civil society, and private sectors in their bid to transform the world by 2030 (WHO, 2024). Albania aligns its public health policies with international frameworks promoted

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by United Nations, the World Health Organization, and European Commission, reflecting a commitment to global health standards and human rights principles (Ministry of Health and Social Protection, 2020).

Despite the alignment, significant challenge persist. Reports indicate that diagnosis in Albania occur during AIDS stage (late stage), pointing to potential gaps in population-level testing, awareness, and engagement with healthcare services (UNAIDS, 2022). This trend highlights the possibility of deficiencies in early diagnosis through the population, especially in between marginalised groups (UNAIDS, 2022; 2024). Marginalised populations, including people who inject drugs, sex workers, male who had unprotected sexual intercourse with men, face additional barriers due to stigma, discrimination, and social exclusion (UNAIDS, 2022). Cultural norms and traditional social structure further contribute to secrecy surrounding HIv status and sexual orientation, complicating efforts to identify and support high-risk groups. Agolli-Nasufi, Ndrio, and Rada (2014), in their research, refer to Albanian society as being a closed, patriarchal and very traditional country, and is still not open-minded and informed towards HIV, or accepting of the homosexual community. Due to the great fear of discrimination, individuals tend to live in secret, making it very difficult to identify high-risk groups.

2. RACIONALITY FOR THIS STUDY

HIV/AIDS remains a significant public health challenge in Albania, despite the long standing classification as a low-prevalence country. Recent increases in HIV cases, as reported by World Health Organisation and UNAIDS, represent an urgent call for action within a small country with limited healthcare resources. The persistence of late diagnosis, combined with social stigma, limited testing coverage, and barriers to accessing prevention and treatment services, suggests that the real burden of HIV may be underestimated.

A comprehensive evaluation of current trends, policies, and structural challenges is necessary to identify in implementation and to construct evidence-based strategies that can strengthen prevention, early diagnosis, and care. This study is also justified in addressing an important public health matter, while research in this topic is totally absent, and to support national efforts in improving HIv related outcomes.

3. AIM

This study aim to evaluate the effectiveness of Albania's National HIV/AIDS response by examining current trends, policy implementation, and barriers to prevention, testing, and treatment, with the goal of identifying potential strategies to improve outcomes and support the achievement of SDG 3 to terminate HIV epidemic by 2030.

Objectives

- To analyse trends in HIV prevalence and diagnosis over the past two decades.
- To systematically analyze and synthesize existing peer-review research, epidemiologic studies, and grey literature reports related to HIV/AIDS in Albania.
- To examine the presence, scope, and implementation framework of national action plans related to HIV/AIDS.
- To identify key structural and cultural barriers affecting HIV prevention and care.

4. MATERIALS AND METHODS

This study adapt a systematic review design with a specific focus on grey literature to evaluate Albanians national response to HIV/AIDS. Grey literature was selected due to its relevance in public health policy analyses, as key information on national strategies, guidelines, and implementation frameworks which are often published outside peer-review journals, and lack of research related to this topic in Albania. This methodological approach follows principals of systematic review methodology to ensure transparency, reproductivity, and minimisation of bias.

5. SEARCH STRATEGY

A structured grey literature search plan was developed in accordance with systematic review protocol. The search strategy incorporated four complementary approaches: (1) target search of grey literature databases, (2) customized Google search queries with preferable key words, (3) screening of relevant organizational and institutional Websites, and (4) consultation with experts, authoritative international and national bodies. Search terms included combination of keywords related to HIV/AIDS,

Albania, national policy, prevention, testing, treatment, awareness, stigma and discrimination.

Grey literature articles are often legal documents, reports, government publications, non-governmental organisations raptors, international bodies reports, research institutes, and health institute. Those articles sourced from target websites of governmental and non-governmental organisations, such as the World Health Organisation, UNAIDS and Albanian Health Ministries, Parliament, and Institute of public Health, all focusing on national HIV/AIDS reports, strategies, and programs documentation.

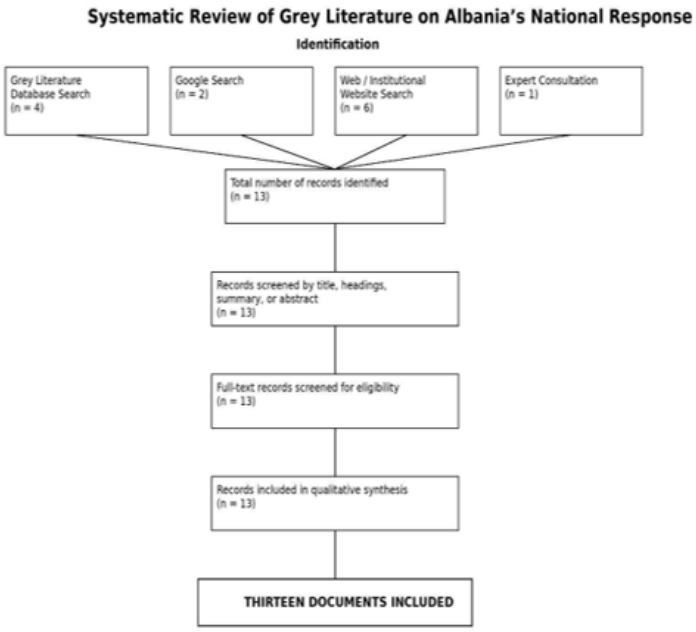
When it comes to systematic review, it requires search methods that are reproducible, and comprehensive, but those standards are difficult to apply to grey literature. Unlikely, academic literature grey literature is challenging to search systematically due to the vast and poorly indexed nature of online information, limited archiving, and inconsistent database coverage. Although various researchers have proposed web-based research approach, there is no established "gold standard" for conducting this type of research, for this reason we have designed this search strategy based in four complementary approaches.

6. ELIGIBILITY CRITERIA

Eligibility criteria were defined as priori to guide the selection of relevant documents. Included sources consisted in national and international reports, policy documents, strategic frameworks, national program, guidelines, and surveillance reports addressing HIV/AIDS in Albania. Documents were required to be published by governmental institutions, international organisations, non-governmental organisations, or recognised public health bodies. Peer-review articles were absent, also opinion and documents not directly related to HIV/AIDS were excluded. Study selection process followed PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. Identified documents were recorded in Excel sheets and duplicates were removed manually. Firstly documents were selected based on their title and summary or abstract. Secondly, full-text screening as concocted to all potentially eligible documents

Data were extracted from each included document using a standardized data extraction sheet. Extracted information include the year of publication, issuing organisation, target population, policy objectives, key interventions, and identified barriers to prevention, testing, and treatment. Data synthesis was conducted narratively, with findings organised thematically to reflect trends, policy implementations, and structural challenges within Albania's HIV/AIDS response.

Figure 1. PRISMA 2020 flow diagram representing searches of databases, registers and other sources



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
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7. ETHICAL CONSIDERATION

As this study is based exclusively on publicly available secondary data and does not involve human participants, formal ethical approval was not required. All sources were appropriately cited to ensure academic integrity and transparency.

8. RESULTS

LEGAL AND POLICY FRAMEWORK ASSOCIATED TO HIV/AIDS in ALBANIA

Albania established its national HIV/AIDS response through Law No. 9952 (2008) and subsequent national strategies. Law No. 9952 defined the legal framework for HIV prevention, diagnosis, treatment, and protection of the rights of people living with HIV. The law mandated confidentiality, access to healthcare services, anti-discrimination measures, and public awareness activities. This legal framework remained unchanged after its last revision in 2011 .

The National Plan for HIV/AIDS Prevention and Treatment 2020-2025 represented the most recent strategic policy instrument. The plan aligned national priorities with Sustainable Development Goals, particularly SDG 3, focusing on prevention, expanding testing, treatment access, stigma reduction, and ensuring international cooperation in combating HIV/AIDS by 2030 (Ministry of Health and Social Protection, 2020).

9. INSTITUTIONAL RESPONSE and EPIDEMIOLOGICAL DATA

National surveillance data indicated that HIV prevalence in Albania remained officially low, however, underdiagnoses persisted (WHO, 2023; UNAIDS, 2025). According to the Global AIDS Monitoring Report, approximately 60% of diagnosed individuals were identified at an advanced stage of infection, indicating delayed and insufficient early detection (UNAIDS, 2022. HIV prevalence was estimated at 0.04%, with an incidence of 3.6 cases per 100,000 population, although data quality limitations were reported (UNAIDS, 2020; WHO, 2023). The available evidence demonstrated a gradual increase in reported HIV cases over time, particularly among key populations, suggesting ongoing gaps in prevention and testing coverage (Institute of Public Health [IPH], 2013; UNAIDS, 2023).

10. MARGINALISED POPULATION

Self-reported transmission data showed heterosexual intercourse as the dominant reported mode of transmission. However, the predominance of male cases and observed serodiscordance within couples suggested underreporting of male-to-male sexual transmission, likely influenced by stigma and social discrimination (UNAIDS, 2020). People who inject drugs (PWID) were identified as a high-risk group, with an estimated HIV prevalence of 1.4%. Most PWID reported injecting in abandoned or public spaces and frequently sharing syringes. The most affected age group was 21–24 years, indicating increased vulnerability among younger populations (UNAIDS, 2020).

Sex workers represented another underreported group. Due to the criminalization of prostitution, routine outreach and testing were limited, and existing prevalence data were considered incomplete (UNAIDS, 2020; WHO, 2024).

11. COLLABORATION WITH NON-GOVERMENTAL ORGANISATION

Collaboration between governmental institutions and non-governmental organizations was reported as central to reaching key populations. NGOs such as ALGA, LGBT Alliance, Aktion Plus, and Stop AIDS, primarily supported through Global Fund financing, provided HIV testing, prevention services, psychosocial support, and harm-reduction interventions in major urban areas (MHSP, 2020; UNAIDS, 2024). Service coverage remained uneven, with limited availability outside major cities.

12. FUNDING AND INTERNATIONAL SUPPORT

Funding for HIV/AIDS programs was provided mainly through the Ministry of Health and Social Protection, supplemented by international donors. The Global Fund invested over USD 12 million in HIV and TB programs in Albania, contributing to the establishment of voluntary counseling and testing centers, free ART provision, laboratory strengthening, and services for key populations (WHO Regional Office for

Europe, 2015). Despite these investments, dependence on external funding remained high.

13. ANTIRETROVIRAL THERAPY

ART services in Albania were centralized at QSUT (Mother Teresa University Hospital). Although ART availability had improved since 2004, national treatment guidelines and practices were reported as not fully aligned with WHO recommendations (WHO, 2014; UNAIDS, 2020). ART provision relied exclusively on clinicians at QSUT, with no decentralized or multidisciplinary support structures in regional health centers.

Until 2020, a regulatory stock commission was not established, product conditions were insufficiently monitored, and inventory systems were underdeveloped. Although full ART stock availability was reported in 2020, testing and treatment coverage remained low, and service centralization continued to pose systemic challenges (UNAIDS, 2020; WHO, 2023).

14. STIGMA and DISCRIMINATION

Despite legal protections, stigma and discrimination against people living with HIV persisted. Evidence demonstrated continued social exclusion, including employment dismissal following disclosure of HIV status (Agolli-Nasufi et al., 2014). Stigma contributed to low uptake of routine HIV testing and underreporting of risk behaviors. Although Albania was classified as a low-prevalence country, stigma-related barriers suggested that the reported burden of HIV was underestimated (Beyrer et al., 2024; UNAIDS, 2023).

15. DISCUSION

National HIV/AIDS Action Plan and Policy

Albania has achieved considerable progress in aligning its national HIV response with international strategies. The Law No.9952 (2008) formulates the legal bases of a multisectoral response, mandating collaboration between public and private institutions to ensure medical, psychological, and social support to affected individuals. It also promotes prevention, awareness, education against stigma and discrimination, diagnosis and treatment in line with international human rights principles. In addition, the National Action Plan for the Prevention and Treatment of HIV/AIDS 2020-2025 is the country's main regulatory plan. Even Though it expired in February 2025, it is still in use and a report has not been released yet. However, this plan is formulated to achieving UNAIDS's 95-95-95 target (2020), for 95% of individuals to be diagnosed. In addition, 95% of HIV positive diagnosed individuals are to be treated with antiretroviral treatment, and 95% of those on treatment to achieve viral suppression (UNAIDS,2020). Moreover, Albania has the Fast-Track Cities Initiative, where Durres, Shkoder, Tirana cities have signed the Paris Declaration to end HIV/AIDS as a public health threat by 2030. Those local-level initiatives supplement the national strategy and reflect Albania's aspiration to be part of the global HIV response (UNAIDS,2024).

Evolution of Healthcare System Response

Despite the policy recommendations, the implementation of HIV/AIDS programs in Albania is complex, where the delayed HIV diagnosis and treatment are prominent. Although the Albanian health system ensures free Antiretroviral treatment and diagnosis,, access to early diagnosis is poor due to numerous factors (WHO Regional Office for Europe, 2015). Public centers often lack infrastructure and equipment, and patients seek the service in private clinics, which are frequently unaffordable for individuals with a low-income background. This not only reinforces health inequalities but also affects the rate of early detection and treatment.

There is also insufficient integration of HIV services within the broader healthcare system, since the testing service is provided only in a few hospitals in big cities throughout the country. Many services are provided in isolation, without proper coordination with other public health sectors such as reproductive health, and mental health.

Impact of Global Support and Challenge of Sustainability

The Global Fund international donors have played a vital role in strengthening Albanian's HIV response. Previous grants helped in establishing testing centers, training the healthcare professionals, and the inclusion of community-based programs. This grant was the financial foundation that has built the system upon which the current response is based (Tereska et al., 2021). However, the withdrawal of Global Fund has resulted in shortage of critical materials and funding for awareness campaigns. Also the NGO that previously relied on this grant has had to reduce the services (Ministry of Health and Social

Protection Republic of Albania, 2020, pg.32).

The transition period has exposed weaknesses in Albanian government preparedness to independently fund and manage its HIV response (UNAIDS, 2025). The national health care budget remains too limited to absorb the financial responsibilities, previously covered by international partners. Without alternative funding mechanisms or strategic partnerships, the country risks reverse the progress made in some sectors (ten Brink et al., 2025). Also, lack of monitoring and evaluating systems has a negative impact in highlighting the real burden and importance to the policy makers (UNAIDS,2020). Data gaps, especially in marginalised groups, limit the ability to target interventions and track the success of national plans (Tereska et al., 2021).

16. CONCLUSIONS

Although Albania is classified as a low-prevalence country, HIV infections are rising among high-risk groups, including men who have unprotected sex with men, people who inject drugs, and sex workers. This trend highlights the urgent need for targeted and more effective prevention strategies. Despite progress in legislation, such as Law 9952 and the National Action Plan 2020–2025, major gaps remain in implementation, funding, infrastructure, and outreach to marginalized populations. HIV testing is largely limited to target groups, with no large-scale population campaigns. Under-reporting and late diagnoses point to weaknesses in surveillance, data collection, and access to testing, especially in rural and small urban areas. Persistent stigma and discrimination within a traditional social context further limit program effectiveness and access for key populations. Continued reliance on international funding, particularly from the Global Fund, underscores the need for a more self-sustaining national HIV response.

17. RECOMANDATIONS

Strengthen Early Diagnosis and Access to Care: Expand HIV testing nationwide, especially in rural and hard-to-reach areas, by integrating services into primary healthcare. Continued NGO involvement through drop-in centers is essential to reach marginalized groups with education, prevention, and testing.

Ensure Sustainable Funding: Increase national health budget allocations for HIV services, including continuous education campaigns, testing, and support for community-based organizations. Public–private partnerships can help reduce dependence on international donors and ensure long-term access to ART and preventive supplies.

Reduce Stigma and Social Inequality: Implement sustained education programs for both the public and healthcare providers to address stigma, which directly affects treatment uptake. Strengthen and enforce anti-discrimination laws to protect people living with HIV in healthcare, education, and employment.

Enhance International and Regional Collaboration: Strengthen cooperation with neighboring Balkan countries to share best practices and resources. Continued engagement with organizations such as WHO and the EU is vital for technical support, workforce training, and transitioning toward sustainable HIV programs.

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ANTI-AGING ESTHETIC TREATMENTS: PSYCHOLOGICAL EFFECTS, EXPECTATIONS, AND CLINICAL OUTCOMES

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Abstract: Anti-aging esthetic dermatology has become an increasingly important area of contemporary medical practice, primarily due to advances in minimally invasive procedures, improved technologies, and growing social interest in maintaining a youthful appearance. In addition to medical and technological progress, psychological and social factors play an increasingly important role in the decision-making process of patients seeking esthetic treatments. Expectations regarding improved self-confidence, social acceptance, and overall quality of life frequently influence the motivation to undergo anti-aging procedures.

The aim of this paper is to analyze psychological factors influencing patients' decisions to undergo anti-aging esthetic treatments and to examine the relationship between patient expectations, perceived outcomes, and overall satisfaction. The study is based on a narrative review of relevant scientific literature in the fields of dermatology, psychology, and medical aesthetics, with particular attention to recent studies addressing patient-reported outcomes, psychosocial determinants of treatment satisfaction, and quality-of-life indicators.

Available evidence indicates that patient satisfaction depends not only on objective clinical results but also on the alignment between expectations and achieved outcomes. Unrealistic expectations, inadequate communication, and insufficient understanding of treatment limitations may lead to dissatisfaction even when clinical results are technically successful. Conversely, effective physician–patient communication, clear explanation of treatment goals, and individualized therapeutic approaches significantly improve both subjective satisfaction and long-term treatment adherence.

Psychological determinants such as body image perception, self-esteem, aging anxiety, and social influence are consistently identified as important predictors of treatment demand and satisfaction. Ethical considerations and professional responsibility are also increasingly emphasized in contemporary esthetic dermatology, particularly in the context of managing patient expectations and ensuring realistic treatment planning.

In conclusion, understanding the psychological background of patients seeking anti-aging esthetic treatments is essential for achieving optimal clinical outcomes and maintaining high levels of patient satisfaction. A multidisciplinary approach that integrates dermatological expertise with psychological awareness represents a key component of safe, effective, and patient-centered anti-aging practice.

Keywords: *anti-aging, esthetic dermatology, patient satisfaction, psychological factors, clinical outcomes*
Field: Medical sciences and Health

1. INTRODUCTION

In recent decades, anti-aging esthetic dermatology has undergone rapid development due to technological progress, increasing life expectancy, and growing societal emphasis on physical appearance. Minimally invasive procedures such as botulinum toxin injections, dermal fillers, and laser therapies have become widely available and increasingly accepted among different age groups. As a result, the number of patients seeking esthetic treatments continues to grow worldwide.

While clinical effectiveness and safety remain essential aspects of esthetic procedures, psychological factors play an equally important role in patient decision-making and treatment satisfaction. Patients often seek esthetic treatments not only to improve physical appearance but also to enhance self-confidence, reduce anxiety related to aging, and improve social and professional interactions (Hemsworth, Hemsworth, & Richmond, 2024; Brown et al., 2025).

Previous research indicates that patient satisfaction in esthetic dermatology is closely associated with realistic expectations, effective communication with healthcare providers, and perceived naturalness of treatment results. Conversely, unrealistic expectations or insufficient understanding of treatment limitations may lead to dissatisfaction, even when clinical outcomes are objectively successful (Aloui, 2024; Germani et al., 2025).

Understanding psychological determinants such as body image perception, self-esteem,

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aging anxiety, and social influences is therefore essential for clinicians working in the field of esthetic dermatology. Studies have shown that social appearance anxiety and the desire for social approval significantly influence acceptance of esthetic procedures (Demir et al., 2024), while exposure to social media content has been associated with increased interest in cosmetic interventions among younger populations (Salameh et al., 2025).

In addition to psychological and social determinants, contemporary research also emphasizes biological and clinical aspects of aging processes, including cellular senescence and tissue regeneration mechanisms, which form the scientific basis of modern anti-aging therapies (Zheng et al., 2024). Systematic reviews indicate that esthetic procedures may positively influence quality of life and psychological well-being, although the strength of evidence varies depending on methodology and patient selection (Hemsworth et al., 2024; Fisher et al., 2025). In parallel with technological and clinical advances, the global demand for minimally invasive anti-aging procedures has increased substantially over the past decade. This growth is associated not only with demographic changes and longer life expectancy but also with evolving perceptions of aging and personal well-being. Contemporary esthetic practice increasingly recognizes that patients seek treatments not merely to correct visible signs of aging, but also to maintain a sense of vitality, confidence, and social engagement. Consequently, modern anti-aging dermatology is gradually shifting from a predominantly corrective approach toward preventive and maintenance-oriented strategies, emphasizing long-term patient satisfaction and holistic treatment outcomes.

The aim of this paper is to analyze psychological factors influencing patient satisfaction in anti-aging esthetic dermatology and to examine the relationship between expectations, clinical outcomes, and perceived treatment success through a review of relevant scientific literature. In recent years, a noticeable shift has occurred in esthetic dermatology, with increasing emphasis on preventive and maintenance-oriented anti-aging treatments rather than solely corrective interventions. This trend reflects broader demographic changes, including population aging, prolonged professional activity, and heightened awareness of personal appearance across all age groups. As a result, anti-aging treatments are no longer perceived exclusively as cosmetic enhancements but increasingly as interventions associated with psychological well-being, self-perception, and quality of life. Understanding these evolving motivations further underscores the importance of integrating psychological assessment into routine esthetic practice, particularly when addressing long-term patient satisfaction and treatment adherence.

2. MATERIALS AND METHODS

This paper was designed as a narrative literature review aimed at analyzing psychological factors associated with patient expectations, satisfaction, and perceived outcomes in anti-aging esthetic dermatology. The review approach was selected because it allows integration of findings from clinical, psychological, and dermatological studies in order to provide a comprehensive understanding of the topic.

Relevant scientific articles were identified through searches of major academic databases, including PubMed, Scopus, and Google Scholar. Search terms included combinations of keywords such as “anti-aging,” “esthetic dermatology,” “patient satisfaction,” “psychological effects,” and “quality of life.” Similar search strategies have been used in previous literature reviews addressing patient expectations and outcomes in aesthetic medicine (Aloui, 2024).

Inclusion criteria consisted of peer-reviewed journal articles published primarily within the last five years, written in English, and addressing psychological, clinical, or social aspects of esthetic dermatology. Priority was given to systematic reviews, cross-sectional studies, and cohort studies focusing on patient-reported outcomes and treatment satisfaction. Recent cross-sectional research examining expectations of patients undergoing facial aesthetic treatments was considered particularly relevant for understanding motivational factors and satisfaction patterns (Germani et al., 2025).

Studies addressing broader determinants of treatment demand, including social and cultural influences, were also included in the analysis. Research investigating the role of social media exposure in shaping interest in cosmetic procedures was considered important in explaining contemporary trends in esthetic treatment demand (Salameh et al., 2025).

Additionally, clinical and biological studies were reviewed to provide context regarding the mechanisms and therapeutic approaches used in anti-aging medicine. Contemporary analyses of cellular senescence and treatment strategies contribute to understanding the scientific basis of anti-aging interventions (Zheng et al., 2024).

Data from selected studies were analyzed qualitatively, focusing on recurring themes such as patient expectations, psychological well-being, quality of life, and determinants of satisfaction. The synthesis of findings was performed descriptively, without statistical meta-analysis, due to differences in study designs,

populations, and outcome measures across the included literature. The narrative review design was considered appropriate for this study because it allows a broader interpretation of heterogeneous findings and facilitates the identification of common psychological and clinical patterns reported in the literature.

3. RESULTS AND DISCUSSION

Analysis of the selected literature indicates that psychological factors play a central role in patient decision-making and satisfaction in anti-aging esthetic dermatology. One of the most consistently reported determinants is the level and structure of patient expectations prior to treatment. Cross-sectional research demonstrates that expectations vary significantly depending on age, previous treatment experience, and individual perceptions of aging, which directly influences post-treatment satisfaction (Germani et al., 2025).

A recurrent finding across studies is that the alignment between expectations and clinical outcomes is a stronger predictor of satisfaction than objective clinical results alone. Systematic literature reviews have shown that unrealistic expectations, inadequate communication, and insufficient patient education represent major predictors of dissatisfaction in aesthetic medicine (Aloui, 2024).

Psychological well-being and quality of life represent another important dimension of treatment outcomes. Evidence suggests that minimally invasive esthetic procedures may contribute to improvements in self-esteem, perceived attractiveness, and social confidence, which are frequently reported by patients following treatment (Hemsworth et al., 2024). Prospective cohort studies evaluating patient-reported outcomes after facial procedures also indicate measurable improvements in psychological well-being and satisfaction with appearance (Nieuwenhuis et al., 2021).

Social and environmental influences further contribute to the growing demand for anti-aging treatments. Studies have shown that social appearance anxiety and the desire for social approval significantly influence the acceptance of esthetic procedures, particularly among younger and professionally active populations (Demir et al., 2024). Similarly, exposure to idealized beauty standards on social media platforms has been associated with increased interest in cosmetic facial injections and other minimally invasive procedures (Salameh et al., 2025).

In addition to psychological and social factors, biological aspects of aging remain an important component of the broader context of anti-aging medicine. Research on cellular senescence and tissue aging mechanisms provides insight into the scientific rationale behind modern therapeutic approaches, including regenerative and minimally invasive procedures (Zheng et al., 2024). Understanding these mechanisms contributes to a more realistic interpretation of treatment possibilities and limitations, which is essential for appropriate patient counseling.

Clinical communication has also been identified as a key factor influencing patient satisfaction and long-term treatment outcomes. Studies in esthetic dermatology emphasize that structured consultations, realistic goal-setting, and individualized treatment planning significantly improve both subjective satisfaction and therapeutic adherence (Sobanko, Taglienti, & Wilson, 2018).

Contemporary systematic reviews indicate that multidisciplinary approaches integrating dermatological, psychological, and communication-based strategies provide the most favorable outcomes. Such approaches not only improve patient satisfaction but also reduce the risk of dissatisfaction and unnecessary procedures, contributing to safer and more ethically responsible practice in esthetic medicine (Fedorchenko, 2024).

Overall, the available evidence suggests that successful anti-aging esthetic treatment depends on the interaction of clinical effectiveness, psychological determinants, communication quality, and realistic expectation management. Recognizing this multidimensional nature of treatment outcomes represents a critical step toward improving patient-centered care in modern esthetic dermatology. In this context, it is increasingly recognized that patient satisfaction should be evaluated not only immediately after treatment but also over longer follow-up periods. Long-term perception of treatment outcomes may change as patients adapt to their appearance, social circumstances evolve, or expectations shift over time. Therefore, understanding satisfaction as a dynamic rather than static outcome provides a more realistic framework for evaluating the effectiveness of anti-aging interventions and highlights the importance of continued physician–patient communication during follow-up.

Further analysis of recent literature highlights that patient expectations are not uniform and frequently vary according to age, previous treatment experience, and cultural background. Younger adults often seek esthetic procedures for preventive and social reasons, aiming to maintain a youthful appearance and remain socially competitive, whereas older patients more commonly pursue restorative outcomes, such as reducing visible signs of aging and improving perceived vitality (Germani et al., 2025). Large-

scale international surveys also indicate that perceptions of aging itself significantly influence treatment motivation, with many older individuals associating esthetic treatments with improved self-confidence and emotional well-being (Brown et al., 2025).

Another important contemporary factor influencing treatment demand is the widespread exposure to social media, where idealized representations of youth and beauty are frequently encountered. Continuous exposure to such content may contribute to increased awareness of appearance-related concerns and a stronger interest in minimally invasive procedures. Research has shown that frequent social media users demonstrate higher levels of social appearance anxiety and a greater willingness to undergo cosmetic facial treatments (Salameh et al., 2025). For this reason, clinicians are increasingly encouraged to address media-driven expectations during consultations in order to help patients develop realistic treatment goals.

In addition to external influences, the psychological benefits associated with esthetic treatments remain an important area of investigation. Multiple studies suggest that minimally invasive procedures can lead to measurable improvements in self-esteem, perceived attractiveness, and social confidence, which may contribute to overall psychological well-being and quality of life (Hemsworth et al., 2024). Clinical outcome studies further confirm that even relatively minor facial interventions may positively influence self-perception and satisfaction with appearance, particularly when expectations are realistic and communication with the physician is effective (Nieuwenhuis et al., 2021).

Ethical considerations and communication strategies represent another essential component of successful treatment outcomes. Clear explanation of treatment possibilities, potential risks, and realistic results has been consistently associated with higher levels of patient satisfaction and better long-term adherence to recommended follow-up care (Sobanko et al., 2018). At the same time, clinicians must carefully identify unrealistic expectations and avoid over-promising results, ensuring that treatment planning remains aligned with patient safety and professional ethical standards (Fedorchenko, 2024).

Taken together, these findings reinforce the view that patient satisfaction in anti-aging esthetic dermatology is shaped by a complex interaction of psychological readiness, social influences, biological factors, and the quality of physician–patient communication. Understanding these relationships is essential for achieving optimal clinical and psychosocial outcomes. To summarize the key psychological determinants identified in the reviewed literature, Table 1 presents the most relevant factors associated with patient satisfaction in anti-aging treatments.

Table 1. Key Psychological Determinants of Patient Satisfaction in Anti-Aging Treatments

Psychological Factor	Description	Evidence from Recent Studies
Body image perception	Self-evaluation of physical appearance and perceived attractiveness	Germani et al., 2025
Self-esteem	General sense of confidence and personal worth	Hemsworth et al., 2024
Social appearance anxiety	Concern about social judgment related to physical appearance	Demir et al., 2024
Aging anxiety	Psychological concern related to visible signs of aging	Brown et al., 2025
Social media exposure	Influence of online beauty standards and trends	Salameh et al., 2025

Source: Author's synthesis based on cited literature.

The factors presented in Table 1 illustrate the multidimensional nature of patient satisfaction in anti-aging esthetic treatments and emphasize the importance of integrating psychological assessment into clinical practice. Beyond individual psychological traits, ethical responsibility and professional judgment play a crucial role in shaping treatment outcomes in anti-aging esthetic dermatology. The literature increasingly emphasizes that clinicians must actively assess patients' motivations, emotional readiness, and expectation frameworks prior to initiating treatment. Failure to address unrealistic or externally driven expectations may result in dissatisfaction, repeated procedures, or psychological distress, even when clinical results are objectively appropriate. Consequently, incorporating structured psychological awareness into clinical consultations is essential for maintaining ethical standards and promoting sustainable, patient-centered care.

4. CONCLUSION

Anti-aging esthetic dermatology represents a rapidly developing field in which clinical outcomes are closely intertwined with psychological, social, and biological factors. The findings presented in this review

indicate that patient expectations, perception of aging, and psychological well-being play a decisive role in determining satisfaction with esthetic treatments.

The analyzed literature consistently demonstrates that realistic expectations and effective physician–patient communication are among the most important predictors of positive treatment outcomes. Patients who receive clear information about treatment possibilities, limitations, and expected results tend to report higher levels of satisfaction and psychological benefit after procedures. This emphasizes that the success of anti-aging interventions cannot be evaluated solely through objective clinical parameters, but must also include subjective and psychosocial dimensions of treatment outcomes.

Psychological determinants such as self-esteem, body image perception, social appearance anxiety, and exposure to social media significantly influence both the decision to undergo treatment and the perception of results. These factors highlight the importance of a patient-centered approach in esthetic dermatology, where clinical expertise is complemented by an understanding of psychosocial aspects and individual patient motivations.

Advances in the understanding of biological mechanisms of aging and the development of minimally invasive therapeutic techniques continue to improve safety and effectiveness in anti-aging medicine. At the same time, the growing accessibility of esthetic procedures requires increased professional responsibility, careful patient selection, and individualized treatment planning in order to prevent unrealistic expectations, overtreatment, and potential psychological dissatisfaction.

Successful anti-aging esthetic treatment therefore depends on a multidisciplinary approach that integrates dermatological knowledge, psychological assessment, and effective communication. Such an approach contributes not only to improved clinical outcomes but also to enhanced patient satisfaction and long-term quality of life. Practical implications for clinical practice include structured patient consultations, assessment of psychological readiness, and individualized treatment planning tailored to patient expectations and clinical indications. Incorporating these strategies may also reduce the frequency of repeated or unnecessary procedures and improve long-term therapeutic adherence.

Another important consideration is the role of continuous professional education and the adoption of evidence-based guidelines in esthetic dermatology. As the field evolves, clinicians are increasingly required to balance patient expectations, technological possibilities, and ethical standards. Strengthening interdisciplinary collaboration between dermatologists, psychologists, and other healthcare professionals may further enhance the quality and safety of anti-aging treatments.

Future research should focus on standardized methods for evaluating psychological outcomes in esthetic dermatology, as well as on developing multidisciplinary protocols that integrate dermatological, psychological, and communication-based approaches in routine clinical practice. Longitudinal studies examining long-term psychological and quality-of-life outcomes following minimally invasive procedures would be particularly valuable for establishing clearer clinical guidelines and improving patient selection criteria.

Ultimately, integrating clinical expertise with psychological insight and ethical responsibility represents a key direction for the future development of esthetic dermatology, enabling safer procedures, more realistic treatment planning, and improved long-term patient satisfaction.

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PREREQUISITES FOR EFFECTIVE COMMUNICATION IN SEASONAL INFLUENZA VACCINATION- A STUDY OF GENERAL PRACTITIONERS IN BULGARIA

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Abstract: This study investigates the prerequisites and barriers to effective communication regarding seasonal influenza vaccination by examining the perspectives of general practitioners (GPs) in Bulgaria. GPs play a crucial role in providing primary healthcare services, including health information, promotion of health, disease prevention, and vaccination programs. However, they face significant challenges related to patient trust in social media and internet sources, patients' tendency to neglect their health, and administrative burdens that can hinder their ability to engage in preventive measures. The survey involved 368 GPs who completed an anonymous questionnaire assessing various aspects of their work and relationships with patients. Results indicate that most GPs believe patients heavily rely on potentially misleading information from social media, which complicates efforts to promote vaccinations. Additionally, many patients tend to neglect their health, making them less receptive to health promotion campaigns. Furthermore, GPs often feel overwhelmed by administrative tasks, limiting their capacity to participate in additional preventive programs. Despite these challenges, GPs recognize the importance of communication skills, with 94% considering them as vital as diagnostic and treatment skills. This highlights the need for ongoing training and development of communication skills to improve interactions with patients and enhance the effectiveness of vaccination programs. In conclusion, addressing misinformation, promoting patient responsibility, and reducing administrative burdens are essential steps towards improving communication and increasing vaccination rates among the Bulgarian population.

Keywords: *General Practitioners (GPs); communication plan; flu vaccination; patient trust; administrative burden*
Field: Medical Sciences

1. INTRODUCTION

The general practitioner (GP) is the leading figure in primary care in Bulgaria. The characteristics and functions of the GP are described in detail in the Medical Standard "General Medicine" (according to Regulation No. 2 of December 23, 2020 of the Ministry of Health), the Law on Medical Institutions and the National Framework Agreement (Ministry of Health, 2020; Law on Medical Institutions, 1999; National Health Insurance Fund & Bulgarian Medical Association, 2023). These documents determine the requirements for competence, the scope of activities and access to medical care.

Along with the diagnostic and treatment activities regulated in the specified documents, the GP also performs health information activities; health promotion, disease prevention and patient monitoring program (dispensarization) (Kirov, L. & Ivanov, G., 2012).

The role as a family doctor requires him/her to be familiar with the social history of health and illness of the people on his patient list, to have well-developed communication and motivational skills in order to adequately respond to the growing health needs and expectations of the population.

During the three-year training in the specialty "General Medicine", doctors consolidate the practices of the patient-centered approach, as well as management skills for medical practice management. The Code of Professional Ethics of Doctors in Bulgaria defines the moral and behavioral characteristics of physicians, such as professional responsibility, humanity, tact and confidentiality, necessary for building trust and an effective "practitioner- patient" relationship (Bulgarian Medical Association, 2000; Garov, S., 2021; Shopnikolova, T., Yanakieva, A., & Vodenicharova, A., 2021).

Vaccines have been among the most significant public health achievements of the past two centuries. Influenza vaccines provide between 70% and 90% protection against clinical disease in healthy adults. Other benefits of seasonal influenza vaccination include helping to maintain health systems during influenza epidemics and pandemics, and providing better preparedness and response in the event of a pandemic (Penchev, D., Zlatanova-Velikova, R., Zlatanova, T. et al., 2024).

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The aim of this paper is to study the prerequisites and barriers for effective communication in seasonal influenza vaccination by examining the opinion of GPs on important aspects of their daily work and relationships with patients.

2. MATERIALS AND METHODS

The presented data are part of a larger scientific study aimed at researching the communication skills of GPs in promotion of recommended seasonal influenza vaccines in Bulgaria.

The following methods were used:

• A documentary method for researching and analyzing the literature available on communication strategies in optional immunizations;

• Questionnaire method: Anonymous direct individual questionnaire among general practitioners in Bulgaria. Respondents were recruited through a personal visit to the outpatient clinic or during two national scientific forums;

• Statistical methods: The specialized statistical package SPSS (Statistical Package for the Social Sciences) version 20 was used to process the data from the study.

The survey was conducted between May 2025 and October 2025. A total of 368 general practitioners were enrolled. An original questionnaire was developed for the purposes of the study.

3. RESULTS AND DISCUSSION

The study involved 368 respondents - doctors with a specialty in "General Medicine". The average age of the respondents in the sample is 57.92 years (min=24.0; max=79.0; SD= 9.67).

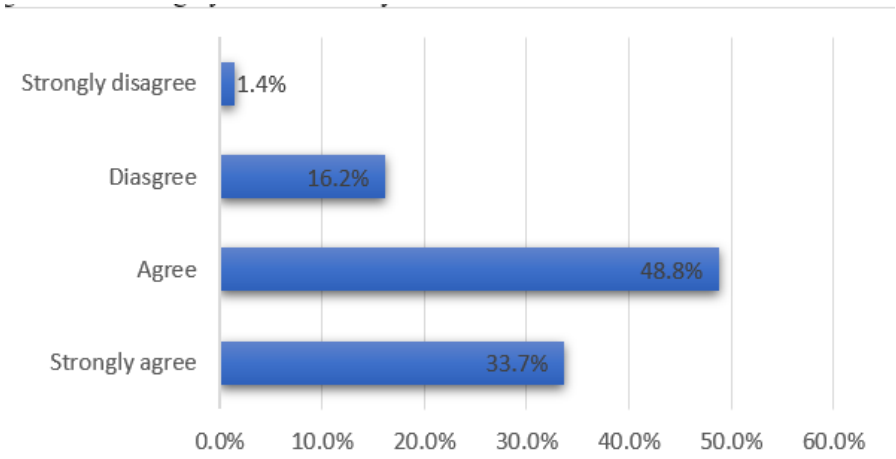
Women significantly predominate (68.2%). According to data from the National Statistical Institute and the Bulgarian Medical Union, by the beginning of 2024, female doctors in primary outpatient care predominate, often exceeding 60-70% of the total number of general practitioners in a number of regions. The gender distribution in the sample corresponds to these national data.

In terms of family status, the largest share of respondents are married - 67.0%; followed by these in a relationship (12.3%), the divorced (8.8%), the single (6%) and the widowed (6%).

Outpatient clinics in a large city (regional city) predominate - 51.8%, followed by practices in a small town (29.6%). 14.2% of respondents reported that their outpatient clinic is located in the capital and 4.4% - in a village.

The average number of patients in the patient list of a GP is 1835.18 people (SD = 912.87), with the average number of patients aged 65 and over, i.e. those subject to immunization under the "National Program for Improving Vaccine Prevention of Seasonal Influenza and Pneumococcal Infections in Persons Aged 65 and Over 2023-2026" being 521.4 (SD = 401.82). A huge share of respondents - 85.2% indicate work experience as a GP over 20 years, and another 7.7% - over 10 years.

Fig. 1. Patients highly trust what they read on social media and other internet sources

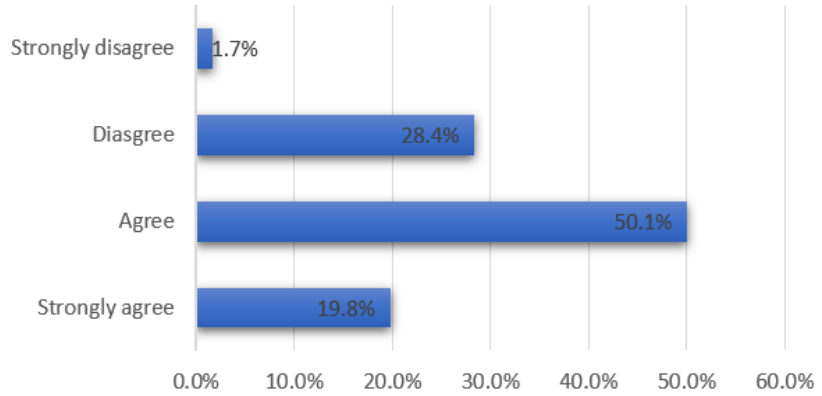


Source: Authors' research

82.5% of respondents believe that patients highly trust what they read on social media and other internet sources. Free access to information, sometimes misleading or completely false, makes it difficult for doctors to conduct information campaigns regarding the benefits of mandatory and recommended vaccinations. The lack of control over information on the internet is a prerequisite for the spread of disinformation and bad practices among people - distrust, fear and refusal of vaccination.

A significant percentage of respondents answered the statement "Most people neglect their health" positively - 19.8% completely agree and 50.1% - agree. 28.4% disagree and only 1.7% strongly disagree with this statement. (Fig. 2) Patients who tend to neglect their health are less responsive to health promotion and disease prevention campaigns, long-term follow-up, which leads to a deterioration in their chronic conditions and quality of life. (Dzuglarska, M., Zlatanova, T., Popov et al., 2023; Dzinsov, K., Georgieva, E., Traykov, et. al., 2023)

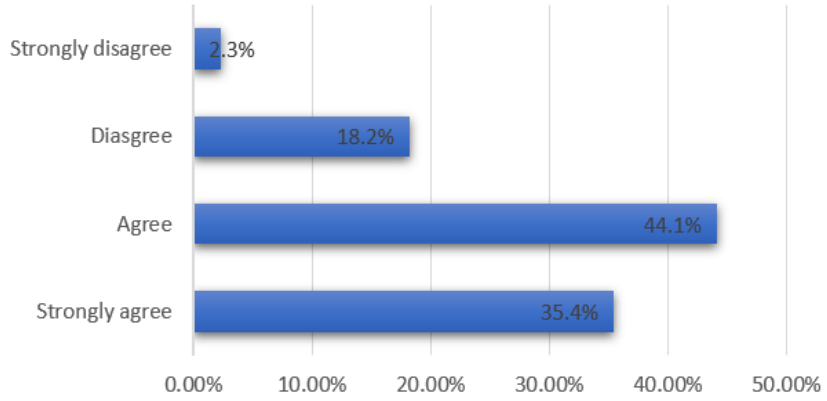
Fig. 2: Most people neglect their health



Source: Authors' research

A large share of the participants in the study (79.5%) are of the opinion that patients have too many rights (Fig. 3). The autonomous model of "doctor-patient" relationships assumes that the patient participates in making decisions regarding his or her own health, after receiving sufficient and accessible information. Optional immunizations are provided at the patient's request for a fee or are free for some groups of the population. Patient awareness is key to making informed choices and the right to information is central to the concept of informed consent (Shtereva-Nikolova, N., 2012).

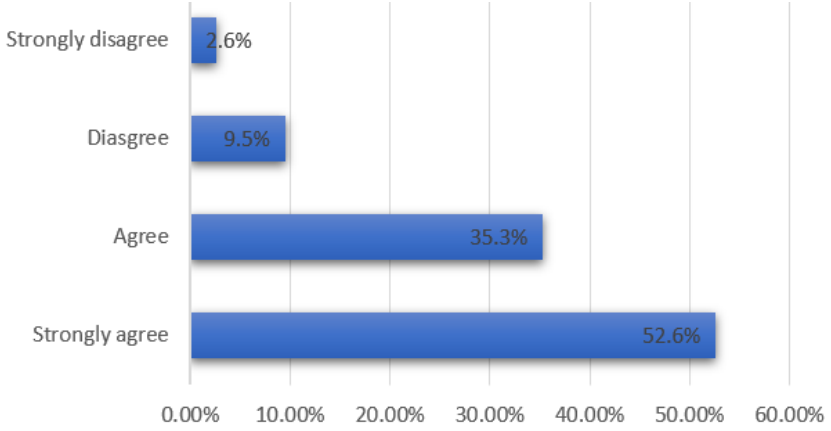
Fig. 3. Patients have too many rights



Source: Authors' research

The following questions concern the routine work of GPs. In addition to their duties towards patients, GPs also have the responsibility to manage their practice (Zlatanova, T. & Zlatanova-Velikova, R., 2012). To the statement "My administrative work is more than my medical work", 52.6% answered "strongly agree" and 35.3% "agree". (Fig. 4) Some authors point out the possibility that GPs do not engage in additional preventive programs precisely because of the administrative and organizational burden associated with implementation, rather than because of reluctance to carry out preventive measures.

Fig. 4: My administrative work is more than my medical work

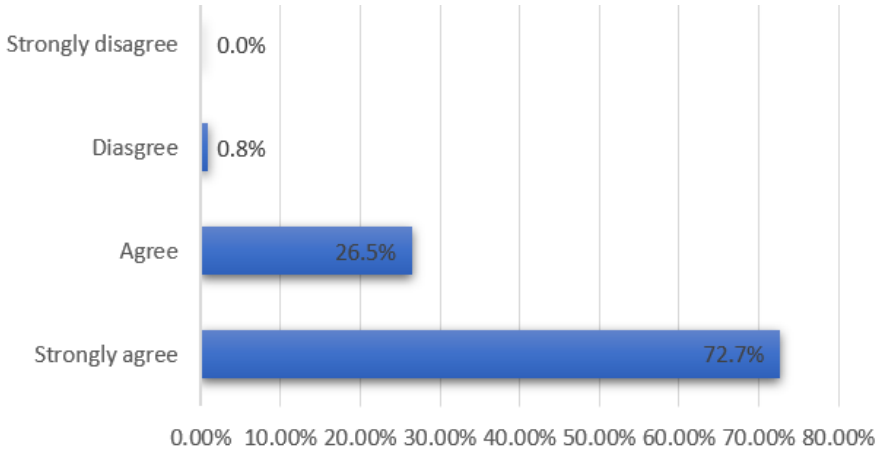


Source: Authors' research

Again, almost all respondents (99.2%) believe that they have an individual approach to their patients, as they know them well. Only 0.8% answered that they disagree with the statement (Fig. 5). An individual approach is an element of patient-centered care, in which the focus is placed not only on health, but also on the goals, values, desires and expectations of the individual (Trendafilova, A, Ivanova, Ts., Garov, Sv., 2025).

The Patient-Centered Outcomes Research Institute (PCORI) in the USA defines patient-centered care as "an activity that supports people and their health care providers to make informed health decisions, allowing the patient's voice to be heard in assessing the value of health care alternatives" (Patient-Centered Outcomes Research Institute [PCORI], n.d.). This is a complex process in which the patients are an active participant in the "doctor-patient" relationship, actively control the flow of information and exercise their right to choose. An individual approach guarantees better success in offering recommended preventive measures such as seasonal flu vaccinations (Goranova-Spasova, R., 2024).

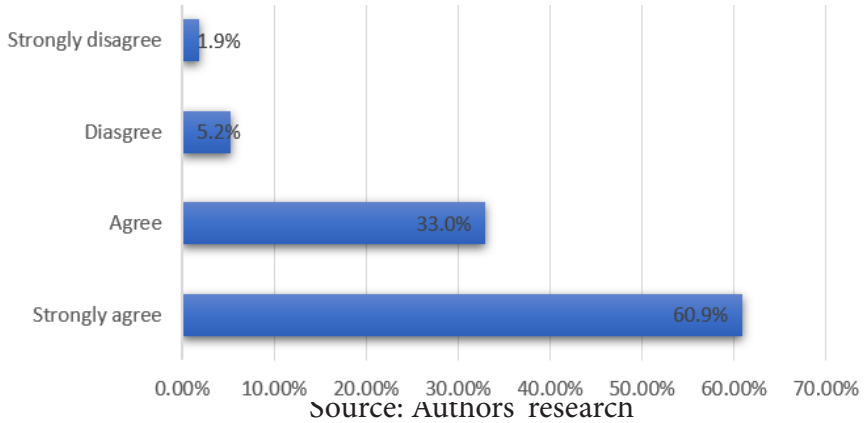
Fig. 5: I believe that I have an individual approach to my patients because I know them well



Source: Authors' research

Of the GP respondents, 60.9% strongly agree and 33.0% tend to agree that communication skills are as important as diagnosis and treatment skills. 7.1% do not attach as much importance to communication skills, answering the statement negatively. (Fig. 6) These results are again encouraging in terms of the readiness to develop better communication skills of GPs (Garov, S., Goranova-Spasova, R., Enchev, A, 2017).

Fig. 6: Communication skills are as important in my work as diagnosis and treatment skills



Source: Authors' research

4. CONCLUSIONS

The data obtained reveal some factors that may hinder the implementation of an effective communication campaign by GPs regarding seasonal influenza vaccination. These include misinformation and lack of trust in the healthcare system; limited personal responsibility for health; imbalance between rights and responsibilities on the part of patients and the administrative workload of doctors.

This fact highlights the need for more active and targeted efforts to increase health literacy and awareness among the population by developing an adequate communication plan for seasonal influenza vaccination for general medical practice.

Continuing education and development of communication skills of GPs should be a priority in order to achieve better understanding and cooperation between doctors and patients, as well as for the successful implementation of recommended preventive programs.

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INFLAMMATION-LINKED PSA VARIABILITY IN BPH PATIENTS TREATED WITH ANTIBIOTICS: A LONGITUDINAL STUDY WITH HISTOPATHOLOGIC CORRELATION

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Abstract: Benign prostatic hyperplasia (BPH) frequently coexists with prostatic inflammation, which may elevate prostate-specific antigen (PSA) and complicate differentiation from prostate cancer. To evaluate longitudinal changes in C-reactive protein (CRP) and PSA parameters following culture-guided antibiotic therapy in men with BPH, and to assess associations with prostate biopsy outcomes. A longitudinal retrospective observational study included 24 men with BPH followed from January to December 2025. CRP, total PSA (tPSA), and free PSA (fPSA) were measured at baseline without antibiotics (January) and at three subsequent timepoints (May, September, December) after antibiotic therapy guided by urine culture and antibiogram. Antibiotic regimens included levofloxacin 500 mg once daily for 28 days, nitrofurantoin 100 mg three times daily for 10 days, and cefixime 400 mg once daily for 10 days. Prostate biopsy was recommended to all patients; those declining biopsy were retained as a descriptive subgroup. Statistical analysis: Continuous variables were summarized as median and interquartile range. Repeated-measures comparisons across four timepoints were performed using the Friedman test. Between-group comparisons were performed using the Mann–Whitney U test. A two-sided p value < 0.05 was considered statistically significant. Results: CRP and PSA parameters demonstrated longitudinal variation over the four timepoints. PSA kinetics differed according to histopathologic findings among biopsied patients. Conclusion: Serial CRP and PSA assessment under culture-guided antibiotic therapy may support risk stratification and biopsy decision-making in BPH patients with suspected inflammation.

Keywords: *benign prostatic hyperplasia, C-reactive protein, prostate-specific antigen, prostatitis*
Field: Medical Sciences and Health

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is frequently accompanied by chronic or subclinical prostatic inflammation (Nickel, 2008; Nickel et al., 2019). Increasing evidence suggests that inflammatory processes within the prostate may significantly influence prostate-specific antigen (PSA) variability, thereby complicating differentiation between benign inflammatory conditions and prostate cancer (De Marzo et al., 2007; Shariat et al., 2022). Contemporary urological research has emphasized that PSA is not a cancer-specific marker but rather a prostate-derived protein whose serum levels may be altered by infection, inflammation, and epithelial disruption (Loeb et al., 2020; Ferro et al., 2024).

Recent studies have highlighted the clinical relevance of PSA kinetics rather than isolated PSA measurements (Loeb et al., 2020). Longitudinal PSA variability has been associated with inflammatory activity in benign prostatic disease, while malignant transformation tends to demonstrate different kinetic patterns (Shariat et al., 2022). Systematic reviews evaluating antibiotic therapy in men with elevated PSA have reported that PSA reduction may occur following treatment; however, PSA response alone cannot reliably exclude underlying malignancy (Buddingh et al., 2017; Mari et al., 2023). Current European and American urological guidelines recommend interpreting PSA dynamics within clinical context, particularly when considering prostate biopsy decisions (American Urological Association, 2023; European Association of Urology, 2024).

In addition to total PSA, the free-to-total PSA ratio is widely used to refine risk stratification in men within the diagnostic gray zone (Heo et al., 2024). Nevertheless, chronic prostatitis may also influence free PSA behavior, limiting specificity and further complicating diagnostic interpretation (Jung et al., 1998;

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Stancik et al., 2004). Moreover, systemic inflammatory markers such as C-reactive protein (CRP) have been investigated as potential adjunctive indicators reflecting inflammatory burden in prostatic disease (Zhou et al., 2023).

Despite these observations, limited real-world longitudinal data exist evaluating combined CRP and PSA kinetics under culture-guided antibiotic therapy, particularly with histopathologic correlation. The present study aimed to evaluate serial CRP and PSA dynamics across four timepoints over a 12-month period in men with BPH, and to examine whether differential biomarker trajectories correspond to biopsy-confirmed chronic prostatitis or prostate carcinoma.

2. OBJECTIVES

To evaluate longitudinal changes in C-reactive protein (CRP) and PSA parameters following culture-guided antibiotic therapy in men with BPH, and to assess associations with prostate biopsy outcomes.

3. MATERIAL AND METHODS

Study Design and Setting

This longitudinal retrospective observational study was conducted at the Department of Urology, General Hospital "Ferid Murad", Gostivar, North Macedonia. Patients were followed from January to December 2025 with serial laboratory assessments at four predefined timepoints.

Participants

A total of 24 men with a clinical diagnosis of benign prostatic hyperplasia (BPH) who underwent repeated laboratory monitoring were included. All patients had elevated PSA values and clinical suspicion of inflammatory contribution. Prostate biopsy was recommended to all patients according to clinical evaluation and guideline-based practice. Twenty patients underwent biopsy, while four declined and were retained as a descriptive subgroup.

Histopathologic findings among biopsied patients were categorized as chronic prostatitis or prostate carcinoma.

Laboratory Measurements

Serum C-reactive protein (CRP, mg/L), total PSA (tPSA, ng/mL), free PSA (fPSA, ng/mL), and the free-to-total PSA ratio (%) were recorded at four timepoints: T1: January (baseline, prior to antibiotic therapy); T2: May; T3: September; T4: December.

Antibiotic therapy was prescribed according to urine culture and antibiogram results. Regimens included:

- Levofloxacin 500 mg once daily for 28 days
- Nitrofurantoin 100 mg three times daily for 10 days
- Cefixime 400 mg once daily for 10 days

Treatment selection was individualized based on microbiological findings.

Statistical Analysis

Continuous variables were summarized as median and interquartile range (IQR). Longitudinal changes across the four timepoints (T1–T4) were analyzed using the Friedman test for repeated measures.

Between-group comparisons of biomarker changes from baseline to T4 (ΔT4–T1) among biopsied patients (chronic prostatitis vs prostate carcinoma) were performed using the Mann–Whitney U test.

The subgroup of patients who declined biopsy was reported descriptively and was not included in inferential between-group comparisons.

All statistical tests were two-sided, and p values < 0.05 were considered statistically significant.

4. RESULTS

A total of 24 men with clinically diagnosed benign prostatic hyperplasia were followed across four timepoints (T1 January, T2 May, T3 September, T4 December). Prostate biopsy was recommended to all patients; 20 underwent biopsy, while 4 declined. Among biopsied patients, 11 were diagnosed with chronic prostatitis and 9 with prostate carcinoma. Baseline characteristics are summarized in Table 1.

Table 1. Baseline Characteristics (T1)

Variable	*Total (N=24) Median (IQR)*	*Prostatitis (n=11)*	*Carcinoma (n=9)*	*No Biopsy (n=4)*
Age (Years)	63.5 (59.0–68.0)	62.0 (59.0–64.5)	65.0 (63.0–71.0)	61.5 (58.8–63.5)
CRP (mg/L)	52.85 (28.50–79.28)	37.60 (28.50–52.30)	78.95 (77.10–83.55	28.10 (20.03–34.35)
Total PSA (ng/ml)	8.92 (6.25–12.41)	8.19 (6.05–8.69)	11.00 (9.89–13.88)	4.85 (3.61–5.39)
Free PSA (ng/ml)	1.66 (1.14–2.29)	1.34 (1.06–2.11)	2.07 (1.80–2.30)	0.75 (0.61–0.92)
Free/Total PSA Ratio %	18.85 (14.63–26.03)	17.10 (13.60–25.50)	18.80 (16.30–21.40)	24.45 (17.78–25.43)

Source: Authors' own data

In the entire cohort, significant longitudinal changes were observed. CRP levels demonstrated a marked and progressive decline from T1 to T4 (Friedman test, p = 0.001). Total PSA levels also changed significantly across timepoints (Friedman test, p = 0.003), with an overall downward trend by T4. In contrast, although the free-to-total PSA ratio showed a rising median pattern across timepoints, the global repeated-measures comparison did not reach statistical significance (Friedman test, p = 0.133) (Table 2).

Table 2. Longitudinal Biomarker Changes (T1–T4)

Parameter	*T1*	*T2*	*T3*	*T4*	*P (Friedman)*
CRP (mg/L)	52.85 (28.50–79.28)	33.15 (24.65–58.45)	23.35 (19.28–43.73)	19.85 (16.65–22.83)	<0.001
Total PSA (ng/ml)	8.92 (6.25–12.41)	6.27 (4.40–9.87)	4.40 (3.25–8.03)	4.35 (3.18–7.93)	0.003
Free/Total PSA Ratio %	18.85 (14.63–26.03)	25.50 (14.80–33.30)	33.15 (19.88–44.83)	36.00 (21.75–48.48)	0.133

Source: Authors' own data

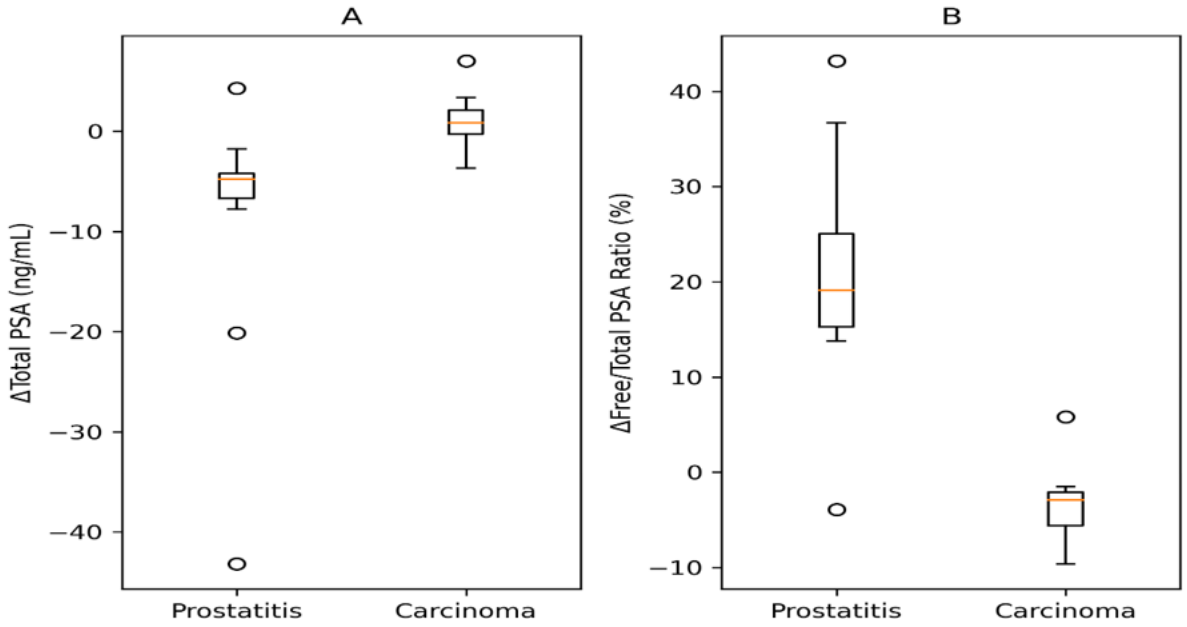
When analysis was restricted to biopsied patients, distinct differences emerged between histopathologic groups. The median change in total PSA (T4–T1) was −4.78 ng/mL (IQR −6.70 to −4.22) in patients with chronic prostatitis, compared with +0.83 ng/mL (IQR −0.25 to 2.09) in patients with prostate carcinoma (p = 0.003). Similarly, the median change in free-to-total PSA ratio was +19.10% (IQR 15.25 to 25.05) in prostatitis and −2.90% (IQR −5.60 to −2.10) in carcinoma (p < 0.001) (Table 3). The distribution of biomarker changes is illustrated in Figure 1. The subgroup that declined biopsy was reported descriptively and was not included in inferential comparisons.

Table 3. T4–T1 Changes in Biopsied Patients

Parameter	*Prostatitis (n=11) Median (IQR)*	*Carcinoma (n=9) Median (IQR)*	*p (Mann-Whitney)*
ΔTotal PSA (ng/mL)	-4.78 (-6.70 to -4.22)	+0.83 (-0.25 to 2.09)	0.003
ΔFree/Total Ratio (%)	+19.10 (15.25 to 25.05)	-2.90 (-5.60 to -2.10)	<0.001

Source: Authors' own data

Figure 1. Boxplot Representation of ΔTotal PSA (A) and ΔFree-to-Total PSA Ratio (B) (T4–T1) According to Histopathologic Diagnosis. Panel A shows ΔTotal PSA (ng/mL). Panel B shows ΔFree-to-Total PSA Ratio (%).



Source: Authors' own data

5. DISCUSSION

The present longitudinal study demonstrates that inflammatory activity and PSA kinetics are closely interrelated in men with benign prostatic hyperplasia undergoing culture-guided antibiotic therapy. While CRP showed a progressive decline across timepoints, total PSA levels also decreased significantly in the overall cohort. However, the most clinically relevant finding emerged when biomarker dynamics were stratified according to histopathology.

Patients with biopsy-confirmed chronic prostatitis exhibited a marked reduction in total PSA accompanied by a substantial increase in the free-to-total PSA ratio. In contrast, patients with prostate carcinoma demonstrated stable or slightly increased total PSA levels and a reduction in the free-to-total PSA ratio. These opposing kinetic patterns suggest that longitudinal biomarker trajectories may provide more meaningful clinical insight than isolated PSA measurements, consistent with prior observations regarding PSA variability and inflammatory contribution (Loeb et al., 2020; Shariat et al., 2022).

Contemporary literature increasingly supports the interpretation of PSA as a dynamic marker influenced by inflammatory processes rather than a cancer-specific biomarker (Nickel et al., 2019; Ferro et al., 2024). Several recent studies have shown that PSA variability may reflect prostatic inflammation, and that short-term PSA reductions after antimicrobial therapy are frequently associated with benign inflammatory conditions (Mari et al., 2023). However, systematic reviews emphasize that PSA decline alone cannot safely exclude malignancy (Buddingh et al., 2017). Our findings align with this perspective, as the pattern of combined PSA and ratio kinetics, rather than PSA reduction in isolation, distinguished inflammatory disease from carcinoma.

The free-to-total PSA ratio remains an established tool for risk stratification in the diagnostic gray zone (Heo et al., 2024), yet inflammatory conditions may alter its behavior (Jung et al., 1998; Stancik et al., 2004). In the present study, ratio increase in prostatitis and ratio decline in carcinoma created a clear separation between groups. This observation reinforces the importance of interpreting PSA derivatives within longitudinal and clinical context rather than as static thresholds.

From a practical standpoint, integration of systemic inflammatory markers such as CRP with PSA kinetics may enhance decision-making in patients with suspected inflammatory contribution. CRP has been investigated as a biomarker reflecting systemic inflammatory burden in prostate disease (Zhou et al., 2023). Serial biomarker assessment under microbiologically guided therapy may provide a structured approach that reduces diagnostic uncertainty prior to biopsy.

Several limitations should be acknowledged. The study was conducted in a single center with a modest sample size. Antibiotic regimens were individualized based on culture results, introducing

treatment heterogeneity. Additionally, the subgroup that declined biopsy was not included in inferential analysis. Larger prospective studies with standardized follow-up protocols are warranted to validate these findings.

6. CONCLUSION

Serial assessment of CRP and PSA parameters across repeated timepoints during culture-guided antibiotic therapy reveals distinct biomarker trajectories in chronic prostatitis compared with prostate carcinoma. Interpretation of PSA kinetics in conjunction with inflammatory markers may support risk stratification and assist clinical decision-making regarding prostate biopsy in selected patients with BPH and suspected inflammatory contribution.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

This research received no external funding.

ETHICAL APPROVAL

This retrospective observational study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Ethics Committee of the General Hospital “Ferid Murad”, Gostivar. Due to the retrospective nature of the study and the use of anonymized clinical data, the requirement for written informed consent was waived by the ethics committee.

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ASSOCIATION OF SCREEN TIME WITH BMI AND ACADEMIC PERFORMANCE AMONG CHILDREN AGED 6-17 YEARS IN TIRANA

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Abstract: Excessive engagement with screen-based devices has emerged as a significant behavioral risk factor in childhood, contributing to sedentary lifestyles and increasing rates of overweight and obesity. Although extensive international research has documented these associations, evidence from Balkan countries remains limited, particularly regarding the combined relationship between screen exposure, body mass index (BMI), and academic performance. The aim of this study was to assess the relationship of daily screen time with BMI status, and academic achievement in schoolchildren aged 6 to 17 years in Tirana, Albania. The research was a descriptive analytical, cross-sectional and observational study conducted in 2025, with 600 pupils selected through a multi-stage probabilistic sampling procedure from public schools. The data collection instrument was a structured questionnaire, designed based on international literature. Variables included socio-demographic characteristics, sleep duration, physical activity, BMI, academic performance, and screen exposure. Screen time was categorized as ≤2 hours/ day and >2 hours per day, while BMI was determined in three categories: underweight, healthy weight, and overweight / obese. Nonparametric tests such as Chi-Square, Mann Whintey U and binary logistic regression were used in the analysis. The level of statistical significance was set at 0.05. Overall, 26.3% of participants reported more than two hours of daily screen exposure. Schoolchildren who spent more than 2 hours/ day on screens were significantly more likely to belong to higher BMI categories. Chi-square analysis demonstrated a significant relationship between daily digital use and BMI categories ($\chi^2 = 23.743$, df = 2, p = 0.000). Watching TV during a meal was significantly related to higher BMI. (χ^2=8.500; p=0.014). Pupils with normal BMI achieved significantly better academic results than their overweight/obese peers (p<0.001). Furthermore, prolonged screen time was independently associated with poorer academic outcomes ($\chi^2 = 35.033$, df = 2, p<0.01). Binary logistic regression indicated that age (OR=1.323; 95%CI: 1.232-1.422; p=0.000) and male gender (OR=2.098; 95%CI: 1.377-3.196; p= 0.000) were associated with higher odds of excessive time spent using a device such as a computer, television, or iPad (>2 hours per day). An increased BMI was a risk factor (OR=1.059; 95%CI: 0.999-1.123; p=0.054). Longer sleep duration (≥9 hours/night) was a protective factor (OR=0.547; 95%CI: 0.352-0.848; p=0.007), and regular physical activity reduced the odds of excessive screen time (OR=1.681 for non-active participants; 95%CI: 1.002-2.818; p=0.049). These results emphasize interrelationship between sedentary behavior, weight status, sleep patterns, and educational attainment. Comprehensive public health strategies aimed at moderating screen exposure and promoting healthier daily routines are warranted to improve both physical health and academic performance among schoolchildren.

Keywords: *Screen time; Body mass index; Academic performance; Childhood obesity; Sedentary behavior*
Field: Medical sciences and Health

1. INTRODUCTION

Over the past two decades, children's lifestyles have undergone profound changes characterized by a substantial increase in sedentary behaviors, particularly screen-based activities. Television viewing time, using smartphones, tablets, computers have progressively replaced active play and outdoor movement in many settings (Tremblay et al., 2011). Accumulated evidences from systematic reviews indicates that prolonged sedentary exposure is consistently related to unfavorable health indicators in pediatric populations (Carson et al., 2016; Stiglic & Viner, 2019).

The growing prevalence of childhood obesity and overweight is closely linked to changes in lifestyle. Globally, shifts toward energy-dense diets and reduced physical activity have contributed to what has been described as a nutritional and behavioral transition (Popkin et al., 2012). Empirical studies

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demonstrate that greater exposure to television and other screen-based media is positively associated with higher BMI in schoolchildren (Hancox et al., 2004; Mitchell et al., 2013). This relationship appears to operate through multiple mechanisms, including reduced energy expenditure, increased snacking during screen viewing, and not being active (Pearson et al., 2014; Sisson et al., 2010).

Sleep patterns represent an additional pathway linking screen exposure and weight status. According to various international studies, long screen time correlates with fewer hours of sleep and less favorable dietary behaviors (Börnhorst et al., 2015). Experimental and epidemiological findings further support the role of insufficient sleep as an independent contributor to weight gain in children and adolescents (Chaput & Tremblay, 2012). In response, integrated movement guidelines recommend limiting recreational screen time while promoting adequate sleep and daily physical activity as complementary components of obesity prevention strategies (Tremblay et al., 2016).

Beyond metabolic and behavioral outcomes, screen time may influence cognitive functioning and school-related performance. Evidence suggests that excessive exposure to digital media is associated with reduced psychological well-being and attention-related difficulties (Stiglic & Viner, 2019). Given the importance of sustained concentration and cognitive engagement for academic success, high levels of recreational screen use may indirectly compromise educational achievement.

At the European level, surveillance data indicate that a substantial proportion of children exceed recommended daily screen limits while failing to reach the appropriate hours of physical activity per day (Whiting et al., 2021; Whiting et al., 2022). Regional monitoring through the WHO COSI initiative continues to document concerning levels of sedentary behavior across participating states (World Health Organization Regional Office for Europe, 2020, 2025). In Albania, recent national reports highlight increasing concerns regarding childhood overweight and lifestyle-related behavioral risks, particularly following the COVID-19 pandemic (UNICEF Albania, 2023, 2025). However, empirical research simultaneously examining screen time, BMI, and academic performance within the Albanian school context remains limited.

Addressing this gap is important for informing targeted public health and educational interventions. The aim of this study was to assess the relationship of daily screen time with BMI status, and academic achievement in schoolchildren aged 6 to 17 years in Tirana, Albania.

2. METHODOLOGY

The research was a descriptive analytical, cross-sectional and observational study conducted in Tirana, Albania, between September and December 2025. The study population was children aged 6 to 17 years in public schools in the city of Tirana. The sample size of the study was 600, selected probabilistically, in multiple stages. Participants with medical conditions affecting growth or physical activity were excluded. A multi-stage probabilistic sampling method ensured representativeness across administrative areas. Public schools were randomly selected, and classes within these schools were randomly chosen. Pupils were proportionally recruited according to class size. The data collection instrument was a structured questionnaire, designed based on international literature. Variables included socio-demographic characteristics, BMI, screen time (television, smartphone, tablet, computer), physical activity, sleep duration, academic performance. Anthropometric measurements were obtained using standardized procedures. Given weight and height data, BMI (kg/m²) was calculated, which was classified into three categories: underweight, healthy weight, and overweight/ obese. Screen time was categorized as ≤2 hours/day and >2 hours per day (Tremblay et al., 2016). Academic performance was assessed using pupils' self-reported grades. Pupils were asked to report their most recent school grades, which were then classified into three categories: very good (9-10), good (7-8.9), and fair/poor (<7). Sleep duration was categorized as <9 and ≥9 hours per night. The statistical package used for data processing and analysis was IBM SPSS Statistics version 27. Descriptive analysis included absolute number and percentages. Nonparametric tests such as Chi-Square, Mann Whintey U were used in the analysis. The level of statistical significance was set at 0.05. Binary logistic regression was used to identify independent predictors of screen time >2 hours per day.

The data collection questionnaire was approved by the Ethics Committee of the University of Medicine, Tirana, within the framework of the third cycle of studies (approval: September 17, 2025; Protocol No. 2002). Before completing the questionnaire in children, parental consent was obtained. All data were anonymized to ensure confidentiality.

3. RESULTS

The analysis presents data for 600 participants. As shown in Table 1, 53.2% were girls and 46.8% were boys. 40.2% were aged 14-17, 32.2% were aged 10-13 and 27.7% were aged 6-9. The majority of children attended schools in urban or semi-urban areas (68.3%). Concerning lifestyle factors, 26.3% of participants reported screen time exceeding 2 hours/day. More than half of the children (51.9%) engaged in 1-2 hours of physical activity daily, while 38.4% reported less than 1 hour/day. Sleep duration was <9 hours/night in 61.2% of participants.

More than half of the participants (58.1%) reported eating meals while watching television. In terms of academic performance, 57.7% achieved very good grades, whereas 8.8% had fair or poor performance.

Regarding BMI status, 53.2% had normal weight, 36.8% were underweight, and 10.0% were overweight or obese. BMI values ranged from 11.9 to 38.3 kg/m², giving a range of 26.4 kg/m². The mean BMI was 20.12 ± 3.73 kg/m², indicating moderate variation in body mass among the participants. The minimum value (11.9 kg/m²) reflects the presence of participants with very low BMI, while the maximum value (38.3 kg/m²) indicates participants with overweight or obesity. The standard deviation of 3.73 kg/m² demonstrates considerable variability in body mass among the study population.

Table 1: Socio-demographics, Lifestyle, Academic, and BMI Characteristics of Participants

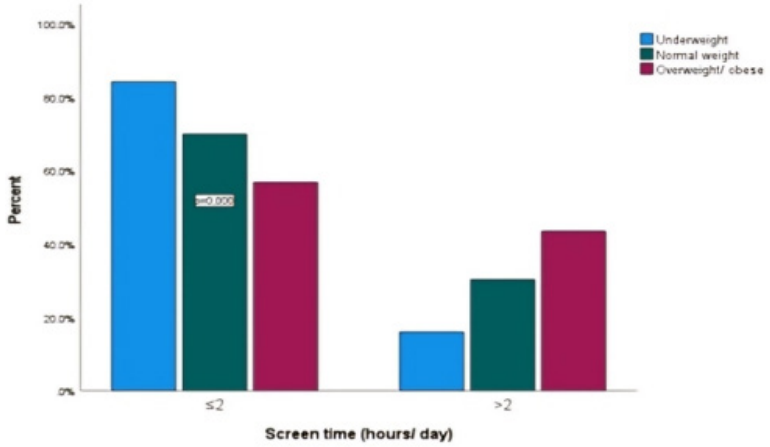
Variable	Category	Absolute number	Percentage (%)
Gender	Boys	281	46.8
	Girls	319	53.2
Age group	6–9 years	166	27.7
	10–13 years	193	32.2
	14–17 years	241	40.2
School location	Urban/Semi-urban	410	68.3
	Rural	190	31.7
	High	127	22.6
Screen time (hours/day)	≤2 hours	441	73.3
	>2 hours	157	26.3
Physical activity (hours/day)	<1 hour	229	38.4
	1–2 hours	310	51.9
	≥3 hours	58	9.7
Sleep duration	<9 hours	366	61.2
	≥9 hours	232	38.8
Eating meals in front of TV	Yes	347	58.1
	No	250	41.9
Academic performance	Very good (9–10)	346	57.7
	Good (7–8.9)	201	33.5
	Fair/Poor (<7)	53	8.8
BMI categories	Underweight	221	36.8
	Normal weight	319	53.2
	Overweight/Obese	60	10.0

*Percentages may not total 100% due to missing data.
Source: Authors' research

Schoolchildren who passed more than 2 hours/ day on screens were more likely to fall into higher BMI categories. Among underweight pupils, 84.1% watched 2 hours or less of TV per day, while only 15.9% exceeded 2 hours ($\chi^2 = 8.500$, df = 2, $p = 0.014$). 30.2% of healthy weight children spent more than 2 hours in front of a screen, this proportion increased to 43.3% among overweight and obese pupils. Chi-square analysis confirmed that this association was statistically significant ($\chi^2 = 23.743$, df = 2, $p < 0.001$), and the linear-by-linear association indicated a significant positive trend. To further examine differences in BMI distribution between groups, a Mann-Whitney U test was conducted comparing students reporting ≤2 hours versus >2 hours of daily screen time. The analysis revealed a significant difference (U = 23,653.50, Z = −5.898, $p < 0.001$), with students exceeding 2 hours of screen exposure showing higher BMI ranks

(Mean Rank = 369.34) compared to those with ≤2 hours (Mean Rank = 274.64). Additionally, eating meals while watching TV was statistically linked to a higher body mass index.

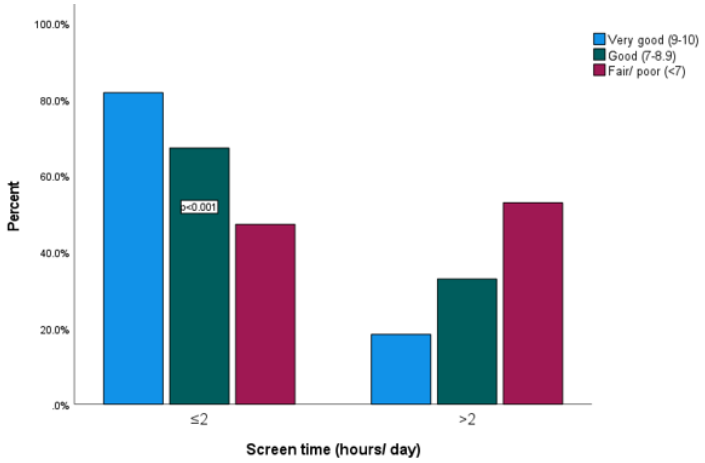
Figure 1: BMI category distribution by daily screen time.



Source: Authors' research, graph obtained from SPSS output

Pupils who passed more than 2 hours/ day on screens showed lower academic performance. Among pupils with high grades (9–10), 81.7% watched 2 hours or less of TV per day, while only 18.3% exceeded 2 hours. In contrast, over half of the students with low grades (<7) reported watching more than 2 hours daily. Chi-square analysis confirmed that this association is statistically significant ($\chi^2 = 35.033$, df = 2, $p < 0.001$), and the linear-by-linear association indicated a significant negative trend, suggesting that increased screen time is linked to reduced academic achievement.

Figure 2: Academic performance distribution by daily screen time.



Source: Authors' research, graph obtained from SPSS output

Using the logistic regression technique, several factors were discovered to be associated with an increased likelihood of spending more than two hours/ day in front of a screen.

Age is significantly linked to excessive screen time (OR=1.323; 95%CI: 1.232-1.422; p=0.000). Every year of age increase the odds of spending more than 2 hours/ day in front of screens by 32.3%.

Gender was a significative predictor (OR=2.098; 95%CI: 1.377-3.196; p<0.001), indicating that boys had approximately two times higher odds of excessive screen time compared to girls.

BMI showed a connection with screen time that was statistically significant (OR=1.059; 95% CI: 0.999-1.123; p=0.054). Although increasing BMI was associated with higher odds of excessive screen time, the confidence interval included 1, suggesting marginal significance.

Sleep duration was inversely associated with excessive screen time (OR=0.547; 95%CI: 0.352-0.848; p=0.007). Children who slept ≥9 hours per night had 45% lower odds of excessive screen time compared to those sleeping <9 hours.

Participants who did not engage in physical activity had 68.1% higher odds of spending more than 2 hours/ day in front of screens compared to those who were physically active (OR = 1.681; 95% CI: 1.002–2.818; p = 0.049), specifies that regular physical activity has a protective effect against excessive time spent using electronic devices such as a computer, television, ipad, etc.

4. DISCUSSION

Findings from this research highlight a significant relationship of screen time with BMI and academic performance to schoolchildren in Tirana. Notable proportion of participants (26.3%) exceeded the recommended screen time of 2 hours/ day, and this excessive exposure was strongly linked to both higher BMI and poorer academic outcomes. Children who belonged to the highest BMI category were more likely to achieve lower grades, whereas pupils with normal BMI generally reported very good academic performance. These results indicate that weight status and screen-related behaviors are closely intertwined with educational achievement.

Excessive screen time appears to influence academic performance through several mechanisms. First, prolonged screen exposure may reduce time available for homework, reading, and cognitively stimulating activities, which can compromise learning outcomes (Stiglic & Viner, 2019). Second, high screen use is often associated with disrupted sleep patterns, as supported by our finding that longer sleep duration (≥9 hours/night) was protective against excessive screen time. Inadequate sleep has been previously linked to impaired attention, memory, and executive function, which are essential for school success (Börnhorst et al., 2015; Chaput & Tremblay, 2012).

Our results also revealed that male pupils and older adolescents were more likely to exceed 2 hours a day in front of the screen. This demographic trend may partly explain observed differences in academic performance, as boys and older pupils with high screen exposure may experience both reduced physical activity and increased sedentary behaviors, contributing to higher BMI and lower grades (Whiting et al., 2022). Furthermore, children who reported eating meals in front of the television were more likely to be overweight / obese, reflecting broader sedentary habits that may indirectly affect school engagement and performance (Carson et al., 2015).

The interplay between BMI and academic performance in this study underscores that obesity is not only a health issue but also an educational concern. Pupils with overweight or obesity had significantly lower academic results, suggesting that interventions targeting healthy weight and lifestyle behaviors could have dual benefits in physical health, educational outcomes (Tremblay et al., 2016; UNICEF Albania, 2023). Promoting regular physical activity, structured mealtimes without screens, and adherence to recommended sleep durations may therefore improve academic performance while mitigating BMI-related risks.

Overall, this study demonstrates that screen time is a modifiable behavioral factor with implications for both BMI and school performance. Public health strategies in the Albanian context should aim to reduce recreational screen use, encourage physical activity, and foster healthy daily routines, particularly among boys and older adolescents, to support optimal cognitive, academic, and physical development (Stiglic & Viner, 2019; Whiting et al., 2021, 2022; UNICEF Albania, 2025).

5. CONCLUSIONS

The study demonstrates that excessive screen time is related to higher BMI and lower academic achievement among pupils in Tirana. Protective factors such as sufficient sleep, regular physical activity highlight of having a healthy daily routine. These findings support targeted public health strategies to improve both physical health and educational outcomes in school-aged populations.

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HYPERCOAGULABILITY AND THROMBOTIC RISK IN BETA-THALASSEMIA: CLINICAL AND LABORATORY INSIGHTS

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Abstract: Beta-thalassemia is increasingly recognized as a multisystem disorder associated with a chronic hypercoagulable state and an elevated risk of thrombotic complications. Beyond ineffective erythropoiesis, chronic anemia, and transfusion-related iron overload, abnormalities in coagulation and vascular function play an important role in long-term morbidity. Accumulating evidence indicates that patients with beta-thalassemia exhibit persistent activation of cellular and plasma components of hemostasis, even in the absence of overt clinical thrombosis. Hypercoagulability in beta-thalassemia is multifactorial, arising from altered red blood cell membrane architecture with phosphatidylserine externalization, chronic platelet activation, endothelial dysfunction driven by hemolysis and nitric oxide depletion, increased circulating procoagulant microparticles and extracellular vesicles, and imbalances in natural anticoagulant pathways. Iron-related oxidative stress and inflammation further amplify vascular activation and thrombin generation. The magnitude and clinical expression of these abnormalities differ substantially across disease phenotypes. Beta-thalassemia trait is generally not associated with clinically significant thrombosis, whereas non-transfusion-dependent thalassemia (NTDT) carries a particularly high thrombotic burden, especially in splenectomized patients. In transfusion-dependent thalassemia (TDT), regular transfusion modifies erythroid-driven procoagulant mechanisms but introduces additional risk modifiers, including iron overload and catheter-related thrombosis. This review summarizes current knowledge on coagulation disturbances and thrombotic complications in beta-thalassemia, integrating pathophysiological mechanisms with clinically relevant laboratory markers. Particular emphasis is placed on global coagulation assays, cellular biomarkers, and phenotype-specific clinical-laboratory patterns, as well as on contemporary monitoring strategies in TDT. A better understanding of these mechanisms is essential for individualized risk stratification and optimization of thrombosis prevention in patients with beta-thalassemia.

Keywords: *Beta-thalassemia, hypercoagulability, thrombotic risk, iron overload*
Field: Medical Sciences and Health

1. INTRODUCTION

Hemostasis represents a balance between procoagulant and anticoagulant mechanisms that maintains vascular integrity. Disruption of this balance may lead to thrombosis, which is a major cause of morbidity and mortality worldwide (Furie et al., 2008). Thrombus formation is a complex process involving platelet activation, thrombin generation, fibrin formation, and changes in the vascular wall (Furie et al., 2008). Beta-thalassemia is an inherited disorder caused by reduced or absent synthesis of β-globin chains, leading to ineffective erythropoiesis, chronic hemolysis, and anemia of varying severity. Advances in transfusion protocols and iron chelation therapy have significantly improved patient survival. As a consequence, long-term complications have become more apparent, including endocrine dysfunction, cardiovascular disease, and thromboembolic events (Cappellini et al., 2015), (Pennell et al., 2005), (Farmakis et al., 2022). In recent years, thrombosis has emerged as an important clinical issue in patients with thalassemia, particularly in those with non–transfusion-dependent thalassemia (NTDT) and in splenectomized patients (Taher et al., 2008), (Eldor et al., 2002), (Cappellini et al., 2012). This review focuses on thrombosis and hypercoagulable state in beta-thalassemia, integrating established pathophysiological mechanisms with clinically relevant laboratory markers. Emphasis is placed on differences between clinical phenotypes and on current monitoring strategies in transfusion-dependent thalassemia (TDT). Particular attention is given to the increasing use of MRI-based assessment of organ iron overload, as well as to dynamic markers of labile plasma iron and oxidative stress (Farmakis et al., 2022), (Kirk et al., 2009), (Pootrakul et al., 2004), (Levi et al., 2018).

Hemostasis encompasses three closely related processes: primary hemostasis, secondary hemostasis (coagulation), and fibrinolysis. Primary hemostasis involves the formation of a platelet plug.

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After vascular injury, platelets adhere to the exposed subendothelium through interactions with von Willebrand factor and collagen. This adhesion leads to platelet activation and aggregation, resulting in the formation of an initial hemostatic plug. Secondary hemostasis stabilizes this plug through activation of the coagulation cascade, which generates thrombin. Thrombin converts fibrinogen into fibrin and further amplifies platelet activation as well as the activation of additional coagulation factors (Furie et al., 2008), (Musallam et al., 2011). Physiological regulation of coagulation is maintained by natural anticoagulant systems, including antithrombin, protein C/protein S pathway, and tissue factor pathway inhibitor, together with a tightly controlled fibrinolytic system. Standard laboratory tests such as prothrombin time (PT/INR) and activated partial thromboplastin time (aPTT) assess isolated components of the coagulation cascade but do not reflect the overall balance between procoagulant and anticoagulant systems. This limitation is particularly relevant in chronic hypercoagulable states, including those associated with thalassemia, where routine tests may appear in the reference range despite an increased thrombotic risk (Eldor et al., 2002), (Singer et al. 2006).

2. THROMBOSIS: MECHANISMS AND CHALLENGES IN LABORATORY ASSESSMENT

Thrombosis is traditionally explained by Virchow's triad, which comprises endothelial injury, abnormal blood flow, and hypercoagulability. These components interact dynamically and their relative contribution varies according to the vascular bed and the underlying clinical context. Venous thrombosis is typically fibrin-rich and is commonly associated with blood stasis, reduced venous flow, and systemic hypercoagulable state. In contrast, arterial thrombosis is predominantly platelet-rich and is usually linked to endothelial disruption, plaque rupture, and conditions of high shear stress, where platelet activation plays a central role (Furie et al., 2008). Laboratory assessment of thrombosis relies on indirect markers of coagulation activation and fibrin turnover. D-dimer is widely used as a marker of fibrin formation and degradation and is particularly useful for excluding acute venous thromboembolism in low-risk settings. However, its specificity is limited in chronic inflammatory conditions, liver disease, pregnancy, and other states associated with increased baseline coagulation activation.

In broader systemic coagulopathies, such as disseminated intravascular coagulation (DIC), diagnostic approaches incorporate composite scoring systems that integrate platelet count, prothrombin time, fibrinogen, and D-dimer or fibrin degradation products. These tools aim to reflect the overall disturbance of hemostasis rather than individual laboratory abnormalities. Expert reviews emphasize that management in such settings is largely supportive and should be tailored to the underlying cause and the patient's bleeding or thrombotic risk (Tripodi et al., 2009). In patients with thalassemia, increasing attention has been directed toward global coagulation assays, such as thrombin generation tests, as well as toward cellular and endothelial biomarkers that may better reflect the prothrombotic milieu of the disease. These approaches are particularly relevant for risk stratification and for understanding phenotype-specific patterns of thrombosis.

3. BETA-THALASSEMIA AND MARKERS OF HYPERCOAGULABILITY

Beyond chronic anemia, beta-thalassemia is increasingly recognized as a systemic disorder with significant vascular and thrombotic complications. The interplay between ineffective erythropoiesis, chronic hemolysis, oxidative stress, and inflammation creates a biological milieu that favours endothelial dysfunction, hypercoagulability, and thrombosis.

Clinically, beta-thalassemia presents with a wide range of phenotypes. Beta-thalassemia minor (trait) is typically associated with mild microcytic anemia, elevated HbA2 levels, and a relatively preserved or increased red blood cell count, and is generally not linked to clinically significant thrombotic risk. At the other end of the spectrum, TDT requires regular lifelong red blood cell transfusions to maintain adequate hemoglobin levels and suppress ineffective erythropoiesis. While transfusion therapy mitigates some disease-related prothrombotic drivers, it introduces additional factors such as iron overload, chronic inflammation, and exposure to central venous catheters, all of which may influence thrombotic risk. NTDT includes intermediate phenotypes characterized by chronic anemia, persistent ineffective erythropoiesis, and intermittent transfusion requirements. This group carries the highest burden of thrombotic complications. Persistent hemolysis, increased intestinal iron absorption driven by hepcidin suppression, and the high prevalence of splenectomy contribute to a vascular risk profile that differs from that observed in TDT patients. Clinical observations consistently demonstrate a higher incidence of both venous and arterial thrombotic events in NTDT, particularly following splenectomy (Taher et al., 2008), (Eldor et al., 2002), (Cappellini et al., 2012).

Hypercoagulability in beta-thalassemia is multifactorial and reflects the interaction of cellular, endothelial, and plasma abnormalities. Accumulating evidence supports the presence of a lifelong prothrombotic state driven by red blood cell membrane damage, chronic platelet activation, endothelial dysfunction, and alterations in natural anticoagulant and fibrinolytic pathways (Eldor et al., 2002)

Red blood cell membrane injury represents a central pathogenic mechanism. Oxidative stress and membrane remodeling lead to externalization of phosphatidylserine (PS) on the erythrocyte surface, providing a catalytic platform for the assembly of coagulation complexes and enhanced thrombin generation (Eldor et al., 2002), (Cappellini et al., 2012). In parallel, chronic hemolysis releases free hemoglobin and heme into the circulation, resulting in nitric oxide scavenging, endothelial dysfunction, and progressive vasculopathy (Taher et al., 2008), (Cappellini et al., 2012). Platelet activation is another consistent feature of beta-thalassemia and is particularly pronounced in splenectomized patients, in whom clearance of activated platelets and circulating cellular fragments is impaired. Associations between platelet activation, pulmonary vascular disease, and hypercoagulability have been reported, supporting a contributory role of platelets in both microvascular and macrovascular complications (Kheansaard et al., 2018). More recently, extracellular vesicles (EVs), including circulating microparticles (MPs) derived from red blood cells, platelets, and endothelial cells, have emerged as important amplifiers of coagulation. Experimental data from β-thalassemia/HbE models indicate that circulating MPs directly promote endothelial dysfunction, supporting a pathophysiological link between EV burden and vascular complications (Klaihmon et al., 2024). In addition, whole-blood viscoelastic assays, such as thromboelastometry, have demonstrated a hypercoagulable profile in splenectomized patients, underscoring the importance of cellular elements that are not captured by conventional platelet-poor plasma assays (Vehapoglu et al, 2014). These observations highlight that thrombotic risk in beta-thalassemia is closely linked to disease pathogenesis and is modulated by clinical phenotype, splenic status, transfusion exposure, and iron burden.

Laboratory assessment of hypercoagulability in beta-thalassemia remains challenging. No single laboratory parameter reliably reflects the overall balance between procoagulant and anticoagulant forces in this condition. Assessment therefore requires a phenotype-oriented approach that combines routine laboratory data with more specialized tests in selected high-risk patient populations. Routine laboratory markers provide indirect but clinically relevant information. Platelet count is often increased, particularly after splenectomy, reflecting both thrombocytosis and heightened platelet activation. Markers of hemolysis, including lactate dehydrogenase and indirect bilirubin, reflect the degree of red blood cell destruction and are closely linked to endothelial dysfunction and nitric oxide depletion. D-dimer levels may be elevated in some patients, but their interpretation is limited by confounding factors including chronic hemolysis, ongoing inflammation, and liver involvement. Global coagulation assays allow for a more integrated evaluation of coagulation potential. Thrombin generation testing reflects the combined contribution of cellular and plasma-based procoagulant mechanisms and has demonstrated increased endogenous thrombin potential in patients with more severe thalassemia phenotypes. Whole-blood viscoelastic assays provide complementary insights and are particularly informative in splenectomized patients, in whom cellular elements play a dominant role in driving hypercoagulability that may not be apparent in platelet-poor plasma based assays (Eldor et al., 2002), (Cappellini et al., 2012), (Vehapoglu et al, 2014). Circulating MPs and other EVs expand the laboratory framework for assessing thrombotic risk. Both experimental and clinical studies in β-thalassemia/HbE have shown that patient-derived microparticles induce endothelial dysfunction, supporting their role not only as biomarkers but also as active mediators to the prothrombotic vascular milieu (Klaihmon et al., 2024).

Available evidence indicates that hypercoagulability in beta-thalassemia is best characterized through a combined assessment of conventional laboratory parameters, global coagulation assays, and cellular biomarkers, interpreted within the appropriate clinical and phenotypic context. Laboratory markers of hypercoagulability exhibit phenotype-specific patterns across the spectrum of β-thalassemia. Conventional coagulation screening tests, including PT and aPTT, are typically within the reference range across all phenotypes (thalassemia minor, NTDT, and TDT), despite well-documented clinical evidence of a prothrombotic state, highlighting their limited sensitivity for detecting chronic hypercoagulability (Al-Sanabra et al., 2025), (Lecut et al., 2015). Exposure of PS on red blood cell (RBC) membranes, reflecting the presence of procoagulant RBCs, is minimal in thalassemia minor, markedly increased in NTDT, and generally moderate in TDT. The higher burden observed in NTDT has been attributed to persistent hemolysis and ineffective erythropoiesis, whereas regular transfusions in TDT partially dilute the population of damaged erythrocytes (Kuypers et al., 2007), (Ibrahim et al., 2014). Markers of platelet activation follow a similar phenotype-dependent gradient. They are usually low in thalassemia minor, significantly increased in NTDT, particularly after splenectomy, and moderate to high in TDT, especially in splenectomized individuals (Cappellini et al., 2012), (Eldor et al., 2002). Splenectomy consistently

emerges as an important modifier, amplifying platelet count, platelet activation, and circulating procoagulant elements. Circulating MPs and EVs, particularly PS-positive microparticles derived from RBCs, platelets, and endothelial cells are increased in both NTDT and TDT compared with minor forms. Levels tend to be especially elevated in splenectomized patients, supporting their contribution to thrombin generation and endothelial dysfunction (Abdel et al., 2022), (Ammar et al., 2014), (Kheansaardet al., 2018). Global coagulation assays provide a more integrated evaluation of thrombotic potential. Thrombin generation testing often demonstrates increased endogenous thrombin potential in NTDT and in high-risk TDT subsets, while whole-blood viscoelastic assays may reveal enhanced clot strength in splenectomized patients (Tripodi et al., 2009). In contrast, signal intensity is usually low or unremarkable in thalassemia minor. Natural anticoagulant (protein C, protein S, and antithrombin) are generally preserved in minor forms but may be reduced in NTDT and TDT. These reductions are often context-dependent and influenced by liver dysfunction, chronic hemolysis, or splenectomy (Ahmadi et al., 2024), (Ali et al., 2024)

Interpretation of thrombotic risk in thalassemia must be phenotype-specific, as hypercoagulability is not a single measurable abnormality but rather the result of interacting cellular, vascular, and treatment-related factors. In beta-thalassemia minor, a consistent laboratory pattern suggestive of hypercoagulability is generally lacking, and clinically relevant thrombotic events are uncommon. Laboratory evaluation in this setting is therefore primarily diagnostic rather than prognostic. In contrast, NTDT is associated with a clearly increased prothrombotic tendency. Clinical studies and large reviews consistently report a higher incidence of thromboembolic events in NTDT, particularly in splenectomized patients. As a result, NTDT represents a clinical setting in which closer surveillance, individualized risk assessment, and consideration of thromboprophylaxis in selected high-risk situations are warranted (Taher et al., 2008), (Eldor et al., 2002), (Cappellini et al., 2012), (Tanno et al., 2007).

In TDT, regular transfusions suppress ineffective erythropoiesis and reduce the proportion of abnormal endogenous red blood cells, potentially mitigating some red cell-driven procoagulant mechanisms. However, this benefit is counterbalanced by a distinct set of modifiers, including transfusional iron overload, chronic low-grade inflammation, and an increased risk of catheter-related thrombosis. Current management increasingly relies on MRI-based quantification of organ iron burden. In particular, cardiac T2* imaging has emerged as a robust predictor of cardiac complications, outperforming serum ferritin and liver iron concentration in stratifying myocardial risk (Kirk et al., 2009), (Levi et al., 2018), (Cappellini et al., 2020). In addition, dynamic iron parameters such as labile plasma iron (LPI) provide insight into short-term chelation effectiveness and exposure to redox-active iron, with potential implications for endothelial dysfunction and hypercoagulability (Pootrakul et al., 2004).

4. MANAGEMENT OF THROMBOSIS IN BETA-THALASSEMIA

Thrombotic complications in beta-thalassemia include venous thromboembolism, such as deep vein thrombosis and pulmonary embolism, as well as cerebrovascular events and pulmonary vascular disease. The clinical presentation and overall thrombotic risk are influenced by several modifiers, including splenectomy, thrombocytosis, severity of hemolysis, transfusion exposure, and the presence of additional acquired risk factors (Eldor et al., 2002), (Cappellini et al., 2012), (Kheansaard et al., 2018). Splenectomy represents one of the most important risk modifiers. Its prothrombotic effect is thought to be mediated by persistent platelet activation, increased levels of circulating MPs and EVs, and alterations in whole-blood rheology. Data from whole-blood viscoelastic testing support the concept that cellular components play a central role in driving hypercoagulability after splenectomy, a phenomenon that is not adequately captured by conventional plasma-based assays (Vehapoglu et al., 2014).

Management of thrombosis in beta-thalassemia should be individualized and based on overall risk assessment. Routine long-term anticoagulation is not universally recommended. However, risk-adapted thromboprophylaxis may be appropriate in selected high-risk situations, including the perioperative period, pregnancy, prolonged immobilization, prior thrombotic events, and the presence of central venous catheters. Decisions regarding anticoagulation should carefully balance thrombotic risk against bleeding risk and consider disease phenotype and comorbidities. In TDT, contemporary management increasingly emphasizes systematic monitoring of iron-related toxicity. Current guideline-based approaches, including those outlined by the Thalassaemia International Federation, recommend defined transfusion targets, individualized chelation strategies, and regular organ surveillance, with particular emphasis on MRI-based assessment of iron burden (Farmakis et al., 2022). Optimized iron control may have indirect but clinically relevant effects on vascular function and thrombotic risk.

Disease-modifying therapies in beta-thalassemia have the potential to influence hypercoagulability indirectly by reducing ineffective erythropoiesis, hemolysis, and transfusion requirements. In a phase

3 clinical trial, luspatercept significantly reduced transfusion burden in patients with TDT (Cappellini et al., 2020). By improving erythroid maturation and reducing red blood cell turnover, such therapies may alter key upstream drivers of the prothrombotic state over time. Advances in the understanding of iron regulation have also highlighted the importance of the erythropoiesis–hepcidin axis. Experimental models have demonstrated that erythroferrone contributes to hepcidin suppression and iron overload in beta-thalassemia, while elevated levels of growth differentiation factor 15 (GDF15) have been shown to further inhibit hepcidin expression (Kautz et al., 2015), (Tanno et al., 2007). These pathways are being recognized as potential therapeutic targets, with possible downstream implications for oxidative stress, endothelial dysfunction and hypercoagulability.

Despite these advances, data specifically addressing thrombosis-related outcomes and longitudinal changes in coagulation biomarkers remain scarce. Further prospective studies are warranted to determine how emerging therapies affect thrombotic risk and whether laboratory markers of hypercoagulability parallel clinical improvement.

5. CONCLUSIONS

Beta-thalassemia is a systemic disorder in which disturbances of coagulation and vascular biology contribute substantially to long-term morbidity. Hypercoagulability results from the interplay of procoagulant red blood cell surfaces, chronic platelet activation, endothelial dysfunction, circulating MPs and EVs, and context-dependent alterations in natural anticoagulant pathways. Differences in clinical presentation and laboratory profiles across beta-thalassemia minor, NTDT, and TDT support a phenotype-adapted approach to thrombosis risk assessment. In modern care, particularly for transfusion-dependent patients, MRI-based quantification of organ iron burden and monitoring of dynamic iron species such as labile plasma iron are increasingly integrated into routine practice and may have important implications for vascular risk and hypercoagulability. A deeper understanding of disease-specific mechanisms, integrated with individualized clinical and laboratory assessment, is essential for optimizing thrombosis prevention and management in β-thalassemia.

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THE EVOLUTION OF GOOD CLINICAL PRACTICE: A COMPARATIVE REVIEW OF ICH GCP E6 (R2) AND E6 (R3)

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Abstract: Good Clinical Practice (GCP) provides the ethical and scientific foundation for conducting clinical trials and safeguarding participant welfare. The transition from ICH GCP E6 (R2) to E6 (R3) represents a significant evolution in response to increasingly complex study designs, digital technologies, and decentralized trial models. These developments require regulatory guidance that remains robust while allowing sufficient flexibility to support innovation. In addition, the globalization of clinical research and the growing involvement of multiple stakeholders have further emphasized the need for harmonized yet adaptable regulatory standards. The aim of this review is to compare ICH GCP E6 (R2) and E6 (R3) and evaluate the practical impact of the updated framework on investigators, sponsors, and other research stakeholders. Specific attention was given to how the revised guidance supports operational efficiency without compromising ethical safeguards or scientific validity. A structured qualitative analysis of both versions was conducted. Key aspects examined included trial design, quality management, data governance, investigator and sponsor responsibilities, monitoring strategies, and participant protection. The review focused on identifying major conceptual shifts and evaluating their significance for contemporary clinical research practice. The analysis demonstrates that ICH GCP E6 (R3) adopts a principle-based, risk-proportionate approach, moving beyond the more prescriptive structure of R2. It prioritizes the identification and management of factors critical to participant safety and data integrity, encouraging sponsors and investigators to tailor processes according to study-specific risks. This approach supports innovative methodologies, including decentralized and hybrid trials, facilitates the integration of digital health technologies, and promotes proactive quality management systems embedded throughout the trial lifecycle rather than relying primarily on retrospective corrective actions. For example, in multicenter oncology trials, monitoring activities may focus on critical safety endpoints and high-risk procedures rather than exhaustive source data verification. Such targeted oversight reduces administrative burden while maintaining scientific rigor and regulatory compliance. Furthermore, R3 provides clearer expectations regarding the validation and oversight of digital systems, the management of diverse data sources, and the maintenance of continuous ethical oversight throughout the trial lifecycle. Overall, ICH GCP E6 (R3) aligns regulatory standards with contemporary clinical research realities, enhancing efficiency, flexibility, and sustained participant protection while advancing innovation in global clinical development

Keywords: *ICH-GCP, clinical trials, participant safety, risk-based monitoring*
Field: Medical Sciences and Health

1. INTRODUCTION

The International Council for Harmonization (ICH) guideline for Good Clinical Practice (GCP) is a globally recognized standard for the design, conduct, recording, and reporting of clinical trials involving human participants, ensuring participant safety, well-being, and data integrity.[1] First introduced over two decades ago, the guideline underwent its second major revision, E6(R2), in 2016.[2]

Since then, the clinical research landscape has evolved considerably. The growing adoption of decentralized and hybrid trial models, patient-centered approaches, and digital health technologies (DHTs) has reshaped traditional trial conduct. These developments have exposed certain operational and structural limitations of E6(R2), particularly in addressing technological innovation and enabling risk-proportionate oversight across diverse trial settings.

The European Medicines Agency (EMA) announced the effective date of ICH GCP E6(R3) as 23 July 2025, marking a shorter revision interval compared with the previous update.[3,4] The transition from E6(R2) to E6(R3) reflects a broader shift toward a principles-based, flexible regulatory framework while maintaining established standards for participant protection and data integrity.

This review compares the key components of ICH GCP E6(R2) and E6(R3), highlighting conceptual and structural changes and evaluating their implications for investigators, sponsors, and other stakeholders within the clinical research ecosystem. Specifically, it aims to: (1) analyze the major differences between E6(R2) and E6(R3) in trial design, quality management, monitoring, and data governance; (2) assess how the updated guidance facilitates innovative methodologies while preserving ethical and scientific standards; and (3) examine the operational impact of E6(R3) adoption on contemporary clinical trial conduct.

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2. MATERIALS AND METHODS

A structured comparative qualitative analysis of the ICH Good Clinical Practice (GCP) guidelines E6(R2) and E6(R3) was conducted. The full texts of both versions were reviewed in detail, focusing on investigator and sponsor responsibilities, trial design and execution, quality management systems, data governance, monitoring approaches, and participant protection. The principal differences between the two guidelines were identified and analyzed.

The review examined significant structural and conceptual changes, emphasizing how E6(R3) transitions from a prescriptive framework to a principles-based, risk-proportionate approach. The potential impact of these changes across the trial lifecycle, from planning to reporting, was explored. Special attention was given to elements relevant to contemporary clinical research, including decentralized and hybrid trial models, the adoption of digital technologies, and risk-based monitoring strategies.

Beyond listing differences, the analysis interpreted the practical implications of these changes for trial operations. To illustrate real-world relevance, examples from recent multicenter oncology trials were used to demonstrate the application of E6(R3) principles in practice. [5,6] This approach provides a structured, practice-oriented assessment of the evolution from E6(R2) to E6(R3) and its implications for modern clinical research across disciplines.

3. RESULTS

The findings highlight major changes from E6(R2) to E6(R3), including developments in risk management, monitoring strategies, and ethical oversight, reflecting a broader evolution in how Good Clinical Practice is conceptualized and implemented.

Principle-Based Approach: E6(R3) adopts a flexible, risk-proportionate framework, allowing trial processes to be tailored to study-specific risks. Rather than prescribing a fixed set of procedures for all trials, the guideline emphasizes prioritizing factors critical to participant safety, data integrity, and scientific validity, and designing trial processes accordingly. [7]

Risk-Based Monitoring: While E6(R2) introduced risk-based monitoring, E6(R3) expands this into an integrated risk-based quality management (RBQM) approach. Monitoring focuses on the most critical aspects of a study, embedding quality proactively throughout trial design and conduct. Key trial activities, including monitoring and data management, are recognized as essential quality control functions. This approach enables trial teams to allocate resources strategically while maintaining high standards for participant safety and data integrity. [5] Under E6(R3), monitoring strategies prioritize critical safety endpoints and high-risk procedures rather than exhaustive source data verification, reducing administrative burden without compromising study quality. [7]

Digital and Decentralized Trials: ICH GCP E6(R3) explicitly acknowledges the growing role of decentralized and hybrid clinical trial models. It recognizes that trial-related activities may occur outside traditional investigative sites, including participants' homes or local healthcare facilities. This reflects the integration of telemedicine, electronic informed consent (eConsent), wearable sensors, and remote data capture platforms into contemporary clinical research. Data originating from multiple digital sources must remain traceable, attributable, contemporaneous, original, and accurate (ALCOA principles), with clear documentation of data flows and system interfaces.

Examples from oncology trials demonstrate that decentralized studies may incorporate remote symptom monitoring through wearable devices while limiting on-site visits to critical assessments such as imaging or complex procedures. Monitoring efforts can thus focus on high-risk data streams and key safety endpoints rather than uniformly verifying all remotely collected data. This risk-proportionate approach reduces logistical burden while preserving scientific rigor. [8]

Ethical Oversight: Whereas E6(R2) emphasized ethics committee approval at study initiation and during major protocol amendments, E6(R3) promotes continuous ethical oversight integrated within quality management systems.[9] Ethical responsibilities are treated as ongoing commitments, systematically incorporated into risk assessment, monitoring strategies, and data governance. The guideline further requires that technological tools enhance, rather than compromise, participant comprehension, confidentiality, and data protection. The framework underscores the need to protect vulnerable populations, safeguard privacy in the context of increasingly large and diverse datasets and maintain transparent communication with participants. Through continuous safety evaluation and adaptive mitigation strategies, E6(R3) shifts from reactive corrective action toward proactive, risk-informed participant protection.

4. DISCUSSIONS

The transition from ICH GCP E6(R2) to E6(R3) represents a conceptual evolution rather than a purely structural revision. While R2 reinforced quality management and introduced risk-based monitoring, it remained largely procedural. In contrast, R3 establishes a principle-driven framework emphasizing critical-to-quality factors, proportionality, and integrated quality across the trial lifecycle.

By prioritizing participant safety and data integrity over standardized procedures, R3 facilitates decentralized trials, adaptive designs, and the use of digital data systems. This approach is particularly valuable in oncology and rare disease research, where remote participation can improve patient access, recruitment, and retention.

For sponsors, R3 requires a cultural shift toward proactive risk identification and integrated quality systems. Quality considerations must be embedded during protocol design, moving beyond a retrospective audit mindset. Investigators may benefit from reduced administrative burden through targeted monitoring, allowing greater focus on clinical oversight and participant care. At the same time, they must actively engage in risk assessment and ensure appropriate supervision of delegated activities, particularly in decentralized settings.

The effectiveness of R3 ultimately depends on meaningful implementation. Organizations that integrate risk-based thinking and cultivate a strong quality culture are more likely to achieve operational efficiency without compromising ethical or scientific standards. By translating principles into practice, E6(R3) provides a flexible yet rigorous framework capable of supporting innovation in trial design and execution.

5. CONCLUSIONS

ICH GCP E6(R3) introduces an updated paradigm for the conduct of clinical trials. While it does not fundamentally alter the structural framework established in E6(R2), it represents a clear shift from a prescriptive model toward a principles-based, risk-proportionate approach aligned with contemporary clinical research practices.

By integrating quality management systems, prioritizing critical-to-quality factors, and supporting decentralized and digitally enabled methodologies, E6(R3) enhances operational flexibility while maintaining rigorous standards for participant safety, welfare, and data integrity. Ethical oversight and robust data governance are further strengthened within this framework.

When effectively implemented, E6(R3) has the potential to improve operational efficiency, foster innovation, and sustain high standards of participant protection in global clinical development.

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FOREIGN BODY INGESTION IN CHILDREN - AN EMERGENCY CONDITION REQUIRING IMMEDIATE EVALUATION

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Abstract: Accidental foreign body ingestion is common in pediatric practice. Young children, especially those under five years, tend to put different kinds of small objects from their environment into their mouths. Sometimes due to the still immature reflexes, they are unintentionally swallowed. Most often these are coins, followed by magnets, button batteries, toys or jewelry, but also many others. Luckily, in most cases, these foreign bodies pass through the gastrointestinal tract without causing any symptoms or injuries. Some of them don't even get noticed or registered. However, it is estimated that in 10 to 20 percent of the cases there is a need for medical intervention.

A critical condition is lodgment in the esophagus because it requires extraction as soon as possible. Most often it occurs in its upper third. At this location the object is able to cause serious clinical discomfort, requiring rapid approach. Even dyspnea by compressing the trachea is possible. Injuries of the tissues, particularly after delayed diagnosis and treatment, might be a further dangerous consequence. Especially lodged button batteries cause critical damage of the esophageal wall in a very short time due to an electrolysis reaction on the site of the negative pole. This generates an alkali burn that might lead to life-threatening complications as perforation, fistulas to the trachea or to major blood vessels. Lethal outcomes are reported. Studies have demonstrated the development of significant injuries even only two hours of impaction. This emphasizes the importance of initiation of the extraction immediately.

Thus, in spite of the overall good prognosis clinicians have to be extremely alert when confronted with a child after foreign body ingestion. Immediate and profoundly evaluation is necessary in order to detect or exclude lodgment in esophagus- a condition requiring quick intervention. Especially when button batteries are involved time is crucial in order to prevent devastating complications.

Keywords: *children, foreign body, ingestion, button battery*
Field: Medical Science and Health

1. INTRODUCTION

The ingestion of foreign bodies in children has the potential of generating critical clinical symptoms and injuries. There are numerous reports of life- threatening conditions and devastating complications. This article aims to sensitize clinicians about the possible risks of this circumstance and to emphasize the importance of rapid evaluation, diagnostics and therapy if indicated.

2. REVIEW

Accidental foreign body ingestion is a common event in the pediatric practice, especially among children younger than 6 years (Manfredi et al., 2025). The most frequently ingested objects are coins (Kramer et al., 2015; Little et al., 2006; Panieri & Bass, 1995), followed by other items such as magnets, button batteries, but also toy parts, jewelry and food particles (Arana, Hauser, Hachimi-Idrissi, & Vandenplas, 2001; Little et al., 2006). It is estimated that 80-90% of the ingested foreign bodies pass uneventfully through the gastrointestinal tract (Gurevich, Sahn, & Weinstein, 2018). However, under certain circumstances, lodgment in the esophagus occurs representing a hazardous condition.

The esophagus has three anatomical constrictions- the upper one at cricopharyngeal level, middle at level of the thoracic aorta and the distal or diaphragm. In the majority of these cases the object can be identified in the upper third of the esophagus, where the narrowest part- the upper esophageal sphincter- is sited (Lin et al., 2007; Little et al., 2006; Russell et al., 2014; Shaffer et al., 2020; Shivakumar, Naik, Prashanth, Yogesh, & Hongal, 2004). At this location a foreign body usually causes clinical impairment, such as dysphagia, pain, swallowing difficulties, drooling and vomiting, that can lead to serious feeding and drinking problems (Lin et al., 2007; Panieri & Bass, 1995). Even a laryngotracheal compression is possible, resulting in respiratory distress and stridor (Kay & Wyllie, 2005). In these cases, immediate

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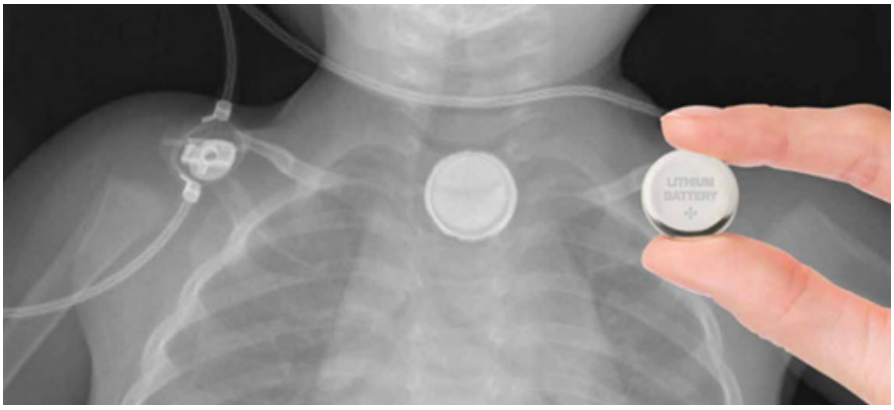
removal is required. However, even in an asymptomatic child, an esophageal lodged object should be extracted within 24 hours, as the risk of injuries to the esophageal wall and adjacent tissues, even when blunt objects ingested, increases with the length of the lodgment duration (Gurevich et al., 2018; Tringali et al., 2017).

In spite of a lower incidence compared to coins, the ingestion of button batteries is a particularly dangerous emergency, especially when larger 20-mm, higher voltage 3V Lithium coin cells are involved, as they are more likely to get lodged in the esophagus and cause severe damage (Jatana et al., 2013; Shaffer et al., 2020). The contact with the mucosa generates an electrical current, resulting in electrolysis reaction with release of hydroxide radicals at the site of the negative pol of the battery and thus causing a severe alkaline caustic injury to the esophageal wall (Völker et al., 2017). Serious tissue injury can be observed in only 2 hours of exposure (Litovitz, Whitaker, & Clark, 2010; Manfredi et al., 2025; Sutherland & Bowen, 2023; Völker et al., 2017) and may potentially progress into critical complications as esophageal perforation, strictures, tracheoesophageal fistulas and vocal cord paralysis (Shaffer et al., 2020) (Duan et al., 2020) (Leinwand, Brumbaugh, & Kramer, 2016) (Krom et al., 2018; Philteos et al., 2022). Another devastating consequence reported is fistulation into major blood vessels as aorta, subclavian artery and thyroid artery, leading usually to a fatal outcome due to exsanguination (Akinkugbe et al., 2022; Leinwand et al., 2016; Pae, Habte, McCloskey, & Schwartz, 2012; Ventura et al., 2017). Retrospective data from the US demonstrated an alarming trend of increasing morbidity and mortality, followed by button battery ingestions in the past 30 years, especially among children younger than 4 years, which paralleled the expanding use in households of larger, higher voltage lithium batteries (Litovitz, Whitaker, Clark, White, & Marsolek, 2010; Sharpe, Rochette, & Smith, 2012). The extent of the tissue damage is mainly dependent on the length of the contact time (Hoagland, Ing, Jatana, Jacobs, & Chatterjee, 2020), so the crucial role of immediate extraction has been clearly emphasized in the literature (Litovitz, Whitaker, Clark, et al., 2010). Considering this, national and international guidelines recommend an emergent (<2 hours) removal of all esophageal impacted button batteries (Eich C, 2016; Guideline, 2018; Kramer et al., 2015; Tringali et al., 2017).

Fig. 1 X- Ray image of neck and thorax of a child. A button battery lodged in esophagus with characteristical double ring or halo sign



Source: https://kidsafesa.com.au

Performing an X-ray image of neck, chest and abdomen is a standard procedure for diagnosis and location of radio-opaque foreign bodies. Furthermore, it might enable distinguishing between coin and button battery. Identification of a double ring at the edge or halo sign is characteristic for a button battery. Flexible or rigid endoscopy is another procedure not only for diagnostic purpose, but also for extraction. Moreover, it enables assessing the extent of damage of the esophageal wall and exploration for further complications as perforations for example. In case of severe damages, long impaction time or persisting symptoms a CT or MR scan might be sensible in order to detect injuries beyond esophageal wall (Mubarak et al., 2021). As alternative therapeutic tool for the extraction from the upper esophagus the use of Magill forceps and (video-)laryngoscope for visualization might be considered (Eich C, 2016).

Another important issue in the case of esophageal impacted button batteries are the strategies for mitigation of the injury prior extraction. Honey is considered to be protective due to coating of the battery and thus limiting the electrolysis reaction. However, it is contraindicated in children under 12 months of age because of botulism risk. Another substance is sucralfate, a weak acid, that is supposed to neutralize the hydroxide in tissue und thus limit the injury severity. The proposed dose of The European

Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) are 2 teaspoons every 10 minutes up to 6 times for honey and up to 3 times for sucralfate. Clinicians should be aware of these strategies that might improve outcome, however they do not justify delay of extraction procedure. Another essential contraindication for both substances is impaction time of more than 12 hours, as perforation of the esophageal wall might have already occurred (Mubarak et al., 2021; Sethia et al., 2021).

3. CONCLUSION

In spite of its overall good prognosis, foreign body ingestion in children is an emergency condition requiring an immediate and profound evaluation, in order to recognize the patients requiring urgent therapy. Lodgment of an object in the esophagus is a critical situation. It may cause serious clinical impairment and significant tissue damage. Especially button batteries have a great potential to generate devastating injuries in a short time leading to life threatening complications or even a fatal outcome. Thus, clinicians involved in pediatric care should be alert about the risk that ingested objects represent and be familiar with their management.

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PRONATED AND FLAT FEET: DISTINCT ENTITIES OR OVERLAPPING CONDITIONS

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Abstract: The terms pronated foot and flat foot are often used interchangeably in clinical practice, despite representing distinct biomechanical and morphological conditions. In many respects, the two conditions present with analogous clinical manifestations and may elicit similar symptomatology; however, their underlying genesis differs. Accurate differentiation between these conditions requires not only advanced expertise in biomechanics and the anatomy of the ankle–foot complex, but also comprehensive knowledge of the distinct stages of foot development from a podiatric perspective.

Misinterpretation of these entities may lead to inappropriate therapeutic strategies and suboptimal clinical outcomes, particularly in pediatric and physically active populations.

The purpose of this article is to clarify the differences between pronated foot posture and flat foot deformity, with emphasis on structural characteristics, functional behavior, and clinical relevance. The paper reviews current concepts of foot biomechanics and presents commonly used plantographic assessment methods, including Clarke's angle and footprint-based indices, to illustrate diagnostic distinctions.

Special attention is given to the clinical applicability and limitations of these assessment tools in routine physiotherapy practice.

Understanding the difference between dynamic pronation and structural flattening of the medial longitudinal arch is essential for accurate diagnosis, appropriate treatment planning, and prevention of misclassification. Clear differentiation between these conditions may improve clinical decision-making in physiotherapy and related disciplines.

Keywords: pronated foot, flat foot, physiotherapy, orthotic treatments
Field: Medical Sciences and Health

1. INTRODUCTION

In clinical practice, the terms "pronated foot" and "flat foot" are often used interchangeably, although they represent different biomechanical conditions. Excessive pronation is characterized by increased calcaneal eversion, forefoot abduction, and reduction of the medial longitudinal arch under load (Redmond et al., 2006). In most cases, it is functional in nature and associated with muscular imbalance and impaired control of the tibialis posterior and intrinsic foot musculature (Murley et al., 2009; Fraser et al., 2022).

Flat foot (pes planus), whether congenital or acquired, involves structural collapse of the medial longitudinal arch, frequently accompanied by ligamentous insufficiency and osseous adaptations (Dombek et al., 2020).

Failure to clearly differentiate these conditions may lead to inappropriate therapeutic goals and suboptimal physiotherapeutic intervention.

The aim of the present study was to compare the corrective potential of pronated and flat feet under an identical Physiotherapeutic and orthotic protocol.

2. MATERIALS AND METHODS

The study was conducted at the National Sports Academy "Vasil Levski" between September 2024 and November 2025.

Participants

Sixteen individuals aged 19–22 years were divided into:

- Pronated feet (n = 8)
- Flat feet (n = 8)

Participants with prior surgical interventions or neurological disorders were excluded.

Assessment Methods

For the definition of the pathologies and the monitoring of outcomes, we used some of the most well-established and validated methods for assessing foot condition.

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- Foot Posture Index (FPI-6) (Redmond et al., 2006)
- Navicular Drop Test (Brody, 1982)
- 3D sensor-based plantography (Multireha system)

Classification:
- FPI +6 to +9 → Pronated foot
- FPI ≥ +10 → Flat foot

Intervention

Both groups received identical intervention:
- Analytical strengthening of tibialis posterior, tibialis anterior, triceps surae
- Short-foot technique (Hashimoto et al., 2023)
- Intrinsic muscle strengthening (Fraser et al., 2022)
- Proprioceptive training
- Corrective insoles with medial arch support

Frequency: 3 times weekly
Statistical analysis: Paired t-test and Mann–Whitney U test
Significance level: $p < 0.05$

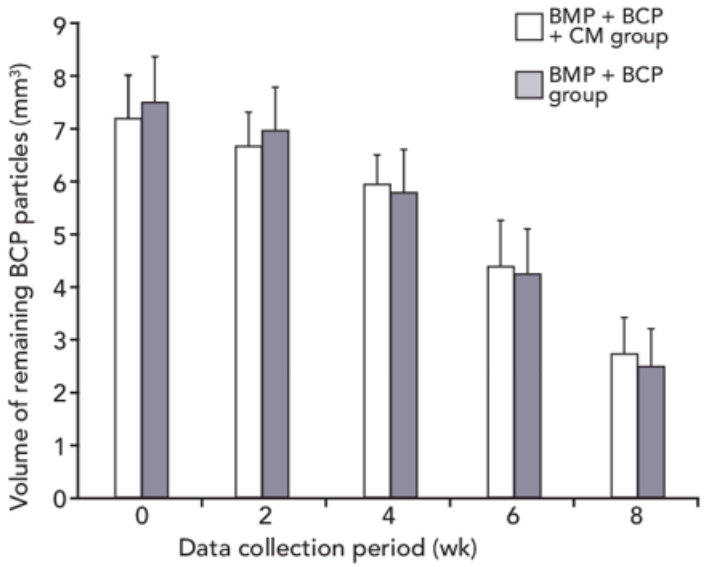
3. RESULTS

The results obtained from the different tests indicate that correction can be achieved more easily in patients with pronated feet compared to those with flat feet.

Results from the FPI-6 test demonstrate a statistically significant improvement in the pronated group.

Pronated: 8.3 ± 0.8 → 4.6 ± 1.1 (p=0.012*)
Flat: 11.4 ± 0.9 → 9.8 ± 1.2 (p=0.087)
A statistically significant reduction was observed in the pronated group only.

Figure 1. FPI-6 values (mean ± sd) before and after intervention



Source: Author's research

The results of the Navicular Drop Test also show a significant change in individuals with pronated feet.

Pronated: 9.6 ± 1.2 → 6.1 ± 1.4 (p=0.018*)
Flat: 13.2 ± 1.5 → 11.9 ± 1.6 (p=0.094)
Between-group difference in corrective potential was significant (p=0.032).

Table 1. Navicular drop (mm) before and after intervention

Parameter	Pronated	Flat	Between-group p
FPI change	−3.7	−1.6	0.032*
Navicular drop change	−3.5 mm	−1.3 mm	0.032*
% correction	65%	33%	—

Source: Author's research

Data from the plantographic assessments indicate improvement in 65% of the participants with pronated feet and a 33% correction rate in patients with flat feet.

Percentage correction toward neutral position:

- Pronated feet – 65%
- Flat feet – 33%

3D plantographic analysis demonstrated dynamic medial collapse in the pronated group and structural arch reduction in the flat foot group

4. DISCUSSION

The findings demonstrate a clear difference in adaptive potential between functional pronation and structural pes planus.

The reduction of FPI from 8.3 to 4.6 in the pronated group indicates preserved structural integrity and neuromuscular responsiveness. Improvement is likely associated with enhanced tibialis posterior activation and intrinsic muscle engagement (Kulig et al., 2004; Fraser et al., 2022).

In contrast, limited improvement in the flat foot group supports the hypothesis of structural restriction (Dombek et al., 2020). Observed changes likely reflect functional compensation rather than structural remodeling.

These results reinforce the distinction between functional pronation and structural pes planus.

Clinically, pronation should not automatically be considered pathological.

5. CONCLUSION

Pronated feet demonstrate significantly greater corrective potential (65%) compared to flat feet (33%) under identical therapeutic intervention.

Pronation represents predominantly a functional deviation, whereas flat foot constitutes structural pathology with limited reversibility.

Accurate differentiation is essential for effective physiotherapeutic planning.

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