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У знак сећања на нашег драгог пријатеља и колегу
г. Синишу Марковића

Постоје људи чије се присуство не мери временом, већ трагом који остављају за собом. Наш драги Силе био је управо таква личност — човек који није припадао само једном времену, већ је својим радом постао један од његових темеља.
Као један од кључних стубова овог удружења, својом визијом, енергијом и непоколебљивом вером у заједништво, успео је да повеже оно што је често деловало неповезиво — људе, идеје и народе широм Балкана. Захваљујући њему, наше удружење никада није било само организација, већ жив простор сусрета, сарадње и пријатељства.
Силе — како смо га сви од миља звали — није био само колега и пријатељ, већ човек изузетне ширине, достојанства и човечности. Његов углед простирао се далеко изван граница — међу здравственим радницима од Казахстана до Словеније, где је био препознат као симбол знања, поверења и искрености.
Оно што га је издвајало није била само професионална стручност, већ начин на који је приступао људима и животу. Знао је да споји одговорност са топлином, рад са радошћу и професију са истинском хуманошћу. Кроз свој организациони рад, али и у свакодневним сусретима, показивао је како се гради заједница — тихо, стрпљиво, али трајно.
Његов одлазак није крај, јер дело које је оставио иза себе наставља да живи у свима нама. У свакој сарадњи, у сваком сусрету, у сваком кораку који правимо напред, остаје нит коју је он исплео.
Зато је Силе више од сећања. Он остаје одговорност, инспирација и путоказ — да чувамо вредности по којима је живео и наставимо путем који је пред нас поставио.

Заувек у нашим сећањима,
заувек у делу које нас повезује.

Од свих чланова BMDA



In Memory of Our Dear Friend and Colleague
Mr. Sinisa Markovic

There are people whose presence is not measured by time, but by the mark they leave behind. Our dear Sile was exactly such a person — a man who did not belong to just one era, but who, through his work, became one of its foundations.

As one of the key pillars of this association, with his vision, energy, and unwavering belief in unity, he succeeded in connecting what often seemed impossible to connect — people, ideas, and nations across the Balkans. Thanks to him, our association was never merely an organization, but a living space of encounters, cooperation, and friendship.

Sile — as we all affectionately called him — was not only a colleague and friend, but a man of exceptional breadth, dignity, and humanity. His reputation extended far beyond borders — among healthcare professionals from Kazakhstan to Slovenia, where he was recognized as a symbol of knowledge, trust, and sincerity.

What distinguished him was not only his professional expertise, but the way he approached people and life itself. He knew how to unite responsibility with warmth, work with joy, and profession with genuine humanity. Through his organizational work, as well as in everyday encounters, he showed how a community is built — quietly, patiently, yet enduringly.

His passing is not an end, because the legacy he left behind continues to live within all of us. In every collaboration, every meeting, and every step we take forward, there remains a thread that he himself wove.

That is why Sile is more than a memory. He remains a responsibility, an inspiration, and a guiding light — reminding us to preserve the values by which he lived and to continue along the path he set before us.

Forever in our memories,
forever in the work that unites us.

From all members of BMDA

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Global Burden of Human Papillomavirus (HPV) Infection and HPV-Associated Diseases

Dimitrov Goran, Micevska Megi

University Clinic for Gynecology and Obstetrics, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia

Abstract

Human papillomavirus (HPV) infection is one of the most prevalent sexually transmitted infections worldwide and is a leading cause of anogenital and oropharyngeal malignancies. Despite advances in vaccination and screening, HPV-related diseases remain a significant public health burden, particularly in low- and middle-income countries.

This review summarises the virology, epidemiology, clinical spectrum, pathogenesis, prevention, and future perspectives of HPV infection, highlighting global disparities and opportunities for disease elimination. More than 200 HPV genotypes have been identified, with at least 14 classified as oncogenic; HPV16 and HPV18 account for over 70% of cervical cancers. Globally, an estimated 604,000 new cervical cancer cases and 342,000 deaths occur annually, with 85% concentrated in low- and middle-income countries. The introduction of prophylactic vaccines has significantly reduced the prevalence of high-risk HPV infections and precancerous lesions; however, inequitable access, vaccine hesitancy, and limited infrastructure impede universal implementation. Advances in molecular diagnostics, including HPV mRNA testing, DNA methylation assays, and artificial intelligence–assisted cytology, provide new tools for precision screening. Emerging therapeutic vaccines targeting viral oncoproteins E6 and E7 represent a promising frontier for secondary prevention.

Comprehensive strategies that integrate vaccination, molecular screening, and digital innovation are essential for achieving the WHO 90–70–90 targets for cervical cancer elimination. Global success will depend on equitable implementation, political commitment, and sustained public trust.

Keywords:

HPV infection, cervical cancer, vaccination, screening, global burden, elimination strategy, molecular diagnostics.

Глобална распространетост на инфекцијата со хуман папилома вирус (ХПВ) и ХПВ-асоцираните болести

Апстракт

Инфекцијата со хуман папилома вирус (ХПВ) претставува една од најраспространетите сексуално преносливи инфекции во светот и водечка причина за аногенитални и орофарингеални малигнитети. И покрај напредокот во вакцинацијата и скринингот, болестите поврзани со ХПВ сè уште претставуваат значителен товар на јавното здравство, особено во земјите со ниски и средни приходи.

Овој преглед ги сумира податоците за вирусологијата, епидемиологијата, клиничкиот спектар, патогенезата, превенцијата и идните перспективи на ХПВ-инфекцијата, нагласувајќи ги глобалните нееднаквости и можностите за елиминација на болеста.

Досега се идентификувани повеќе од 200 генотипови на ХПВ, од кои најмалку 14 се онкогени, при што ХПВ16 и ХПВ18 се одговорни за над 70% од случаите на цервикален карцином. Глобално, се проценува дека годишно се јавуваат околу 604.000 нови случаи на рак на грлото на матката и 342.000 смртни исходи, при што 85% од нив се концентрирани во земјите со ниски и средни приходи. Воведувањето на профилактичките вакцини значително ја намали преваленцата на високо-ризични ХПВ-инфекции и преканцерозни лезии; сепак, нееднаквиот пристап, колебливоста кон вакцинацијата и ограничената инфраструктура ја отежнуваат универзалната имплементација. Напредокот во молекуларната дијагностика – вклучувајќи ХПВ mRNA тестови, анализи на ДНК метилација и цитологија со помош на вештачка интелигенција – нуди нови алатки за прецизен скрининг. Новите терапевтски вакцини насочени кон вирусните онкопротеини Е6 и Е7 претставуваат ветувачка насока за секундарна превенција.

Сеопфатни стратегии кои ги интегрираат вакцинацијата, молекуларниот скрининг и дигиталните иновации се клучни за постигнување на целите на СЗО 90–70–90 за елиминација на цервикалниот карцином. Глобалниот успех ќе зависи од правичната имплементација, политичката посветеност и одржливата доверба на јавноста.

Клучни зборови: инфекција со ХПВ, рак на грлото на матката, вакцинација, скрининг, глобална распространетост, стратегија за елиминација, молекуларна дијагностика.

Introduction

Human papillomavirus (HPV) infection is one of the most widespread sexually transmitted viral infections worldwide, affecting both men and women across all regions and socioeconomic groups. More than 200 HPV genotypes have been identified, of which at least 14 are classified as high-risk types capable of inducing malignant transformation [1]. Persistent infection with oncogenic types, particularly HPV16 and HPV18, is a well-established cause of cervical cancer, accounting for more than 90% of all cases globally [2]. However, HPV is also implicated in a substantial proportion of other anogenital and oropharyngeal cancers, highlighting its role as a major global oncogenic pathogen [3].

In 2020, an estimated 604,000 new cervical cancer cases and 342,000 deaths were attributed to HPV, with nearly 85% occurring in low- and middle-income countries (LMICs) where organised screening and vaccination programmes remain limited [4]. The World Health Organization (WHO) launched the Global

Strategy to Accelerate the Elimination of Cervical Cancer in 2020, defining the 90-70-90 targets to be achieved by 2030 [5]. Despite the availability of highly effective prophylactic vaccines and molecular screening tools, inequities in access, infrastructure, and awareness continue to sustain the global burden of HPV-related disease. Recent analyses show that although vaccination coverage has increased in many regions, significant global gaps remain, particularly in low-resource settings. Integrated strategies involving vaccination, screening, and surveillance are required to reduce morbidity and mortality worldwide. [6,7].

Virology, Transmission and Natural History of HPV

Human papillomaviruses (HPVs) are small, non-enveloped, double-stranded DNA viruses of the *Papillomaviridae* family, characterised by icosahedral symmetry and a diameter of approximately 52–55 nm [1]. The ~8 kb circular genome encodes early (E1–E7) and late (L1, L2) proteins, as well as a long control region (LCR) that regulates replication and transcription [8]. The viral capsid consists mainly of the L1 major structural protein, which forms the antigenic basis for the currently available prophylactic virus-like particle vaccines [9].

HPV genotypes are classified according to their oncogenic potential. Low-risk types, such as HPV6 and HPV11, cause benign epithelial lesions, including anogenital warts and recurrent respiratory papillomatosis. High-risk or oncogenic types - most notably HPV16, 18, 31, 33, 45, 52 and 58 - are aetiologically linked to high-grade intraepithelial lesions and invasive carcinomas of the cervix, anus, penis, vulva, vagina, and oropharynx [10,11]. Phylogenetically, these types cluster within the alpha-papillomavirus genus, exhibiting strong mucosal tropism and the ability to cause persistent infection.

Transmission of genital HPVs occurs primarily through sexual contact, including both penetrative and non-penetrative skin-to-skin interaction. Non-genital cutaneous types may spread via direct skin contact or contaminated fomites [12]. The virus enters through micro-abrasions in the epithelium, targeting basal keratinocytes where replication begins. Viral genome maintenance occurs in episomal form in basal cells, while productive replication and virion assembly are restricted to the upper differentiating layers of the stratified epithelium [13]. The life cycle is closely linked to epithelial differentiation, and virions are released with desquamated superficial cells, without inducing cytolysis or inflammation - features that enable immune evasion and long-term persistence [14].

HPV infections are typically subclinical and transient. In immunocompetent hosts, 80–90% of new infections are cleared by innate and adaptive immune responses within one to two years [15]. Clearance likely involves both cytotoxic T-cell–mediated destruction of infected keratinocytes and production of neutralizing antibodies against L1 epitopes [16]. In contrast, persistent infection - defined as detection of the same high-risk HPV type for ≥12 months - is the principal risk factor for development of high-grade

intraepithelial lesions and invasive cancer [17]. Persistence is promoted by viral immune evasion, integration of viral DNA into host chromosomes, and deregulation of the E6 and E7 oncoproteins, which inactivate the tumour suppressors p53 and pRb, driving genomic instability and uncontrolled proliferation [18,19].

The progression from initial infection to invasive carcinoma is a multistep process that typically spans 10–20 years [20]. Several cofactors influence the likelihood of persistence and malignant transformation, including cigarette smoking, long-term use of oral contraceptives, high parity, coinfection with other sexually transmitted pathogens, host immunosuppression (notably HIV), and cervicovaginal microbiome dysbiosis [21,22]. Disruption of the *Lactobacillus*-dominated microbiota has been associated with reduced viral clearance and increased risk of cervical intraepithelial neoplasia [23].

Understanding the virology and natural history of HPV infection is fundamental for public health strategies. The close coupling of viral replication with epithelial differentiation and the absence of viraemia explain why HPV infection remains localised, evades systemic immune detection, and establishes persistent reservoirs that may progress to neoplasia over time [1,24].

Epidemiology and Global Burden of HPV Infection

Human papillomavirus is the most prevalent sexually transmitted viral infection worldwide, affecting both men and women across all age groups and regions. More than 80% of sexually active individuals will acquire at least one HPV type during their lifetime, with the highest incidence occurring within a few years after sexual debut [4]. The infection is typically asymptomatic and transient; however, persistent infection with high-risk HPV genotypes - especially HPV16 and HPV18 - represents the central aetiological factor for cervical cancer and several other anogenital and oropharyngeal malignancies [2].

Globally, an estimated 604,000 new cervical cancer cases and 342,000 deaths occurred in 2020, making it the fourth most common cancer among women [5]. Over 85% of these cases arise in LMICs, where organised screening and vaccination programmes are limited or absent [7]. Sub-Saharan Africa, Latin America, and parts of South-East Asia have the highest age-standardized incidence and mortality rates, reflecting deep inequities in prevention and health infrastructure [25].

The global prevalence of high-risk HPV infection among women with normal cytology is estimated at 11–12%, with substantial regional variation - ranging from 22% in Sub-Saharan Africa to below 6% in Northern Europe and North America [11]. The most common oncogenic genotypes worldwide are HPV16, 18, 31, 33, 52, and 58, which together account for nearly 90% of HPV-related cervical cancers [10]. Non-cervical malignancies also contribute significantly to the total disease burden: HPV is responsible for approximately 90% of anal cancers, 70% of vaginal cancers,

50% of penile cancers, 40% of vulval cancers, and about 30–40% of oropharyngeal cancers [3].

Table 1. Global Epidemiological Overview of Human Papillomavirus (HPV) Infection by Region

Region	HPV prevalence (any type)	High-risk HPV prevalence (% in women with normal cytology)	Cervical cancer incidence (per 100,000)	Vaccination coverage (%)	Main challenges
Sub-Saharan Africa	25–30%	22%	34.8	<20%	Limited access, HIV co-infection
Latin America	15–20%	14%	23.1	60–70%	Programmatic inequality
Eastern Europe	12–16%	11%	17.5	40–60%	Vaccine hesitancy
Western Europe	7–10%	6%	6.5	>80%	Saturation, declining uptake
North America	8–12%	5%	7.1	>75%	Misinformation, coverage gaps
East Asia	9–14%	10%	11.0	50–65%	Resource heterogeneity
Global	11.7%	—	13.3	41% (girls, 9–14 yrs)	Implementation gaps

Source: Adapted from Bruni et al., HPV Information Centre Summary Report 2023; Muñoz et al., N Engl J Med 2003; Drolet et al., Lancet 2019; Brisson et al., Lancet 2020.

Recent global analyses show a rising incidence of HPV-related oropharyngeal squamous cell carcinoma, particularly in men from high-income countries, where HPV-positive oropharyngeal squamous cell carcinoma now surpasses cervical cancer incidence in some regions [26]. Immunocompromised populations, including individuals living with HIV and organ transplant recipients, demonstrate higher rates of HPV acquisition, persistence, and progression to malignancy. In a Brazilian cross-sectional study, HPV infection was detected in 70% of HIV-positive versus 21% of HIV-negative women, confirming the strong association between immunosuppression and high-risk HPV persistence [27].

The WHO launched the *Global Strategy to Accelerate the Elimination of Cervical Cancer* in 2020, aiming to achieve the "90-70-90" targets by 2030: 90% of girls fully vaccinated with HPV vaccine by age 15, 70% of women screened by age 35 and

again by 45, and 90% of women identified with cervical disease receiving appropriate treatment [5]. Modelling studies predict that full implementation of vaccination and screening in LMICs could reduce cervical cancer incidence by over 80% and prevent more than 60 million cases by the end of the century [25].

The epidemiology of HPV infection highlights the magnitude of its global public health impact. Despite being a vaccine-preventable and screen-detectable infection, persistent disparities in access, awareness, and infrastructure continue to sustain a disproportionate burden in resource-limited regions. Global elimination of HPV-related diseases will depend on equitable implementation of evidence-based vaccination, screening, and treatment strategies across all settings.

Clinical Presentation and Spectrum of HPV-Associated Diseases

Benign HPV-Associated Lesions

HPV infection presents across a broad clinical spectrum, raging from asymptomatic or transient infections to benign epithelial proliferations and invasive cancers. Most HPV genotypes are non-oncogenic and cause self-limiting lesions. Low-risk types, primarily HPV6 and HPV11, cause anogenital warts (condylomata acuminata)—exophytic lesions of the vulva, penis, perianal area, and genital mucosa. Although benign, these lesions impose a considerable psychosocial and economic burden on affected individuals and health systems [28]. The same genotypes cause recurrent respiratory papillomatosis, a chronic condition characterised by the growth of benign papillomas in the larynx and trachea, often requiring multiple surgical interventions to maintain airway patency [29]. Additionally, cutaneous HPV types, particularly those from the β-papillomavirus genus, are associated with common and flat warts and, in immunocompromised hosts, may contribute to the development of cutaneous squamous cell carcinoma [30].

Pre-cancerous Lesions (Intraepithelial Neoplasia)

Persistent infection with high-risk HPV types - most notably HPV16, 18, 31, 33, 52, and 58—can lead to intraepithelial neoplasias, which represent the precursor stages of malignant transformation. The best-studied model is cervical intraepithelial neoplasia (CIN), histologically graded from CIN1 (low-grade) to CIN3 (high-grade). Progression from low- to high-grade lesions involves viral DNA integration, deregulated E6/E7 oncoprotein expression, and accumulation of genomic damage [18,20]. Similar processes occur in vulvar (VIN), vaginal (VaIN), anal (AIN), and penile intraepithelial neoplasias (PIN), which are biologically analogous to cervical lesions but generally have lower malignant potential [31]. Host immunosuppression, such as HIV infection, promotes persistent HPV infection and accelerates progression to high-grade lesions. A study from Brazil demonstrated a 70% HPV prevalence among HIV-positive women compared with 21% among HIV-negative controls [27].

Invasive Cancers (Cervical, Anal, Oropharyngeal, etc.)

HPV is the causative agent for nearly all cervical cancers, with HPV16 and HPV18 accounting for over 70% of cases worldwide [10]. Anal squamous cell carcinoma is associated with HPV16 in up to 90% of cases, with increased incidence in men who have sex with men and individuals living with HIV. The burden of HPV-positive oropharyngeal squamous cell carcinoma has risen sharply, particularly in high-income countries, where incidence among men now exceeds that of cervical cancer in some regions [26]. Vulvar, vaginal, anal, and penile carcinomas also show a strong association with high-risk HPV infection, although the proportion of HPV-negative tumours increases with age and keratinising histology [32,33].

Table 1 Clinical Spectrum of HPV-Associated Diseases

Disease Entity	Predominant Genotypes	Key Clinical Features
Anogenital warts	HPV6, HPV11	Benign, recurrent; psychosocial burden
Recurrent respiratory papillomatosis	HPV6, HPV11	Airway obstruction; requires repeated surgery
Cervical intraepithelial neoplasia (CIN1–3)	HPV16, 18, 31, 33	Precancerous lesions; risk of progression if persistent
Anal intraepithelial neoplasia (AIN)	HPV16, 18	Precursor to anal carcinoma
Oropharyngeal carcinoma	HPV16	Rising incidence, better prognosis if HPV+
Vulvar/vaginal/penile cancers	HPV16, 18	Less common but with high morbidity

Source: Adapted from Kombe et al., Front Public Health 2021; Castellsagué et al., Ann Oncol 2016; WHO HPV Information Centre Summary Report 2023; Gultekin et al., Int J Cancer 2023.

Pathogenesis: From Infection to Malignancy

Molecular Events in Oncogenic HPV Infection

Human papillomaviruses (HPVs) infect basal keratinocytes following micro-abrasions in epithelial tissue. Once the viral DNA enters the nucleus, it establishes itself as an episome and replicates in synchrony with host cell division. In high-risk HPV infections, regulation of the viral oncogenes E6 and E7 is disrupted, leading to uncontrolled cell proliferation and impaired apoptosis [1,20]. These viral genes are central mediators of oncogenesis through degradation of tumour-suppressor proteins and alteration of host cell checkpoints.

E6 and E7 Oncoproteins and Host Cell Targets

The E6 oncoprotein promotes ubiquitin-mediated degradation of p53, a key regulator of the DNA damage response, thereby preventing apoptosis [19]. At the same time, E7 binds the retinoblastoma protein (pRb), releasing E2F transcription factors and forcing the cell into S-phase replication [13]. The combined disruption of p53 and pRb pathways induces genomic instability, accumulation of chromosomal aberrations, and cellular immortalisation [18]. These mechanisms form the biological basis for transformation from productive HPV infection to precancerous lesions.

Viral Integration and Genomic Instability

A hallmark of malignant progression is the integration of high-risk HPV DNA into host chromosomes [34]. Integration often disrupts the E2 gene, a negative regulator of E6/E7 transcription, resulting in constitutive oncoprotein expression [35]. Large-scale genomic analyses have identified recurrent HPV integration hotspots near fragile chromosomal regions and proto-oncogenes such as *MYC* and *TERT*, leading to focal genomic instability [36]. These integration events act as "molecular switches" that convert persistent infection into malignant transformation.

Host and Environmental Co-factors

Although viral oncogene expression is necessary, it is not sufficient for cancer development. Progression is influenced by host immunity, hormonal milieu, and environmental co-factors. Immunocompromised individuals, particularly those co-infected with HIV, exhibit higher viral loads, longer persistence, and accelerated transformation due to impaired cell-mediated immunity [37]. Additionally, chronic inflammation, smoking, multiparity, and long-term use of oral contraceptives contribute to oxidative stress and mutagenic DNA damage, further supporting malignant evolution.

Microbiome and Local Immune Regulation

Emerging evidence highlights the importance of the vaginal microbiome in modulating HPV persistence. Lactobacillus-dominant microflora appear protective, while microbial dysbiosis characterised by *Gardnerella*, *Atopobium*, and anaerobic overgrowth increases local inflammation and reduces viral clearance [38]. These findings underscore the complex host–virus-microbiome interactions that govern the natural history of HPV and identify potential biomarkers for personalised risk stratification.

Prevention and Control: Vaccination, Screening, and Global Strategies

HPV Vaccination and Long-Term Efficacy

Prophylactic vaccination remains the cornerstone of primary prevention against HPV infection and its associated malignancies. Long-term follow-up from the Costa Rica Vaccine Trial demonstrated sustained efficacy of the bivalent vaccine (Cervarix®) against HPV-16/18 infection and related precancerous lesions for over 11 years, with no evidence of waning immunity or need for booster doses [39]. This durable protection confirms the long-term immunogenic stability of HPV vaccination and its pivotal role in reducing the incidence of cervical intraepithelial neoplasia. Complementary meta-analytic evidence has shown that the introduction of national HPV vaccination programmes led to significant declines in both vaccine-type HPV prevalence and high-grade lesions in young women, indicating strong herd protection [40].

In 2022, the WHO Strategic Advisory Group of Experts (SAGE) recommended introducing a single-dose HPV vaccination schedule to improve feasibility, equity, and coverage, particularly in LMICs [41]. Such simplified protocols could accelerate global uptake and help achieve the WHO's elimination target by 2030.

Gender-Neutral Immunization and Global Coverage

Despite demonstrated efficacy, global HPV vaccination coverage remains uneven. A systematic review of 148 countries found that only 125 have incorporated HPV vaccination into their national immunisation programmes, with full two-dose coverage averaging below 40% in LMICs [42]. Barriers include financial constraints, logistical challenges, and vaccine hesitancy.A growing focus in global health policy is the inclusion of boys and men in vaccination strategies. Evidence shows that gender-neutral immunization improves herd immunity, reduces transmission, and provides direct protection against male HPV-associated diseases, such as anal and oropharyngeal cancers [43]. Including both sexes is increasingly seen as essential for sustainable HPV control.

Screening and Early Detection Strategies

While vaccination prevents new infections, screening remains essential for secondary prevention by detecting precancerous changes before progression. HPV molecular testing, including both DNA and mRNA assays, has largely replaced cytology as the preferred primary screening method due to higher sensitivity and negative predictive value [44]. In particular, mRNA assays targeting E6/E7 transcripts have demonstrated superior specificity in identifying clinically relevant infections compared to DNA testing, reducing overtreatment rates in screening programmes.

Integration of the WHO Global Strategy to Accelerate the Elimination of Cervical Cancer emphasises the "90-70-90" framework achieving 90% vaccination coverage, 70% screening coverage, and 90% treatment access by 2030 [45]. Successful implementation relies on combining primary and secondary prevention, especially in resource-limited settings.

Emerging Tools for Triage and Risk Stratification

Beyond traditional screening, innovative approaches such as self-sampling for HPV testing have significantly improved participation among under-screened populations, particularly in rural and marginalised groups [46]. This strategy shows high acceptability and diagnostic accuracy comparable to clinician-collected samples.

Additionally, epigenetic biomarkers - particularly DNA methylation panels - are emerging as effective tools for triaging HPV-positive women. A recent meta-analysis confirmed that methylation assays can accurately identify those at highest risk for cervical intraepithelial neoplasia grade 3 or higher (CIN3+) and serve as a cost-effective adjunct to current screening algorithms [47].

Global Strategies Toward Elimination

Finally, tertiary prevention also includes adjuvant vaccination after surgical excision of high-grade lesions. Meta-analytic evidence shows that post-treatment HPV vaccination reduces the recurrence of cervical intraepithelial neoplasia by up to 60%, reinforcing its role in comprehensive disease management [48].

The WHO's global initiative integrates these interventions into a cohesive strategy: vaccination as the foundation, molecular screening as the surveillance tool, and adjuvant vaccination as a safeguard against relapse. Sustained political commitment, financial investment, and equitable access to vaccines and molecular diagnostics remain the decisive factors in achieving the goal of cervical cancer elimination within the twenty-first century.

Challenges and Future Perspectives

Despite major achievements in HPV prevention, significant challenges persist across epidemiological, socioeconomic, and technological domains. The global distribution of HPV-related disease burden remains uneven, reflecting disparities in vaccine access, screening infrastructure, and health literacy between high-income countries and LMICs [6,49]. Implementation gaps arise not only from logistical and financial constraints but also from sociocultural and political factors that influence public health priorities. As Branda et al. [6] emphasise, the success of HPV immunisation strategies depends on equitable global access, strengthened surveillance, and sustainable funding mechanisms.

Vaccine Coverage and Hesitancy

Although global vaccine programmes have expanded substantially since the WHO's 2020 elimination strategy, coverage remains far below the 90% target in many LMICs [49]. In several regions, including parts of Africa and Southeast Europe, national HPV vaccination programmes are hindered by inadequate infrastructure, fragmented supply chains, and limited community engagement [6,49]. Vaccine hesitancy is another critical obstacle. As Karafillakis et al. [50] demonstrate, mistrust of institutions, misinformation on social media, and cultural misconceptions about adolescent sexuality

have collectively undermined public acceptance. Addressing hesitancy requires transparent risk communication, the inclusion of trusted healthcare voices, and the integration of vaccination within broader reproductive health education.

Therapeutic and Next-Generation Vaccines

While prophylactic vaccines have proven highly effective in preventing infection, they offer no therapeutic benefit for individuals already infected with high-risk HPV types. Novel therapeutic vaccines targeting the E6 and E7 oncoproteins are being developed to induce cytotoxic T-cell responses and eliminate transformed cells Early-phase clinical trials suggest that combining these vaccines with immune checkpoint inhibitors or viral vectors may enhance antitumour immunity [51]. Such advances may redefine HPV control from primary prevention to integrated therapeutic management.

Molecular and Digital Innovations

Beyond vaccination, precision diagnostics are advancing rapidly. DNA methylation profiling provides a robust triage tool for HPV-positive women, potentially improving specificity in identifying high-grade lesions [47]. Current research focuses on molecular biomarkers such as methylation of viral L1/L2 regions, detection of integrated HPV DNA, and E6/E7 mRNA expression for clinical triage. Understanding integration signatures and viral-host epigenetic interactions offers new pathways for precision screening and early detection of HPV-driven malignancies [2,6]. Concurrent advances in artificial intelligence (AI) and digital cytology have shown diagnostic accuracy comparable to expert pathologists in large multicentre trials [52]. These technologies could transform screening in low-resource settings by automating cytological interpretation and reducing human error. However, ethical concerns regarding data privacy, algorithm transparency, and equitable access must be addressed before widespread adoption.

Modeling Elimination and Policy Integration

Predictive modelling studies project that cervical cancer elimination is achievable this century if vaccination and screening programmes reach target coverage [53]. However, elimination timelines vary widely by region due to differences in baseline incidence, healthcare capacity, and socioeconomic conditions. Integrating modelling data into national policies enables evidence-based resource allocation and prioritisation of interventions [53]. As Davies et al. [54] argue, achieving the WHO 90-70-90 targets requires simultaneous investment in vaccination, screening, and treatment pillars, supported by real-time data monitoring and cross-sectoral collaboration..

Global Vision

The next decade will determine whether HPV elimination can move from vision to reality. Achieving this goal requires a multifaceted approach that addresses inequalities in access, fosters public confidence in vaccination, leverages technological innovations, and ensures policy coherence at both global and national levels. The convergence of immunisation, molecular screening, and digital innovation

offers unprecedented opportunities, but only sustained political will, funding, and community engagement will translate scientific potential into lasting public health success.

Conclusion

Human papillomavirus infection remains one of the most significant preventable causes of cancer worldwide, with a broad clinical spectrum raging from benign warts to invasive malignancies across anogenital and oropharyngeal sites. Considerable progress has been made through vaccination and molecular screening, yet global inequities persist, particularly in low- and middle-income regions where the disease burden is highest. Advances in prophylactic and therapeutic vaccines, methylation-based biomarkers, and artificial intelligence–driven cytology are transforming prevention, diagnosis, and management. However, sustained success will depend on equitable implementation, robust surveillance systems, and strategies to address vaccine hesitancy and infrastructural limitations. Achieving the WHO's 90-70-90 targets for cervical cancer elimination will require not only scientific innovation but also political commitment, public trust, and global collaboration. The integration of vaccination, precision screening, and digital health technologies provides an unprecedented opportunity to move from control to elimination, transforming HPV-associated diseases from a leading cause of morbidity and mortality into a preventable public health success story.

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THE IDENTIFICATION AND MANAGEMENT OF ARTERIAL HYPERTENSION IN CHILDREN: REVIEW

Rina Rus MD PhD - University Medical Centre Ljubljana Hospitals and Health Care

Correspodence: Rina Rus rina.rus@kclj.si

Abstract

Arterial hypertension is one of the risk factors to accelerate arterial aging and also has a negative impact on heart structure and function not only in adults, but also in children and adolescents. Therefore, to prevent early pathological cardiovascular changes, it is important to start measuring blood pressure in children at 3 years of age or younger if there is an increased risk for arterial hypertension. The article describes the importance of measuring blood pressure in children and adolescents. It also provides instructions on how to interpret measured blood pressure values and describes the management of children and adolescents in whom arterial hypertension has been confirmed.

Izvleček

Arterijska hipertenzija sodi med dejavnike tveganja za pospešeno staranje arterij in negativno vpliva na strukturo in delovanje srca ne le pri odraslih, temveč tudi pri otrocih in mladostnikih. Zaradi omenjenega negativnega vpliva na srčno žilni sistem ter z namenom preprečevanja zgodnjih patoloških kardiovaskularnih sprememb je pomembno, da krvni tlak pri otrocih pričnemo meriti že v starosti 3 leta ali tudi manj, če obstaja povečano tveganje za arterijsko hipertenzijo.

Članek opisuje pomen merjenja krvnega tlaka pri otrocih in mladostnikih. Podaja tudi navodila za interpretacijo izmerjenih vrednosti krvnega tlaka in opisuje obravnavo otrok in mladostnikov z arterijsko hipertenzijo.

Introduction

The ageing of blood vessels is a natural process that begins at birth. However, several factors are known to accelerate vascular ageing in children by promoting the chronic inflammatory disease of the arterial wall known as atherosclerosis, which leads to an earlier onset of cardiovascular diseases in adulthood. Risk factors that accelerate atherosclerosis include hypercholesterolemia, obesity, diabetes, chronic kidney disease, chronic inflammatory diseases, and arterial hypertension (1). Arterial hypertension in childhood therefore has a significant impact on the early development of cardiovascular diseases in adulthood (2). A recent systematic review demonstrated that children and young adults with primary hypertension show signs of impaired vascular structure and function. It was shown that the increase in carotid and femoral artery pulse wave velocity (cf PWV) in children and young adults with primary hypertension is almost exclusively explained by the effect of blood pressure. However, changes in carotid artery intima-media thickness (cIMT) appear to be multifactorial and dependent not only on hypertension, but also on immunometabolic abnormalities (3). Arterial hypertension in young people affects not only the accelerated ageing of

blood vessels, but also the structure and function of the heart. Left ventricular hypertrophy was observed in at least one-fifth of children and young adults with primary hypertension (4) .

The systematic review and meta-analysis indicated that hypertensive children and adolescents exhibit signs of hyperkinetic function of the left ventricle, demonstrated by increased left ventricular strain and impaired diastolic function compared to normotensive controls (5).

The literature clearly shows that arterial hypertension significantly impacts the heart and vascular system in both adults and children. Numerous studies in adults have revealed the encouraging fact that physical activity, weight reduction, and antihypertensive therapy have beneficial effects on the regression of left ventricular hypertrophy and reduce peripheral vascular resistance (6-10). Similar interventions in children also appear effective in lowering blood pressure in those with arterial hypertension. Blood pressure control is most likely improved after physical activity interventions, reduction of abdominal obesity, and antihypertensive treatment . According to the literature, it is clear that changes in the blood vessels and heart caused by arterial hypertension can be reversed with appropriate measures, making the detection of arterial hypertension especially important in children and adolescents (11-15).

When and how should blood pressure be measured in children

To identify arterial hypertension in children for early intervention and to reduce cardiovascular morbidity and mortality, it is essential to measure blood pressure, which is the key component in assessing arterial hypertension. According to the latest European guidelines, blood pressure should be measured in all children from the age of three years. In normotensive children, it is recommended that blood pressure be re-evaluated every two years, while in those with high normal blood pressure and no organ damage, it should be checked annually (16). In children aged three years and older, blood pressure should be measured at every healthcare encounter if they are obese, have diabetes, congenital heart defects, kidney disease, or are taking medications known to increase blood pressure (17). Before the age of three years, blood pressure should be checked when there is an increased risk for elevated blood such as preterm birth, low birth weight, neonatal disease requiring intensive care, congenital heart disease, kidney disease, treatment with medications known to increase blood pressure, malignancy, solid organ or bone marrow transplantation, or increased intracranial pressure (16).

It is essential to measure blood pressure in children correctly. The younger the child, the more challenging it is to measure blood pressure. It is recommended to measure blood pressure in children in a quiet environment. The child should be relaxed before the measurement begins and, if possible, remain still for 3 to 5 minutes beforehand. If the child is older, they should lean back with their feet on the floor. (16,17).

Blood pressure should be measured on the right arm using a suitably large cuff, with a width covering 40% of the upper arm circumference. The inflatable part of the cuff should cover 80 to 100% of the upper arm circumference (16,17).

If the first blood pressure measurement is above the 90th percentile, two additional blood pressure measurements must be taken three minutes apart. The average of

the last two measurements should then be calculated (16).

The first blood pressure measurement can be taken using an oscillometric device, if properly calibrated, or by the auscultatory method, which is particularly recommended if elevated blood pressure was recorded with the oscillometric device (16,17).

It is recommended that blood pressure be measured on both arms at the first visit to identify any differences. Subsequent measurements should be taken on the upper arm of the limb with the higher blood pressure (16).

When the auscultatory method is used, the bell of the stethoscope should be placed over the brachial artery in the antecubital fossa, with the lower end of the cuff 2 to 3 cm above it. The cuff should be inflated 20 to 30 mm Hg above the point at which the radial pulse disappears. Over-inflation of the cuff should be avoided. The first Korotkoff sound represents the systolic blood pressure and the fifth the diastolic blood pressure (16).

American guidelines recommend that in newborns and children who do not yet participate in the measurements, blood pressure should be measured with oscillometric devices on the right arm (17).

Interpretation of blood pressure measurements in children

After blood pressure has been properly measured, interpretation of the values should follow. It is important to note that the definition of arterial hypertension in children is based on the normal distribution of blood pressure in healthy children, not on cardiovascular morbidity and mortality associated with specific blood pressure values, as in the adult population. The diagnosis of arterial hypertension is based on blood pressure distribution for age, sex, and height up to 16 years of age according to European guidelines (16), and up to 13 years of age according to American guidelines (17). European and American guidelines differ in the diagnostic criteria for arterial hypertension (18). According to American guidelines, the normal distribution of blood pressure is based on healthy children, excluding obese and overweight children, which is not the case in European guidelines (16, 17). Calculators have been developed by COST Action to assess paediatric home blood pressure, paediatric office blood pressure, and paediatric 24-hour ambulatory blood pressure. All calculators are based on the 2016 European Society of Hypertension guidelines and were developed as useful instruments for paediatricians and other clinical professionals working with children and young people in Europe and elsewhere. The calculators are available at the following website: https://hyperchildnet.eu/.

A recent study by Lurbe et al. provides useful information on blood pressure in healthy, normal-weight European children and adolescents using the oscillometric method, which is currently the most widely used in Europe in both clinical and out-of-office settings (19).

Epidemiology of arterial hypertension in children

Studies on children in the United States of America, conducted between 2007 and 2017, showed that the prevalence of arterial hypertension in children ranged between 2% and 4%. These estimates were

based on the 2004 Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (20-22). Central European studies during that period were similar to those in the USA, with a prevalence between 2.2% and 4.9% (23-25). Data from Southern Europe showed a higher prevalence of arterial hypertension, between 9 and 13% during that period. However, it is important to note that the normative values used in those studies differed from those in the USA and Central Europe, and were mostly based on national normative values. Additionally, there were some variations in the methods of measurement. (26-28). After 2017, the prevalence of elevated blood pressure (previously termed prehypertension) in the USA increased from 14.8% according to the Fourth Report to 16.3% under the American Academy of Pediatrics guidelines published in 2017. This rise in elevated blood pressure was due to differential classification changes among younger and older children. The prevalence of confirmed hypertension remained at 2% to 4% in this population. However, under the 2017 guidelines, smaller children under 13 years of age, as well as taller and older children aged 13 and above, are systematically more likely to be diagnosed with hypertension (29). A higher prevalence of arterial hypertension was also confirmed in obese and overweight children (30-32).

Management of a child with arterial hypertension

When arterial hypertension is confirmed, secondary causes should be promptly identified and the underlying cause addressed to prevent target organ damage. If no underlying disorder is found, hypertension is considered primary, and the first line of management consists of preventive measures such as lifestyle changes, as recommended by American and European guidelines (16,17). It is well established that inactivity, diets high in sugar and salt, and excess weight account for nine out of ten cases of high blood pressure in children and adolescents (33). Therefore, lifestyle changes, including weight reduction, maintenance of normal weight, and limitation of dietary salt, are of utmost importance (16,17). The DASH diet (Dietary Approach to Stop Hypertension), which is rich in fresh vegetables and fruits, low in fat, enriched with whole grains, fish and poultry, and low in sodium, has been shown to effectively reduce blood pressure (34). Families should be encouraged to eat together and adopt healthy habits together (35). Avoiding alcohol, smoking, and energy drinks is important in preventing arterial hypertension. Another key factor in lowering blood pressure is physical activity or exercise, a low-cost intervention with proven health benefits. Physical activity induces vascular adaptations, such as increased vascular compliance and reduced total peripheral resistance, leading to lower blood pressure and cardiac afterload. It also decreases sympathetic nerve activity and systemic inflammation, helping to prevent arterial stiffening. Physical activity is linked to weight loss, improved glycaemic control, and beneficial changes in lipoprotein metabolism, resulting in positive vascular effects (36). A notable effect of physical activity on blood pressure regulation is its impact on endothelial function. Through various molecular mechanisms, physical activity enhances vascular remodelling by

regulating endothelial cells and smooth muscle remodelling (37,38). Physical activity is recommended for patients with arterial hypertension not only in adults, but also in children and adolescents. European and American guidelines (16,17) recommend moderate to vigorous physical activity at least 3 to 5 days per week (30 to 60 minutes per session) for children aged 5 to 17 years (16). These guidelines also recommend stress reduction (17) and avoiding sedentary activities for more than 2 hours at a time each day (16). A recent survey confirmed that more than 8 hours of daily screen time (representing a sedentary lifestyle) and fewer than 12,000 steps per day (representing physical activity) were associated with higher diastolic blood pressure and lower HDL cholesterol among racially diverse adolescents (39). The expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents provided recommendations regarding physical activity and screen time based on the child's age (40). For newborns and infants, parents should create an environment that promotes and models physical activity and limits sedentary time. TV viewing should be discouraged entirely. For children aged 1 to 4 years, parents should allow unlimited active playtime in safe and supportive environments. Total media time should be limited to no more than 1 to 2 hours of quality programming per day. For children aged 2 years, TV viewing should be discouraged entirely. There should be no TV in a child's bedroom regardless of age. Parents should be encouraged to have family activities at least once per week. For children aged 5 to 10 years, moderate to vigorous physical activity every day, at least 3 times per day for 1 hour, should be encouraged. Additionally, daily leisure screen time (TV, video, computer) should be limited to no more than 1–2 hours per day of quality programming. For children aged 11 to 17 years, moderate to vigorous physical activity is recommended every day for at least one hour, and time spent on TV, video, or computer should be limited to no more than 1 to 2 hours per day of quality programming. In this and younger age groups, energy intake and activity should be balanced. It is important to support regular family activity at least once per week (39).

Despite numerous recommendations regarding appropriate diet and physical activity, obesity-related hypertension in children and adolescents is increasing worldwide. It has been proven that weight reduction in obese and hypertensive children and adolescents has a positive effect on lowering blood pressure (41, 42). Therefore, various educational multidisciplinary programmes have been established, including blood pressure measurements, physical exercise, and nutritional and behavioural counselling. The most effective programmes are those that include physical exercise in addition to nutritional counselling (43).

The purpose of the above-mentioned non-pharmacological measures is to lower blood pressure in children and adolescents below the 95th percentile. The recommended blood pressure for children with diabetes mellitus is below the 90th percentile. In children with chronic kidney disease without proteinuria, the goal is to lower blood pressure below the 75th percentile. However, in children with

chronic kidney disease and proteinuria, the recommended blood pressure is below the 50th percentile (16).

According to European guidelines, pharmacological treatment of arterial hypertension in children should be initiated when hypertension becomes symptomatic, in cases of diabetes mellitus, target organ damage, and in children with secondary hypertension. Persistent hypertension despite lifestyle changes and weight loss also requires initiation of antihypertensive therapy (16).

Conclusions

Arterial hypertension is a factor that accelerates pathological changes in the cardiovascular system, so it is essential to begin measuring blood pressure in early childhood. If primary arterial hypertension is confirmed, the first step is to change lifestyle, including diet and physical activity. A sedentary lifestyle should be avoided. Persistent hypertension despite lifestyle changes requires the initiation of antihypertensive therapy.

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Caregiving Role During Palliative and Home Healthcare

Yasemin Özkaya, Yasemin Kılıç Öztürk***

** Izmr City Hospital, Family Medicine Department Izmir, Turkiye*

Orcid ID:0000-0003-2620-8275

*** University of Health Sciences Turkey, Izmir Faculty of Medicine Tepecik Training and Research Hospital, Family Medicine Department, Izmir, Turkiye*

Orcid ID:0000-0003-1463-6627

Correspodent: Yasemin Özkaya, Yasemin Kılıç Öztürk** MD PhD*

University of Health Sciences Turkey, Izmir Faculty of Medicine Tepecik Training and Research Hospital, Family Medicine Department, Izmir, Turkiye

dryko38@gmail.com

Abstract

This review synthesises the roles, burdens, and needs of caregivers in palliative and home healthcare, as well as strategies for effective support. Caregivers perform daily and clinical care tasks, provide emotional support and manage administrative responsibilities; these multidimensional duties can cause psychological, physical, social, and economic strain. Burden increases with care intensity, limited social or financial resources, and the unplanned assumption of the caregiving role. To ensure effective and sustainable care, routine assessment of caregivers, targeted education and psychosocial support, respite services, coordinated home care and palliative team interventions, technology-enabled solutions, and supportive policy instruments (such as protected leave and social insurance) are necessary.

Key words: caregiver, palliative care, home healthcare, health policy

Özet

Bu derlemede palyatif bakım ve evde sağlık hizmetlerinde bakım verenlerin rollerini, yüklerini ve ihtiyaçlarını, etkili destek stratejileriyle birlikte değerlendirmek amaçlanmaktadır. Bakım verenler yalnızca günlük ve klinik bakım görevlerini değil, aynı zamanda duygusal destek ve idari sorumlulukları da üstlenirler; bu çok boyutlu görevler bireylerde psikolojik, fiziksel, sosyal ve ekonomik baskı yaratabilmektedir. Bakım ihtiyacının yoğunluğu, sınırlı sosyal/finansal kaynaklar ve bakım verme rolünün plansız üstlenilmesiyle birlikte bakımverenlerin yükü de artma eğilimindedir. Etkili ve sürdürülebilir bakımı sağlamak için, bakım verenlerin rutin değerlendirilmesi, hedefli eğitim ve psikososyal destek, dinlendirme hizmetleri, koordineli evde bakım-palyatif ekip müdahaleleri, teknoloji destekli çözümler ve etkin politika araçları (örneğin, korumalı izin, sosyal sigorta) gereklidir.

Anahtar kelimeler : Bakımveren, palyatif bakım, evde sağlık hizmetleri, sağlık politikası

Introduction

Advances in science and technology have improved living standards, enhanced the effectiveness and accessibility of health services, and, in parallel, increased average life expectancy. While this demographic transition allows longer lives, it also brings new challenges, including a higher prevalence of chronic disease and disability, reduced functional capacity, and greater reliance on assistance with activities of daily living. Consequently, population ageing is accompanied by a marked increase in demand for healthcare services utilisation (1).

Home healthcare consists of integrated set of services - diagnosis, treatment, nursing care, and rehabilitation - delivered in the patient's residence by multidisciplinary teams to individuals who are bedridden or face barriers to accessing healthcare facilities. In practice, eligibility prioritises adults aged ≥80 years; adults aged ≥65 years with chronic disease who are fully or highly dependent in activities of daily living; device- and/or home-bound patients; those requiring palliative care or post-discharge home follow-up; and individuals with conditions such as diabetes, heart failure, stroke, COPD, Alzheimer's disease/dementia, neurodegenerative disorders, terminal cancer, multimorbidity, the post-operative period after major fractures (hip/knee/shoulder), and amputation (2).

Palliative care is a comprehensive, person- and family-centered approach that aims to enhance the quality of life for children and adults facing serious illness through early recognition and relief of pain and other sources of physical, psychosocial, or spiritual suffering (3,4,5). It is provided by a multidisciplinary team and includes care planning aligned with the patient's values and goals, symptom management, nutrition, pain relief, communication and shared decision-making, and bereavement support. Global estimates suggest that approximately 57 million people would benefit from palliative care each year, yet access is available to only about one in seven worldwide. When integrated early, palliative care improves quality of life and is associated with fewer preventable hospital admissions and reduced use of acute health services (4).

Population ageing and the increasing prevalence of chronic conditions are driving demand for home-based and palliative services. According to the United Nations World Population Prospects 2024, the proportion of people aged ≥65 years will rise rapidly over the coming decades, and the WHO "Ageing and Health" brief indicates that the population aged ≥80 years will nearly triple between 2020 and 2050 (6). This demographic shift makes the expansion of palliative care and home health services a strategic priority for health-system sustainability and equity.

The success of home- and palliative-care models relies not only on consistent professional input but also on the active participation of family or informal caregivers who provide day-to-day care. A caregiver is the person who, when physical or cognitive limitations prevent an individual from performing activities of daily living, meets essential needs, coordinates in-home care, and monitors

clinical processes and interactions with health services (7). This role is usually taken on within the family, often without prior planning. Caregivers ensure continuity of care, including medication monitoring and dose adjustment, nutrition and hydration oversight, maintenance of hygiene and prevention of pressure injuries, mobilisation and positioning, wound and device care, systematic observation of symptoms such as pain, dyspnoea, agitation, and nausea, environmental safety, and coordination of appointments, transport, and communication with the care team. They also provide psychosocial support through continuous presence, emotional reassurance, and efforts to sustain hope and meaning. Additionally they manage administrative and financial tasks, accompany patients to visits, and act as advocates to ensure that patient preferences and rights are respected in clinical decision-making.

Evidence showes that family caregivers in home and palliative care often experience persistent, unmet needs. Key gaps include lack of knowledge and practical skills particularly in symptom management, medication administration, and navigating the health system as well as insufficient emotional support and limited access to respite (8-10). These issues are frequently compounded by restricted communication with healthcare professionals, delayed service availability, and poor coordination between formal and informal supports (11-13). As a result, caregivers commonly report high levels of stress, fatigue, anxiety, and, in some cases, depression; the expectation of 24/7 availability further worsens physical exhaustion and health decline (8,12,14). Coping strategies vary: some caregivers share responsibilities, seek professional assistance, or renegotiate their role boundaries to adapt; without adequate guidance, others rely on “trial and error,” taking on additional risk (8,9,12). Overall, these findings highlight the need for early, integrated, and holistic home and palliative care approaches with regular review (8,13). In addition to patient-focused care, systematic assessment of caregivers as individuals with their own health, needs, and challenges can significantly improve care processes and outcomes

Caregiver Burden

Zarit and colleagues define caregiver burden as the perceived adverse impact of caregiving on emotional, social, financial, and physical domains (15). Burden has been associated with increased mortality risk, diminished self-care, social isolation, depression and anxiety, and financial strain (7,15,16). Major risk factors include female gender, low educational attainment, co-residence with the care recipient, greater hours of care, pre-existing depression/loneliness, financial stress, and assuming the role without choice (16).

Caregiving is not merely the acquisition of practical skills; it constitutes a transformative process involving meaning and making, personal growth, and reorganization of social relationships (17). This trajectory is shaped by prior preparedness and experience, the availability of support networks and resources, concordance with the patient, perceived readiness for the role, and the need to master new competencies (18). Accordingly, burden should be

conceptualized not only as the sum of tasks but as the combined effect of readiness for caregiving, psychological status, unmet needs, vulnerability within social relationships, and existential confrontation with hope, meaning, and mortality (18).

In advanced cancer which is one of the major conditions requiring caregiving family caregivers are predominantly women, typically aged 50–65 years. Due to the nature of cancer care, caregiving is intensive and often time-compressed; providing more than 20 hours per week is common, with daily commitments ranging from a few hours to as much as 17 hours (19). Such demands lead to fatigue and loss of personal time, jeopardising continuity of care. Although roughly half of caregivers remain employed, many reduce their hours or leave work altogether. Frequent hospital visits, prolonged accompaniment, and treatment-related expenses impose additional burdens. While some caregivers report positive aspects such as finding meaning, personal growth, and strengthened relationships sleep disturbance, weight loss, fatigue, anxiety, and depression are also prevalent (19). Accordingly, caregivers should be recognised not merely as "informants" or "helpers," but as individuals in their own right.

Caregivers' observations on symptom trajectories, treatment adherence, and potential complications should be shared regularly with health professionals and incorporated into clinical decision-making. Key domains for assessment include: co-residence, competing caregiving responsibilities, employment conditions and , available social supports, the caregiver's capacity and willingness to provide care, physical and mental health, financial resources, and the patient's functional or cognitive status and self-care abilities as reported by the caregiver. With the patient's consent, clinician–caregiver meetings held separately from the patient can protect confidentiality while improving the quality of care.

In a single-centre home health care study from Turkey, most caregivers were middle-aged women; a substantial proportion reported incomes insufficient to meet expenses, prolonged caregiving durations, and pervasive needs for education or counselling. Caregivers frequently described deterioration in self-rated health, poor sleep quality, use of antidepressants or hypnotics, burnout, and feelings of powerlessness or helplessness. The most burdensome tasks were bathing, diaper or continence care, inability to leave the patient unattended, and lifting or transfers (20).

A separate investigation found no clear "very good/very bad" global change in caregivers' lives; however, subdomains revealed adverse effects, including declines in physical health, stress management, friendships, time for social activities, energy, emotional well-being, and physical functioning. Factors associated with greater impact included unemployment, being a first-degree relative, female sex, age 43–78 years, lower educational attainment, being single, and living with the patient. On the patient side, female sex, age 75–84 years, low education, and certain cancer types (such as multiple myeloma, brain tumour, and leukaemia) increased caregiver burden (21). In another study, caregiver stress was found to be higher among caregivers with chronic

illnesses and was also greater when the care recipient was male and highly bed-dependent (22).

Although caregivers may be formal or informal, reports indicate that informal family caregivers often spouses or adult children experience identity strain as they transition from their previous familial roles to that of a "primary caregiver," frequently describing a sense that everyday life has been "put on hold (8,12)." Because the patient's home is a private space, professional practice in this setting requires a careful balance between clinical expertise and a posture of "guesthood," highlighting the need for specific training in boundary management (such as permission-based interactions, observation-informed communication, and preparing families to sustain care during professional absences (23). In terms of control and autonomy, informal caregivers often assume full responsibility by remaining constantly available; however, inadequate support and limited resources increases stress and burnout (24). Accordingly, periodic reassessment of the care arrangement, explicit household rules for care delivery, and deliberate task-sharing protect caregiver well-being (13,24).

Families should be clearly informed that concentrating the entire burden on one individual reduces the sustainability of home and inpatient palliative care and lowers the likelihood of completing intended care plans. Multi caregiver models with planned rotation should be encouraged. Professionals should co-produce decisions while respecting patient autonomy and the unpredictability of the home environment, connect families with support networks, and safeguard continuity of care (23).

Strengthening the role of family caregivers in palliative and home care must include clearly defined safeguards for patient autonomy, privacy, and representation. Regular assessment of decision-making capacity, written documentation of the patient's preferred level of information and participation during informed-consent processes, and explicit designation of a surrogate decision-maker with specified proxy access rights all enhance continuity and safety of care.

In paediatric palliative and home care, the dynamics differ from adult practice. Children and adolescents with early care needs present distinct challenges. Parents are the legal surrogates, but the child should be involved as far as is developmentally and cognitively appropriate, with preparation that enables expression of preferences and reduces anxiety (25). The scope extends beyond symptom control to include the concurrent management of school and peer participation, the right to play and education, growth and developmental goals, siblings' needs, and the intersection of parenting roles with clinical tasks. Correspondingly, caregiver burden is multilayered: constant vigilance and chronic sleep deprivation; substantial administrative demands such as reimbursement, equipment and supply procurement and disability documentation; stress from coordinating school, hospital, and home interfaces; perceptions of neglect and behavioural risks among siblings; and, for parents, anticipatory grief, guilt, oscillations between hope and

hopelessness, and trauma-like stress reactions.

Moreover, just as the care recipient's age shapes caregiver roles, the caregiver's own age and life stage also influence the caregiving trajectory. Among younger and mid-life caregivers, psychological stress, financial strain, and social isolation tend to be more pronounced due to competing demands of employment, child-rearing, and career development; in older caregivers, multimorbidity and the physically demanding nature of tasks increase somatic burden, with particular difficulties in night care and patient transfers.

Assessment and follow-up of caregivers

In clinical practice, standardised scales are routinely used to evaluate caregivers and the caregiving context, particularly to measure burden and strain. During follow-up, a brief caregiver burden instrument should be administered alongside an anxiety and depression screening tool, with reassessment at high-risk points such as hospital discharge, exacerbations, the final days of life, and the first three months after bereavement.

Support for caregivers should be planned in a multilayered manner. Core components include structured education covering disease and treatment information, symptom management, medication administration, safe transfer techniques, and home safety; individual and group-based psychosocial counselling and peer support; and coordinated services provided by home-care teams and palliative-care centers. At the policy level, social protection mechanisms that ensure leave entitlements, insurance, and financial support are needed; in patient-specific situations, paid or partially paid caregiving leave and measures that encourage sharing of caregiving duties within the family should be considered. In resource-limited settings, insufficient family and social support increases burden. For migrant or live-in caregivers, additional vulnerabilities related to language and cultural barriers, legal status, and access to rights require targeted adaptations and protective regulations.

Although uncommon, risks of abuse and neglect should be screened for and reporting and protection pathways must be followed in accordance with applicable regulations. For patients without family support or adequate caregiving capacity, home-care and palliative teams, day centers, short-stay options, residential care, and social services should be mobilised to secure an appropriate care setting, and the patient's preferences should be documented in writing. It should not be forgotten that caregivers, in particular, often postpone their own physical health and increase their health risks by neglecting immunisation and periodic health examinations. Well- organized respite care opportunities should be planned to protect caregivers' health.

Education and Skills Building

Effective communication with caregivers is essential to meeting the needs and preferences of patients and families. Family conferences provide an appropriate forum to clarify care plans and goals, ensure accurate information sharing, and jointly establish care preferences (26); they can reduce perceived unmet needs, enhance preparedness for caregiving, and potentially improve bereavement outcomes.

Caregiver education is vital for continuity and safety of care for both patient and caregiver. Core content should include disease stage, potential treatment options, management of adverse effects, and the joint setting of realistic short- and long-term goals. Instruction should be delivered stepwise and tailored to evolving needs. For increasingly complex clinical tasks, such as medication management, subcutaneous or injection techniques, wound and device care, hands-on training with nursing and pharmacy support is essential. While prioritising pain control and early recognition of clinical deterioration, programmes should also promote caregiver self-care, routine medical follow-up, and access to respite. Bereavement support should be offered when indicated.

Although face-to-face education is effective, distance, transport, and time constraints may limit access. Therefore, remote interventions are a feasible alternative to enhance caregiver preparedness. Telehealth consultations, video-based micro-learning, SMS/app reminders, and online peer groups can streamline planning, enable post-discharge follow-up and symptom-management coaching, reduce travel and lodging costs for professionals, and minimise caregivers' time away from the care recipient. Programme effectiveness should be monitored routinely using indicators such as caregiver preparedness, competence, burden, anxiety, and depression (27).

Research indicates that systematic assessment of caregivers' needs, preferences, and care goals is essential. Not every family caregiver requires intensive services; however, all need structured education, access to resources when needed, and skills to manage evolving challenges. Therefore, programmes should engage all families at regular intervals, recognising that unmet needs change over time, and provide timely reassessment and tailored support (28).

Conclusion

Caregiving in palliative and home-care settings extends far beyond daily tasks; it is a complex process with psychological, social, economic, and spiritual dimensions that reshapes identity and family relationships. Sustainability in this field depends on integrating early palliative care into routine systems; developing individualized, patient-and-caregiver-centered plans; providing structured education and respite; ensuring access to psychosocial supports; complementing care with digital/remote solutions; and reinforcing delivery through enabling policy instruments. Positioning the caregiver as an equal, active partner in the care team guaranteeing participation in decision-making, routinely monitoring well-being, and responding systematically to needs can substantially improve quality of life for both patients and families.

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Functional magnetic stimulation (FMS) in the treatment of stress urinary incontinence in women

Funkcionalna magnetska stimulacija (FMS) u liječenju stresne urinarne inkontinencije kod žena

Rajko Fureš[1-4], Damir Hodžić[1,2], Biljana Gorgievska Sukarovska[2,,3], Dora Fureš[3], Željka Fureš[2,3], Dalibor Hržica[1]

[1]Croatian Society for Pelviperineology.

[2]Faculty of Dental Medicine and Health Osijek. Josip Juraj Strossmayer University of Osijek, Osijek, Croatia.

[3]Zabok General Hospital and Croatian Veterans Hospital, Zabok, Croatia.

[4]Faculty of Health Studies, University of Rijeka, Croatia.

[5]Special Hospital for Medical Rehabilitation Krapinske Toplice, Croatia

Correspodent: Rajko Fureš MD PhD

Zabok General Hospital and Croatian Veterans Hospital, Zabok, Croatia

rajko.fures@gmail.com

Abstract

Functional magnetic stimulation (FMS), applied to patients seated in a magnetic chair, is simple to use and highly effective for numerous indications, with stress urinary incontinence being the primary application. The method is non-invasive, painless, and has no negative side effects reported in the literature. Improvements are often visible within a very short period after starting treatment. FMS strengthens and accelerates the regeneration of the pelvic muscles, and non-contact magnetic stimulation significantly enhances pelvic muscle strength without any invasive procedures.

Functional magnetic stimulation (FMS), administered to patients seated in a magnetic chair, is easy to use and highly effective for various indications, with stress urinary incontinence as the primary application. The method is non-invasive, painless, and no negative side effects have been reported in the literature. Improvements are often observed within a short period after beginning treatment. FMS strengthens and accelerates the regeneration of pelvic muscles, and non-contact magnetic stimulation significantly increases pelvic muscle strength without invasive procedures.

Keywords: functional magnetic stimulation (FMS), stress urinary incontinen

Funkcijska magnetska stimulacija (FMS) u tretmanu stresne urinarne inkontinencije

Sažetak

Sama funkcijska magnetska stimulacija (FMS) koja se primjenjuje kod pacijenata koji sjede u magnetskom stolcu je jednostavna za primjenu i vrlo učinkovita u brojnim indikacijskim stanjima, pri čemu na prvome mjestu ističemo

tretman stresne urinarne inkontinencije. Metoda je neinvazivna, bezbolna te nema u literaturi opisanih negativnih nuspojava, a poboljšanja tijekom njene primjene vidljiva su u vrlo kratnom periodu od početka primjene. Kod njene primjene dolazi do jačanja i ubrzavanja regeneracije mišića zdjelice, a korištenjem beskontaktne magnetske stimulacije u značajnoj se mjeri jača mišićna muskulatura zdjelice bez ikakve invazivne komponente u liječenju.

Suvremena funkcijska magnetska stimulacija ima vrlo značajno mjesto u tretmanu stresne urinarne inkontinencije, gdje je iznimno učinkovita, pri čemu se njeno indikacijsko područje primjene svakim danom sve više proširuje, s primarnim naglaskom na učinkovitost i korist naših pacijenata.

Ključne riječi: funkcijska magnetska stimulacija (FMS), stresna urinarna inkontinencija

Introduction

Uncontrolled urination, or urinary incontinence, occurs when the sphincter, pelvic floor muscles, and bladder muscles do not function properly or in synchrony due to weakness or overactivity. This common and unpleasant problem affects people of both sexes and all age groups. In young women, the most common type is stress incontinence, where urine leaks through an otherwise intact urethra. The main cause of this disorder is debated, but reduced function of the pelvic floor muscles, leading to a weakened bladder mechanism, is often implicated. In addition, older women frequently experience urge incontinence, where urine leaks following a sudden, urgent need to urinate due to an overactive bladder. In such cases, patients may need to use the toilet more than eight times a day, with the urge to urinate also occurring at night. Older women often experience a combination of stress and urge incontinence, known as mixed urinary incontinence (1-3).

Treatment of stress urinary incontinence

It is important to emphasise that functional magnetic stimulation (FMS) of the pelvic muscles is an effective and highly acceptable method for treating various forms of urinary incontinence. The method involves a coil, which generates an electromagnetic field with pulses lasting up to 100 microseconds, a frequency of up to 160 Hz, and a power of up to 3 Tesla, embedded in the seat of the chair on which the patient sits. Electromagnetic stimulation suppresses involuntary contractions of the detrusor while simultaneously increasing the tone of the internal urethral sphincter. The electromagnetic field also induces repeated contractions of the levator muscles, producing an effect similar to Kegel exercises for the pelvic floor muscles. Research to date has shown significant improvement or complete resolution of symptoms in cases of static or predominantly stress urinary incontinence, as well as the effectiveness of magnetic stimulation in detrusor instability following spinal cord injury and in idiopathic unstable detrusor. Pelvic FMS is comfortable for patients, who remain fully clothed during therapy. According to current literature, no adverse effects have been reported in the therapeutic application of electromagnetic fields (4-7).

Muscle stimulation by electromagnetic fields

It is important to note that rapid changes in the strength of the electromagnetic field induce an electric current in the neuron. This phenomenon is called electromagnetic induction. In this case, when the electric

current reaches a certain value, the neuron achieves an action potential. These conditions cause depolarisation of neuronal cells, which ultimately leads to complete muscle contraction (8-10).

Magnetic chair in clinical practice

The magnetic chair was developed for the treatment of stress urinary incontinence and pelvic floor muscle dysfunction, utilising the benefits of FMS. The magnetic field generated by this device induces contractions of the pelvic floor muscles. This therapy is suitable for all types of urinary and faecal incontinence. It has been shown to significantly improve rehabilitation after urogenital surgery and childbirth. FMS also benefits patients with sexual dysfunction and chronic pain in the pelvic area and lumbar spine. Magnetic stimulation increases the strength and endurance of the sphincter and pelvic floor muscles. During stimulation, the patient focuses on muscle contractions, which facilitates learning the correct technique for performing exercises. The therapy has positive effects on sexual intercourse, erection, the ability to achieve orgasm, and contraction of the groin and gluteal muscles. Ultimately, magnetic stimulation increases the strength and endurance of the sphincter and pelvic muscles (11-12).

Functional magnetic stimulation and indications for its use.

There are many indications for the use of functional magnetic stimulation, with the most common listed below. The primary indication is stress urinary incontinence. Other important indications include urge urinary incontinence, mixed urinary incontinence, incontinence following radical prostatectomy, faecal incontinence, postpartum recovery, milder forms of bladder and uterine prolapse (cystocele, descensus uteri), rehabilitation after pelvic surgery, chronic prostatitis, and erectile dysfunction (7-12).

Technical instructions for the use of functional magnetic stimulation

The therapy is straightforward and does not require special patient preparation. During treatment, the patient sits comfortably in a chair while fully clothed. The patient focuses on muscle contractions during stimulation, which is an effective way to learn the exercises. The therapy is non-invasive, painless, and free from negative side effects. Improvement is usually observed after several sessions, with therapy administered two to three times per week for 20 minutes (13-14).

The therapy programme is determined for each patient individually after a consultation and physical examination by a specialist, depending on the symptoms and diagnosis. Strengthening and accelerating the regeneration of the pelvic muscles through functional magnetic stimulation is an alternative or improvement to electrical stimulation therapy for incontinence. In this approach, contactless magnetic stimulation visibly strengthens the pelvic muscles without the discomfort of electrode insertion. The therapy is administered two to three times a week for 20 minutes. There is no contact with the skin, and the therapy is painless, with no unpleasant sensations or side effects. It is worth noting that in 1998, the American FDA approved functional magnetic stimulation as a method for treating urinary incontinence (15-16).

Functional magnetic stimulation chair used in pelvic and lumbar stimulation

The latest generation of FMS chairs for treating the lower back (Tesla Care, Iskra Medical, Slovenia, with a magnetic field strength of 3 Tesla and a frequency range of 1–160 Hz) is used therapeutically as a painless, non-invasive, and effective treatment for lower back problems. The therapy stimulates muscles and increases circulation without direct contact with the skin. The procedure is simple and does not require special preparation of the patient. During therapy, the patient sits in the chair, and the exact area of stimulation in the lower back can be adjusted by changing the position of the applicator in the backrest of the chair (15-18).

Hand-held applicator for functional magnetic stimulation

In clinical practice, modern FMS devices are equipped with a hand-held FMS applicator and are used in physical medicine and rehabilitation. The hand-held FMS applicator can be used to quickly locate the area for activation of the appropriate muscle and stimulate it. FMS provides a pulsating magnetic field that activates and strengthens weakened muscles. The therapist can perform the therapy manually using the FMS applicator or by attaching it to the body. The therapist can quickly locate trigger points and effectively perform stimulation by moving the applicator. The magnetic field affects all tissues under the applicator, and the treatment is extremely effective for a wide range of indications in physical medicine and rehabilitation. The FMS hand-held applicator is available in two different sizes. Hands-free operation is achieved by placing the FMS applicator on a special mechanical arm or attaching it to the body with rubber bands (16-20).

Conclusion

FMS is a deep stimulation of muscle structures that is more effective than electrostimulation. The method is painless and non-invasive, making it suitable for patients who do not respond to electrotherapy. There is no contact with the skin, and therapy can be administered with or without a physiotherapist. The main advantage of this therapeutic method is that it can be considered minimally invasive. Functional magnetic stimulation is a highly effective, efficient, painless, inexpensive, and non-aggressive therapeutic method with no harmful effects on patients. Based on these factors, it holds an important place in the treatment of stress urinary incontinence, and its area of application is expanding daily for the benefit of patients.

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APPROACH TO PRESSURE ULCERS

Prof. Dr. Hüseyin CAN, Dr. Merveözge KAHRAMAN

Izmir Katip Çelebi University Faculty of Medicine Department of Family Medicine

drhuseyincan@hotmail.com

ORCID: 0000-0002-4686-7879

Dr. Merveözge KAHRAMAN

Izmir Katip Çelebi University Faculty of Medicine Department of Family Medicine

mrvebebek@gmail.com

ORCID: 0009-0001-3533-3900

Abstract

Chronic wounds typically occur in patients with comorbidities such as diabetes, obesity, immune deficiencies, peripheral vascular disease, and cardiopulmonary diseases. Pressure ulcers are localised injuries to the skin and underlying soft tissues over bony prominences or in relation to medical devices, resulting from prolonged pressure and shear. The National Pressure Injury Advisory Panel (NPIAP) defined this condition in 2016 and updated its guidelines in 2019. A pressure injury is defined as “local damage to the skin and underlying soft tissue usually over a bony prominence or related to medical or other devices, caused by sustained and/or intense pressure with a shearing force.” The most frequent risk factors for pressure ulcers include immobility, increased skin moisture, inadequate nutrition, loss of sensory perception, advanced age, cognitive and physical impairment, urinary incontinence, oedema, microcirculatory disorders, hypoalbuminaemia, and malnutrition. The most effective treatment for pressure ulcers is prevention of wound formation, which can only be achieved through a multidisciplinary and holistic approach.

Özet

Kronik yaralar genellikle diyabet, obezite, bağışıklık sistemi yetersizlikleri, periferik vasküler hastalık ve kardiyopulmoner hastalık gibi ek hastalıkları olan hastalarda ortaya çıkmaktadır. Basınç yarası, genellikle kemik çıkıntıları üzerinde veya tıbbi cihazlarla ilişkili olarak uzun süreli basınç veya kayma nedeniyle deri ve deri altı dokularında oluşan lokalize hasardır. Ulusal Bası Yarası Danışma Paneli (NPIAP) 2016 yılında bu tanımı yapmış, 2019 yılında da rehberini güncellemiştir.

Buna göre basınç yaralanması, "makaslama etkisi ile yoğun ve/veya uzun süreli basınç sonucu, genellikle kemik çıkıntısı üzerinde veya tıbbi ya da başka bir cihazla ilişkili olarak deri ve alttaki yumuşak dokuda oluşan lokalize hasar" olarak tanımlanmaktadır.

Basınç yaralarının en sık görülen risk faktörleri; hareketsizlik, artmış cilt nemi, yetersiz beslenme, duyusal algı kaybı, ileri yaş, kognitif ve fiziksel bozukluklar, üriner inkontinans, ödem, mikrodolaşım bozukluğu, hipoalbuminemi ve malnütrisyon gibi komorbid durumları içermektedir. Basınç yarasının en etkin tedavisi yara oluşumunun önlenmesidir ve bu da ancak multidisipliner ve bütüncül bir yaklaşım ile gerçekleşebilmektedir.

Definition and Evaluation

Chronic wounds typically occur in patients with comorbidities such as diabetes, obesity, immune deficiencies, peripheral vascular disease, and cardiopulmonary diseases. The most common causes include diabetic foot (diabetic ulcers), venous leg ulcers (venous ulcers, varicose ulcers), pressure ulcers (pressure injuries, decubitus ulcers, bedsores), arterial insufficiency ulcers (atherosclerotic, vasculopathic), and radiation-induced damage (1). Pressure ulcers are localised injuries to the skin and underlying soft tissues over bony prominences or in relation to medical devices, resulting from prolonged pressure and shear. The National Pressure Injury Advisory Panel (NPIAP) defined this condition in 2016 and updated its guidelines in 2019. A pressure injury is defined as “local damage to the skin and underlying soft tissue usually over a bony prominence or related to medical or other devices, caused by sustained and/or intense pressure with a shearing force.” The most frequent risk factors for pressure ulcers include immobility, increased skin moisture, inadequate nutrition, loss of sensory perception, advanced age, cognitive and physical impairment, urinary incontinence, oedema, microcirculatory disorders, hypoalbuminaemia, and malnutrition (2). The most effective treatment for pressure ulcers is prevention of wound formation, which can only be achieved through a multidisciplinary and holistic approach.

Staging

The National Pressure Ulcer Advisory Panel (NPUAP) and the European Pressure Ulcer Advisory Panel (EPUAP) have developed evidence-based guidelines for prevention and treatment that classify pressure ulcers according to depth and tissue involvement (3,4). Stage I pressure injury: Intact skin with non-blanchable redness; this is the key finding. It is difficult to detect in individuals with dark skin. Stage II pressure injury: Localised loss of dermal tissue. It may present as a superficial ulcer without necrotic tissue, as blister-like liquid-filled vesicles, or as yellow necrotic tissue. Stage III pressure injury: Full-thickness loss of skin and subcutaneous tissue, with no involvement of bone, muscle, or tendon. Subcutaneous fat may be visible; the wound may include pockets or tunnels. Stage IV pressure injury: Full-thickness tissue loss with exposure of muscle, tendon, or bone, and possible involvement of other structures. Unstageable pressure injury: Depth cannot be determined because the wound bed is

covered by yellow necrotic tissue or eschar, preventing assessment of the true depth. Debridement is required to determine the actual stage. Deep tissue injury: Intact skin with a deep, red, maroon, or purple localised area of tissue necrosis or a blister; the area may be firm, painful, and have a boggy or mushy consistency on palpation (3,4).

Prevention

Prevention of pressure ulcers requires a multidisciplinary and holistic approach. Effective management starts with risk identification. For individuals who are bed- or chair-bound, potential pressure areas should be identified and monitored using risk assessment tools such as the Braden Scale. Regular skin inspection, cleansing, and moisturising are essential. Incontinence-associated dermatitis should be managed with barrier products, and regular repositioning to relieve pressure over affected areas is necessary. Any factors compromising circulation should be addressed. Pressure-relieving devices, including air-supported surfaces or cushions, should be used to minimise prolonged pressure. Adequate nutrition, including sufficient protein, vitamins, minerals, and appropriate daily fluid intake should be ensured. Education of the patient and caregiver about pressure ulcer prevention and management is crucial. All interventions should be documented with ongoing observation and records (5-10). In individuals with pressure ulcers, it is important to manage pain, nausea and vomiting, dry mouth, mucositis, depression, and other factors that can adversely affect nutrition. Caloric and protein intake should be maintained and tailored to the patient; typically around 30 kcal/kg/day and approximately 1.5 g/kg/day of protein. Non-protein calories should be planned with roughly 60–70% as carbohydrates (glucose) and 30–40% as lipids. When providing nutritional support, all critically ill patients should receive vitamins (B1, B6, B12, and vitamin D), omega-3 fatty acids, and trace elements (11,12).

Pressure Ulcer Management

Following clinical assessment of the patient with a pressure ulcer, anthropometric measurements and laboratory tests should be performed to establish the baseline condition. The management plan should then be formulated using a holistic approach. In pressure ulcer management, the TIMERS principles are applied for initial wound assessment (13). These are: T (Tissue management): Debridement of necrotic or infected tissue that impedes wound healing, while preserving healthy tissue. I (Inflammation/Infection control): Prevention of infection or biofilm formation at the wound site, treatment of existing wound infections, and maintenance of infection control. M (Moisture balance): Maintaining optimal moisture at the wound site and protecting it from excess moisture or dryness that could hinder healing. E (Edge of wound): Supporting epithelialisation and advancement of wound edges while managing the wound to promote new tissue formation. R (Regeneration/Repair): Use of appropriate growth factors and healing-promoting agents to stimulate tissue regeneration and strengthen weakened tissue. S (Social factors):

Consideration of psychosocial status, nutrition, sociocultural context, and lifestyle in the patient's care. The TIMERS principles provide a holistic framework that accelerates healing and enhances clinicians' control over the process (13).

Treatment

Pressure ulcers are dynamic, variable, and persistent problems. Each patient and each wound have unique characteristics.

Key considerations in the treatment process include:

Implement wound management according to the TIMERS principles.

Identify and address factors delaying healing, such as necrotic tissue, infection, and foreign bodies, and resolve them with appropriate methods.

Use wound care products suitable for the wound type and stage.

Maintain a clean wound environment.

Control conditions that cause pressure on the skin.

Manage the wound healing process to transition the chronic wound towards an acute, physiological healing trajectory.

Educate the patient and caregiver about the treatment and process.

Document the treatment process in detail.

When conditions allow, surgical debridement should be considered as part of chronic wound management. If surgical debridement is not feasible, mechanical, autolytic, or enzymatic debridement may be used. After infection control and removal of necrotic tissue, wound care should be tailored to the wound type and stage using appropriate dressings. Protective barrier creams should be used to support skin under pressure. The skin should be protected from excessive moisture, dryness, friction, and similar stressors. Modern wound care products can accelerate healing by addressing deficiencies, but no single product is suitable for all wounds; selecting the right product depends on the clinician's knowledge and expertise. Therefore, healthcare professionals should be trained in chronic wound care and management. Pressure ulcers are largely preventable with appropriate precautions. Early identification of risk factors and a multidisciplinary approach can prevent wound formation and, with effective treatment strategies, improve patients' quality of life. (14).

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Digital transformation of family medicine clinics: opportunities and challenges of using artificial intelligence in family medicine

Primož Rus, MD, GP, SSM

Group practice, Ljubljana, Head Doctor

primoz.rus@ambulanta-rus.si

Izvleček

Digitalizacija, ki jo prinaša razvoj interneta z uporabo sodobnih tehnologij, se je že izkazala z množico povsem novih in neznanih odzivov ljudi v vsakdanjem življenju. Te spremembe se dogajajo izjemno hitro in so zato pogosto nepredvidljive. Digitalna transformacija predstavlja ključni vidik modernizacije zdravstvenega sistema v svetu. Pravilna uporaba umetne inteligence (UI) je izjemnega pomena, saj lahko pomaga izboljšati trenutne procese, od administrativnih do kliničnih poti, in je bistvena pri iskanju novih rešitev v zdravstvu za zagotavljanje boljše in kakovostnejše strokovne obravnave naših pacientov. V tem članku bomo opisali priložnosti in izzive, ki jih prinaša uporaba umetne inteligence (UI) v ambulantah družinske medicine, in dodali nekaj izkušenj z delom z UI v naših ambulantah za skupinsko medicino, kar je edinstven model v Sloveniji.

Abstract

Digitalisation, driven by the development of the Internet and the use of modern technologies, has already demonstrated itself through numerous new and unfamiliar responses from people in everyday life. These changes occur very rapidly and are therefore often unpredictable. Digital transformation is a key aspect of modernising the healthcare system in nearly all countries worldwide. The correct use of Artificial Intelligence (AI) is of paramount importance, as it can help improve current processes, from administrative to clinical pathways, and is essential for finding new solutions in healthcare to provide better and higher-quality professional treatment for patients. In this article, we describe the opportunities and challenges presented by the use of AI in family medicine clinics, drawing on our experience working with AI in our Group Practice Clinics, a unique model within Slovenia.

A general view of the development of artificial intelligence (AI) applications in healthcare

No country in the world today has faced the challenges brought by the digitalisation of our society to our lives. Our real, analogue world is gradually disappearing into a different world, filled with unfiltered, unverified, and even false or fabricated information, which for an individual can mean anything they imagine at that moment. In this flood of information, people often become lost, which is particularly

concerning when it comes to health. The current era of digitalisation has developed so rapidly, especially with the advent of the Internet, that people can no longer keep pace with the speed at which all types of information are disseminated online. This is the reality today, when we all have extremely powerful computers in the form of mobile phones in our hands, which we constantly check, browsing through information as if sifting through rubbish or a cluttered attic. We are searching for something, while various companies and international corporations bombard us with advertisements, offers, and a range of information, which is unfortunately often malicious (1). Increasingly, our patients arrive at family medicine clinics equipped with AI-generated information. Many already believe they know what is wrong with them and demand referrals, among other things. If they encounter health care staff who are not educated about this new, increasingly AI-informed patient, errors, abuse, and inadequate communication between the patient, their relatives, employers, and health care workers can quickly arise. Without the appropriate knowledge and skills, effective and accurate communication between doctor and patient can rapidly break down, trust can be lost, and serious conflicts may result, potentially ending in court. This is certainly not the goal that AI offers in the health system, nor the path it represents. It is clear from the literature that the use of AI in primary health care is still in its early stages. However, promising results are already emerging, particularly in individual, mainly administrative areas such as communication, documentation, and clinical support (2-6). Many experts in this field do not share a unified opinion regarding the introduction of AI into health systems. Some emphasise the positive effects of AI on the administrative efficiency of the health system (3,7). Opponents, however, stress the need for caution in replacing human judgement with AI (8). The diversity of approaches is also reflected in different methodological approaches and attitudes towards AI. Some advocate the gradual implementation of AI with extensive training for all health personnel (2), while others propose immediate integration of AI with strong technological support (9). Proponents of a moderate pace of AI implementation highlight the importance of a tailored approach based on the specifics of each institution (10). These differing approaches and perspectives reflect the great complexity of AI implementation and the need for in-depth interdisciplinary expert analysis.

The importance of digital transformation in healthcare systems and AI in healthcare is significant. AI is already used in various areas of patient care, from diagnostics to data management. Today, advanced analytical technologies enable the analysis of large volumes of data, leading to more accurate findings and, consequently, faster and more efficient patient treatment. At the same time, the quality of data processing is improving, as are patient monitoring, disease prediction and prognosis, and personalised patient treatment.

AI tools are already being used to help doctors make faster and more accurate diagnoses in certain areas and to assist in treatment decisions (11). Administrative relief is one of the main areas of AI application in primary healthcare, and AI is being integrated into this sector worldwide. As many as 92% of healthcare executives surveyed agreed that automation is crucial in addressing the increasing shortage of healthcare personnel (12,13). AI-based systems provide much greater transparency and control, such as automatic coding of diagnoses, report generation, and error detection in documentation (7,8). AI has also been successfully applied in diagnostics and data management. Advanced analytical technologies facilitate the analysis of large datasets, which leads to improved monitoring, disease prediction and management, and the personalisation of comprehensive healthcare. Increasingly, AI-designed systems are supporting doctors and their teams in decision-making. This approach enables doctors to diagnose diseases more quickly and accurately, resulting in better collaboration and patient management (11).

Communication effectiveness and quality of communication with patients can be improved with AI, which can help address these and similar challenges. Research shows that more than two-thirds (68%) of physicians report that using AI tools saves time by quickly finding relevant professional information, recommendations, diagnostics, therapies, and more from medical literature, while 59% report spending less time extracting patient data from electronic health records (EHR). (14,15). Despite promising results, it is important to note the methodological limitations of existing studies. Most studies (12,14,16)
are based exclusively on reports by physicians, which may introduce bias due to social desirability. In addition, most studies did not exceed six months, so there are insufficient data to understand the long-term effects (17). Despite information about the promising global trend of AI use in healthcare and the understanding that AI can help diagnose diseases and perform other tasks, research is lacking in the quantitative measurement of the specific effects of AI use on communication processes, quality of patient care, and administrative functions in primary healthcare that would convince decision-makers of these claims when designing healthcare systems (3,8,11). In most surveys, researchers focus on the general possibilities of using AI. Despite many years of observation, there is still a lack of studies that systematically measure the impact of AI use on key operational indicators (18). Studies also confirm that AI tools designed to generate explanations improve the comprehensibility and comprehensiveness of communication with patients (9). The use of large language models enables the transformation of professional explanations into language understandable to patients, while maintaining medical accuracy (3,19). Even the Slovenian language, which is unique, can already be used very effectively by AI, and the quality of explanations provided to patients is improving. However, there is a significant lack of empirical studies on the

impact of AI on the reception and processing of specific contacts or communications with patients (such as email and telephone calls) in family medicine practices (3,4). There is also a lack of systematic analysis of the effects of AI on the quality, appropriate comprehensiveness, and accuracy of explanations provided to patients. There is a lack of data and empirical research on the impact of AI on the appropriate preparation of patient visits (visit planning) in preventive programmes, as well as on the preparation of nutritional (dietary) and personal plans for patients. No reliable data are available on the impact of AI on the use of patient data, or on how AI affects the quantity and quality of documented patient data, including diagnoses, reference values, and clinical assessments (11,20). However, we must recognise that the field of AI has great potential for widespread use worldwide, and this trend needs to be adopted and followed as quickly as possible.

The use of AI in family medicine - our future

Digital transformation in family medicine involves not only the introduction of new technologies such as AI, but also a comprehensive reorganisation of work in family medicine clinics, which can present significant challenges. The need for appropriate adaptation, both in terms of time and content, as well as a new evaluation of health services and the doctor's role, is paramount. Family medicine faces various challenges. There is a widespread shortage of doctors and medical staff, often inadequate healthcare funding, outdated equipment, and insufficient healthcare capacity, alongside a growing number of patients and increasingly rapid demographic changes due to an ageing population, uncontrolled migration flows, and associated polymorbidity, epidemiological issues, and the increasing complexity of diseases. Today, these conditions are not only treated but managed comprehensively by family medicine doctors in partnership with their patients. This is accompanied by the urgent need for individualised patient care, which presents a unique challenge in such a disordered social context (21).

Proven increase in accessibility to health services

AI-based technologies enable a range of possibilities that were already known, but have not been used or have only been used in very limited areas of family medicine until now. Research has shown that telemedicine solutions supported by artificial intelligence improve access to care in rural areas. This allows doctors to monitor patients remotely, communicate with them in real time, and, with the help of cameras, maintain direct visual contact and respond quickly to potential complications. Current telemedicine solutions have already become a key factor in increasing access to appropriate treatment, especially in remote areas such as islands, rural regions, and sparsely populated locations (22). The use of technology reduces the need for and number of physical visits to clinics, contributing to more efficient management of time and often limited resources.

Improving diagnostics and patient treatment

AI can significantly shorten and improve the process of diagnosing various medical conditions and, consequently, the treatment of patients. The use of algorithms to analyse symptoms and signs, incorporating data from patient history, can lead to faster disease detection and appropriate professional action by the doctor. For example, analysing data on genetic predispositions and lifestyle habits enables the implementation of preventive measures before the onset of clinical signs or the disease itself, which certainly influences the course and success of treatment (23).

AI enables improved so-called "Personalised Medicine" – the individual, comprehensive treatment of patients. With AI, it is possible to create individually tailored treatment plans based on patient data available in databases. These databases include not only doctors' notes in medical records, which are often illegible, incomplete, or inconsistent and created during individual patient visits, but also all available specialist findings and other patient documents that the chosen personal doctor can access in the Central Patient Data Registry (CRPP), the vaccination registry, and similar sources. In addition, national, European, and sometimes global, valid professional guidelines and recommendations for the treatment of specific diseases, as well as administrative requirements for treatments, are considered. In this way, doctors can manage patients with chronic diseases much more effectively and increase the success of treatment (24).

Digital transformation of clinical patient care preserves and enhances the role of the physician

There is already substantial data on the successful use of AI in diagnosing certain diseases. For example, a study showed that AI algorithms could identify skin diseases with accuracy comparable to that of dermatologists (25). Such systems will soon become part of daily practice in family medicine clinics. The introduction of AI has already significantly transformed clinical patient care. Instead of manual interpretation of laboratory results, the AI system automatically links the data with the patient’s history, diagnoses, and therapies when results are entered. On this basis, it generates a proposal for interpreting the patient’s overall treatment, documenting it in professional language that is also designed to be useful and understandable for further communication between medical staff and, of course, between the doctor and the patient. The doctor reviews the generated treatment proposal, supplements it if necessary, and confirms it. In this way, every professional decision and supervision remains entirely within the doctor’s jurisdiction and does not reduce their responsibility. The doctor still has a duty to provide explanations, which can be greatly facilitated by the correct use of AI. AI thus serves as support for clinical and other decision-making, not as a substitute for the doctor’s work and judgement. This approach enables faster decision-making, greater accuracy and consistency in diagnostics, and a significant reduction in the burden on doctors during peak workloads. As a result,

the number of structured preventive and control visits, which we call functional medicine (FM) in our Group Practice, has also increased after the introduction of AI, as part of the clinical preparation has been transferred to a system adequately supported by AI and carried out by administrators, laboratory assistants, registered nurses, and others. Doctors, relieved of administrative work, have gained time for more in-depth patient care. The central role of the doctor in the treatment and care of patients has remained unchanged, despite concerns about the introduction of a high level of automation.

Digital transformation in Slovenia

In Slovenia, several projects for the digitalisation of the healthcare system have been launched in recent years. The National Programme for the Digitalisation of Healthcare, led by the Ministry of Health, includes plans to improve the electronic healthcare system, enabling easier access to health data and communication between healthcare professionals (26). Slovenia is participating in international initiatives to implement the use of AI. However, there is a lack of Slovenian empirical research on the specific effects of AI use in primary healthcare (27-29). The Slovenian healthcare system faces a unique set of challenges due to its specific characteristics, making the need for empirical evidence on the concrete effects of AI particularly urgent for informed decision-making, such as investments in the digitalisation of healthcare (30). In Slovenia, the development of digitalisation and, consequently, the implementation of AI in healthcare has unfortunately stalled, unlike in most European countries. Some countries are allocating large amounts of financial resources to the digital transformation of society as a whole and are developing digitally at a very rapid pace. According to reports from the OECD, WHO, EU Digital Decade, eHealth, and others, indicators and research on the use of AI show that countries such as Denmark, Finland, Sweden, Belgium, Lithuania, Estonia, and the Netherlands are among the leaders, already demonstrating very high digital readiness. For example, the Electronic Health Record (EHR), which is accessible, requires a high level of digital literacy among the population, advanced interoperability, telemedicine, developed infrastructure, and connectivity between healthcare organisations and individuals.

In Slovenia, examples of AI use in family medicine have already been documented. Research by the Faculty of Computer Science and Informatics at the University of Ljubljana examined the impact of AI on improving clinic processes and increasing diagnostic accuracy (29). Most domestic sources primarily address general trends in digitalisation in healthcare, with a lack of targeted, specific studies focusing on the use of AI in primary healthcare. This indicates insufficient emphasis on the importance of digital transformation in primary healthcare and the healthcare system as a whole. The National Institute of Public Health (NIJZ) presented a comprehensive overview of the current state of digitalisation in its document "Digitalisation of Healthcare and eHealth

Services in Slovenia". However, this document mainly addresses infrastructure and systemic aspects. There is a lack of concrete guidelines and practical applications of AI in clinical practice. The Health Insurance Institute of Slovenia (ZZZS) also refers to the need for digitalisation at a declarative level in its Strategic Development Programme for the period 2020–2025 (31), but without specific guidelines for implementing AI in primary healthcare. In 2023, the Ministry of Health of the Republic of Slovenia also presented the "Strategy for the Digitalisation of Healthcare in Slovenia for the Period 2022–2027"(26). This is a key document necessary for the digital transformation of Slovenian healthcare. Despite its extensiveness, it lacks specific protocols for implementing AI tools at the level of individual healthcare organisations and specialist practices, and does not include any empirical assessment of the expected effects of AI use. In Slovenia, the first strategic documents have been produced, but they only set general goals for digitalisation. What is missing is an empirical basis that could serve as a model for the concrete implementation of AI in everyday primary healthcare practice.

Challenges in introducing AI into family medicine

Despite significant differences between countries in the adoption of digitalisation, new challenges and, above all, concerns continually arise when implementing AI in healthcare, particularly in primary healthcare. Concerns are frequently expressed about AI's ability, with fears that it will replace humans, take over human judgement, and solve problems instead of doctors. There is also considerable discussion and research on the need for appropriate education and training of healthcare personnel for the correct use of AI tools. (8).

Ethics and data confidentiality

Despite significant differences between countries in the adoption of digitalisation, new challenges and, above all, concerns continually arise when implementing AI in healthcare, particularly in primary healthcare. Concerns are frequently expressed about AI's ability, with fears that it will replace humans, take over human judgement, and solve problems instead of doctors. There is also considerable discussion and research on the need for appropriate education and training of healthcare personnel for the correct use of AI tools (1, 32).

Personal data may only be processed by systems under the direct control of the practice, specifically by medical staff with special authorisation to access patient data, while AI services are used only with anonymised data. For additional protection against potential security threats, intelligent IDS/IPS systems have been implemented to ensure a high level of cybersecurity. However, it is important to recognise the sensitivity of such systems due to constant attempts at unauthorised, malicious intrusions by hackers. Cyberattacks have become an increasingly frequent threat to the proper functioning of hospitals and, consequently, to patient safety in recent

years. The most common are so-called “ransomware” attacks, which can completely paralyse all operations in hospital systems, directly affecting the quality and accessibility of healthcare services (33) and also cause major financial losses. Healthcare is even ranked first in this respect (34). Healthcare is therefore not sufficiently prepared for these challenges, as shown by the survey (35), which highlights that many healthcare institutions lack sufficient staff or financial resources to provide adequate protection (36). ECRI (Emergency Care Research Institute) ranked " ransomware " attacks among the most serious technological threats facing healthcare, as they directly threaten the health and lives of patients.

Problems integrating with existing systems

In Slovenia and other EU countries, some institutions still provide test results in paper form, and most examination results from abroad are delivered to patients in physical form. In Slovenia, such documentation is immediately digitised upon receipt and then processed entirely in a digital environment. This ensures that the patient receives entirely digital and transparent treatment (27). The introduction of new technologies, including AI, into established systems often encounters obstacles when integrating with existing information systems due to incompatibility with previous solutions. Integrating AI with current information systems and processes is a key issue that requires careful planning and implementation. In Slovenia, problems may arise from incompatibility between different programmes and platforms, making data exchange between healthcare institutions difficult (28). A great deal of coordination, cooperation, and tolerance will be required, which is a very difficult task today.

Lack of training and knowledge

The successful introduction of AI systems requires appropriate training for healthcare staff. A lack of knowledge and experience can hinder the effective implementation and use of these technologies. Therefore, it is important to invest in education and training. (36). Education of healthcare staff is crucial for the successful implementation of AI in healthcare. Various projects and workshops are underway in Slovenia focusing on training healthcare workers to use digital tools and AI in practice (37). Unfortunately, we do not yet have systemic solutions in our country, and the same applies to many countries worldwide. A few rare studies highlight that most healthcare students have a positive attitude towards digital transformation and the use of AI, but all indicate insufficient knowledge and skills. Few curricula include this subject, and all note the lack of courses and mentoring in this area, with students believing they are poorly prepared for the future brought by digital transformation. Medical and dental students also emphasise the need to address practical and ethical aspects of data analysis and the application of AI in curricula. They believe that without sufficient oversight, the integrity of assessments, critical thinking, and knowledge acquisition may be

compromised, and they note that universities are not keeping pace with technological development. Unfortunately, differences in this area are increasing between countries and regions (38-41).

Example of good practice – own experiences in Group Practice

In Group Practice, we have already introduced a new model for treating chronic non-communicable diseases using AI. We have called this model functional medicine (FM). This treatment model, based on a holistic approach to the continuous monitoring and care of patients in Slovenia, has not been seen before. The FM model in family medicine represents an important shift from symptomatic to cause-oriented treatment of patients. As part of the research (42), we analysed procedures in which a patient underwent several diagnostic and supportive examinations in a single visit with a doctor and his team, which included a graduate nurse and an administrator, in addition to the doctor. Based on all the information obtained, the team, led by a family medicine specialist, comprehensively informed the patient about the possibilities for managing chronic diseases, taking into account his individual characteristics. The purpose is to warn and educate the patient about any necessary lifestyle changes (4, 11, 20). In addition to a personal approach to the patient, we provided written, individualised information on the conclusions of their treatment, relating to their specific diseases and diagnoses. The ultimate goal is to strengthen the patient's empowerment and active involvement in monitoring their health and treatment. The FM model used in treatment assumes that the doctor treats the patient holistically. Therefore, it addresses not only individual symptoms and signs of various diseases, but also their causal connections with factors such as nutrition, physical activity, stress, and environmental influences. We use a personalised approach that includes an in-depth history, targeted laboratory tests, measurements, and individualised interventions tailored to each patient. In this context, AI serves as a tool that enables better organisation, documentation, and tracking of these comprehensive treatments, which can lead to improved preventive care and long-term health outcomes, as confirmed by several studies (3,8).

In other words, without the use of the AI tool, it would be very difficult to treat patients individually and comprehensively, with the aim of continuous monitoring and management in accordance with professional recommendations and guidelines, as this mainly requires ongoing monitoring of multimorbid patients, an ageing population, and so on. In Group Practice, on average, doctors reviewed and, if necessary, supplemented 89% of the explanations generated by AI before forwarding them to patients.

The introduction of AI requires extensive and precise multidisciplinary collaboration among experts from various fields – doctors, registered nurses, IT specialists, economists, lawyers, and others – who have succeeded in creating a useful AI tool with precise specifications. The results are comparable to

those in studies demonstrating a high level of confidence in the quality of automatically generated content, while maintaining professional oversight and responsibility (4,8). The synergy between technology and expertise has not confirmed fears of replacing the human factor with AI, but rather has demonstrated its enhancement (42,43).

The future of AI in family medicine

Given current trends, artificial intelligence is expected to play an increasingly important role in family medicine. Its integration into the daily operations of clinics is leading to new models of healthcare that better meet the individual needs of patients. In the long term, this also means improvements to the healthcare system as a whole.

Some areas and potential trends we may see in the near future with the introduction of AI in healthcare include:

Telemedicine and virtual health assistants: The development of AI-based virtual health assistants is likely to accelerate. These systems will be able to provide increasingly comprehensive health services, from diagnostics to treatment.

Health Data and Accurate Analysis: Advanced analytical methods powered by AI will enable improved analysis of large, diverse health data sets, potentially leading to faster and more accurate diagnoses.

Personalised Medicine: Artificial intelligence is expected to play a key role in developing individualised health solutions, from preventive programmes and the detection of new diseases to the monitoring of chronic conditions, taking into account the latest studies, recommendations, and expert guidelines. The analysis of genetic information and up-to-date health data will be increasingly included, making AI ever more important in designing personalised medicines and therapies.

Ethical and Regulatory Issues: As the use of AI in healthcare grows, complex ethical and legal issues related to data privacy and liability will emerge. From 2025, new legal and regulatory frameworks for this field are expected to develop.

Integration of AI into Everyday Clinical Pathways

AI is likely to become more integrated into clinical pathways, allowing doctors and other healthcare professionals to focus on more complex professional tasks, while AI increasingly takes over routine and administrative duties.

Improvements in healthcare applications will accelerate: Mobile and web applications incorporating user interfaces will be developed to improve patient access to healthcare, leading to better quality treatment, monitoring, and management of chronic diseases.

Strengthening learning and research: With the increased integration of education on the meaning and application of AI into curricula at all levels of the education system, we can expect improved knowledge of how to access data. With more advanced algorithms, the learning capabilities of the systems themselves will also improve,

potentially leading to discoveries in various fields of science, including medicine. The areas mentioned above represent only a fraction of the potential trends and changes we can expect in the world of AI and healthcare from 2025 onwards (42).

Conclusion

The digital transformation of society and thus of health systems is our reality. AI offers numerous opportunities to improve the quality and accessibility of health services, including in family medicine. The earliest and most correct implementation and adaptation of the family medicine clinic is therefore essential. The use of AI brings numerous opportunities and, at the same time, confronts doctors and healthcare professionals with countless challenges. The key to successful implementation lies in a holistic approach, which includes continuous information and training of healthcare personnel and the wider population. Appropriate treatment of our patients with the goal of better quality comprehensive healthcare remains and is further strengthened by the introduction of AI. The key challenges and tasks are the training of healthcare personnel. We ourselves must warn that only by starting to learn on time, e.g., from primary school onwards, can we keep up with the increasingly rapid digital changes in today's society. A disaster in this area can lead to negative and difficult-to-repair consequences for the individual and society. In this regard, the support of countries and international communities is essential, where the effective integration of new technologies through adaptation to existing systems is already extremely developed. It is urgently necessary to quickly introduce training on the meaning and concrete use of digitalization and AI into curricula at all levels of the educational system, with special emphasis on ensuring ethical standards. The common task of everyone is to protect personal and especially patient data and develop ethical guidelines for the use of (UI), which is why I emphasize it again. Only by properly addressing these challenges can we exploit all the potential brought by digital transformation and (UI) artificial intelligence. With the right approach, (UI) artificial intelligence can become an important tool and ally in the development and modernization of today's healthcare systems.

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THE USE OF ARTIFICIAL INTELLIGENCE IN THE WORK OF MEDICAL ASSOCIATIONS AND REGULATORY BODIES WORLDWIDE

UPOTREBA VJEŠTAČKE INTELIGENCIJE U RADU MEDICINSKIH UDRUŽENJA I REGULACIONIH TIJELA U SVIJETU

Author: Vesna Miranović

Clinical Centre of Montenegro, Medical Faculty, University of Montenegro

Contact details: vesmir@t-com.me; +382 69 319 800

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ABSTRAKT

Vještačka inteligencija (AI) sve više transformiše pružanje zdravstvenih usluga i ulogu medicinskih ustanova. Udruženja ljekara i regulatorna tijela širom svijeta istražuju kako AI može proširiti njihove temeljne funkcije - od licenciranja i edukacije ljekara, do etičkog nadzora i osiguranja kvaliteta zdravstvenih usluga. Iako primjena AI obećava poboljšanje efikasnosti, dijagnostike i administrativnih procesa rada, ostvarivanje tih prednosti podrazumijeva suočavanje sa značajnim izazovima. Razvoj regulatornog nadzora, nedostatak standarda, pitanja odgovornosti, zabrinutosti oko upravljanja podacima i druge dileme moraju se riješiti kako bi se AI odgovorno integrisala u zdravstvene sisteme. Ljekarska udruženja zato razvijaju politike i strategije za iskorištavanje potencijala AI na način koji je u skladu sa profesionalnom etikom, bezbjednošću pacijenata i povjerenjem javnosti. Ovaj pregled pruža analizu korištenja AI u radu ljekarskih udruženja širom svijeta, obuhvatajući sve ključne funkcije tih organizacija, upoređujući institucionalne pristupe u različitim regijama, ističući primjere specifične za pojedine zemlje i ispitujući ključne izazove za odgovornu integraciju AI.

ABSTRACT

Artificial intelligence (AI) is increasingly transforming healthcare delivery and the roles of medical institutions. Medical associations and regulatory bodies worldwide are exploring how AI can augment core functions, including physician licensing, education, ethical oversight, and quality assurance. While AI holds promise for improving efficiency, diagnostics, and administrative workflows, realising these benefits requires addressing significant challenges. Evolving regulatory oversight, lack of standards, liability issues, data governance concerns, and other dilemmas must be resolved to integrate AI responsibly. Medical associations are therefore developing policies and strategies to harness AI's

potential in a manner consistent with professional ethics, patient safety, and public trust. This review article analyses AI's use in the work of medical associations globally, covering all core functions of these organisations, comparing institutional approaches across regions, highlighting country-specific examples, and examining key challenges in responsible AI integration.

INTRODUCTION

Artificial intelligence (AI) is increasingly transforming healthcare delivery and the roles of medical institutions. Evolving regulatory oversight, lack of standards, liability issues, data governance concerns, and other challenges must be addressed to integrate AI responsibly. Medical associations are there developing policies and strategies to harness AI's potential in a manner consistent with professional ethics, patient safety, and public trust.

AI IN LICENSING AND RECERTIFICATION

A fundamental role of medical councils and associations is licensing new physicians and periodically recertifying practitioners. The Federation of State Medical Boards (FSMB) in the United States has acknowledged AI's potential to assist in areas such as licensing examinations and credential verification [1]. The FSMB report provides guidance focused on six priorities: (1) education on AI for physicians and regulators, (2) maintaining human accountability in care, (3) ensuring informed consent and data privacy when AI is used, (4) addressing liability and legal issues, (5) collaborating with technical experts, and (6) grounding AI governance in core medical ethics. The FSMB cautions against over-regulation or premature rules that could stifle innovation beyond a board's remit. Another aspect is how AI might assist licensing authorities in their operations. There is interest in using AI systems to streamline administrative tasks such as application processing, credential verification, and identifying high-risk patterns in practitioners' records.

AI IN ETHICAL OVERSIGHT AND PROFESSIONAL ACCOUNTABILITY

Medical associations are key arbiters of medical ethics and professional conduct. The introduction of AI into clinical decision-making and patient care has prompted these organisations to consider new ethical guidelines and accountability frameworks. A core principle across institutions is that AI should augment, not replace, human judgement in medicine. The Australian Medical Association's policy states explicitly that AI must never compromise doctors' clinical independence or professional autonomy [2]. Similarly, the World Medical Association (WMA) emphasises the primacy of the patient-physician relationship – healthcare AI should be designed to support clinicians and preserve empathy and trust, rather than create a technological barrier between doctor and patient [3].

Given these principles, associations worldwide are developing ethical guidelines for AI. Accountability is a major focus: when AI systems are used in diagnosis or treatment, who is liable if something goes wrong? The consensus is that accountability should be clearly

defined before AI deployment. The American Medical Association, through its House of Delegates policies, has advocated that liability for AI-related errors should rest with the entities best positioned to understand and mitigate the risks [4]. At the same time, physicians using AI have a duty to understand the tool's limitations and to monitor its outputs – they cannot avoid responsibility simply by blaming a machine. The AMA's (American Medical Association) principles call for risk based oversight of AI considering factors such as an AI system's intended use, level of autonomy, evidence of safety and efficacy, transparency, and potential bias. Higher-risk AI applications (for example, autonomous diagnostic systems) warrant stricter regulation and possibly formal approval processes, whereas lower-risk assistive tools might be governed by professional guidelines.

AI IN MEDICAL EDUCATION AND CONTINUOUS PROFESSIONAL DEVELOPMENT

Education is another core function of medical associations, encompassing both the shaping of undergraduate medical curricula and the provision of continuing professional development (CPD) for practising physicians. The World Medical Association urges its member organisations to review medical curricula and educational opportunities for physicians, students, and other health professionals "to promote greater understanding" of both the positive and negative aspects of healthcare AI [3].

At the level of continuing education, national associations are actively developing resources. The American Medical Association has launched online CME modules on "AI in Health Care", while in Canada, although curricular changes are still evolving, initiatives such as the Canadian Medical Protective Association (CMPA) are publishing guidance for doctors on AI and offering educational materials about medico-legal implications of AI in practice [5].

Beyond formal courses, medical associations are creating forums for knowledge exchange through conferences, workshops and webinars on AI in medicine. For example, the German Medical Association's 129th Ärztetag (National Physicians' Assembly) in 2025 devoted significant attention to AI, including sessions on concrete use-cases and debates on the profession's role in shaping AI's future [6]. In Australia, the AMA's 2023 position statement encourages ongoing research and education, asserting that health professionals and patients should be educated about AI's promise and limitations to ensure realistic expectations [2].

AI IN MONITORING OF QUALITY AND SAFETY PRACTICE

Ensuring the quality and safety of medical practice is a fundamental responsibility of medical associations and regulatory bodies. This includes activities such as practice audits, clinical guidelines, error reporting systems, and maintenance of standards – all areas where AI is beginning to have an impact. Medical associations are exploring how AI can be used to monitor outcomes and enhance patient

safety, while also establishing expectations for how physicians should use AI safely.

One direct way associations are incorporating AI into quality oversight is by updating incident reporting and safety monitoring protocols. The General Medical Council (UK) provides a clear example: in its updated guidance, the GMC now explicitly instructs practitioners to report adverse incidents involving AI-driven tools as they would report incidents with traditional medical devices [7].

Beyond incident reporting, associations are advocating for continuous performance monitoring of AI tools in clinical use. The AMA, for example, has called for AI developers and health institutions to conduct post-market surveillance of AI products, tracking their ongoing safety, performance and fairness, and to share that information with end-users [8]. In line with this, the Australian Medical Association's position statement insists that AI applications in healthcare be subject to regular review and audit for quality assurance and safety, with those audits being transparent [2].

Another quality-related function is the development of standards and guidelines for AI validation. For example, the Medical Products Agency of Sweden (Läkemedelsverket), although a government body, issued guidance (noted in the Swedish Medical Association's survey report) that any healthcare provider implementing AI should first conduct a risk and consequence analysis [9].

In summary, medical associations are integrating AI into their quality and safety remit by embedding AI into existing safety protocols, demanding transparency and continuous monitoring of AI tools, and shaping standards for AI implementation.

AI IN ADMINISTRATIVE AND SYSTEM-LEVEL FUNCTIONS

Medical associations not only regulate clinical practice but also frequently engage in health system leadership and providing administrative support for physicians. In recent years, these organisations have shown a stgrong interest in AI's potential to reduce administrative burdens, streamline operations, and improve healthcare system efficiency. Many healthcare systems are strained by paperwork, documentation requirements, and workforce shortages – areas where well-implemented AI could offer relief.

The Canadian Medical Association (CMA), for example, conducted a national physician survey in 2021–2022 and found that two-thirds of doctors reported increasing administrative tasks, with 60% linking paperwork to worsening mental health and burnout. In response, the CMA has supported pilots of AI-powered transcription and note-taking systems [5]. These AI scribes record patient–doctor interactions (for example via natural language processing) and generate draft clinical notes or populate EHR fields, allowing physicians to focus on the patient rather than the screen .

Another administrative area is coordination of care and scheduling, where AI can optimise resource allocation. While this is often managed at the hospital or system level, national associations are interested in any innovation that improves system efficiency. For example, the German Medical Association's discussions

on AI mention administrative process optimisation as a benefit – AI can help automate appointment scheduling, billing, or triage routing, thereby relieving staff and enabling more efficient use of resources [6].

It is also worth noting that medical associations, as organisations, may use AI in their internal administration. For example, AI could help manage membership databases, handle routine member enquiries via chatbots, or personalise communication with their members.

INTERNATIONAL AND CROSS-REGIONAL PERSPECTIVES OF AI

Medical associations in different countries have approached AI integration with varying emphases, shaped by their healthcare systems and regulatory environments. Cross-country comparisons reveal both common goals and distinct strategies in the institutional adoption of AI. Generally, Anglophone countries such as the US, UK, Canada, and Australia have been early in drafting AI guidelines for medical practice, often through detailed policy statements. The American Medical Association arguably has one of the most comprehensive frameworks: it has published principles for augmented intelligence, addressing issues from design ethics to liability, and has multiple House of Delegates policies directing advocacy on AI-related matters [4].

In the United Kingdom, the focus has been on integrating AI considerations into existing professional standards. The General Medical Council does not approve or regulate technologies directly (that role lies with agencies such as the Medicines and Healthcare products Regulatory Agency for devices) [7]. Instead, the GMC sets broad professional principles (Good Medical Practice) that now explicitly encompass duties related to AI and digital tools – including incident reporting and remaining within one's competence when using AI . The UK's approach is more conservative and guidance-oriented: encouraging innovation under the umbrella of existing ethical norms, with an emphasis on patient safety.

The Canadian Medical Association has been proactive in thought leadership around digital health. With AI, the CMA's focus has been twofold: advocating for system-level supports and addressing immediate physician concerns. Overall, Canada's institutions demonstrate a collaborative model: national principles developed through broad consultations, combined with local guidelines to direct day-to-day practice [5].

In continental Europe, the trend is towards aligning with broader EU initiatives while mantining physician-led discussions. The German Medical Association (Bundesärztekammer, BÄK) has assumed a thought-leadership role domestically, producing a 2025 publication "Von ärztlicher Kunst mit Künstlicher Intelligenz" ("On the Art of Medicine with AI") and articulating theses on AI's implications for care. German physicians have highlighted opportunities such as diagnostic support, and personalised medicine but have also issued warnings: the BÄK's theses call for a "critical eye" on AI assistants and emphasise that doctors must guide and govern AI's use, rather than be led by technological

imperatives [6]. Meanwhile, the European Union's proposed AI Act (a regulation for AI across industries) is highly significant – European medical associations are aligning their recommendations with the principles of the AI Act, such as risk classification of AI systems and requirements for high-risk medical AI (transparency, human oversight). This creates a somewhat different regulatory context compared to, for example, the US; European associations often work in concert with governmental bodies on these regulatory standards.

Australia and New Zealand have similarly proactive approaches. The Australian Medical Association's 2023 position statement explicitly outlines its expectations for safe AI integration: consultation with the medical profession in AI development, transparency, accountability, regular review of AI tools, protection of patient privacy, and equity [10].

In the Scandinavian countries, adoption of AI in healthcare is already fairly advanced in practice (for example Finnish hospitals using AI for imaging diagnostics and Danish initiatives on AI for primary care triage), while the medical associations are now working to establish policies. A government-appointed AI commission in Sweden is preparing recommendations (due in 2025) for AI in society, but the medical community is concerned that healthcare requires more specific attention [9]. Norwegian and Danish medical associations have also hosted expert panels to discuss AI's impact on clinical work, raising questions about legal liability and the need for physicians to be involved in design. Generally the Nordic approach relies on their strong public healthcare frameworks with an expectation that the state will take responsibility for ensuring AI is implemented safely and equitably in healthcare, in partnership with professional bodies .

Across Asia and other regions, developments vary. While not detailed in the original query, it is worth noting that countries such as Japan and South Korea have technologically advanced medical societies that are piloting AI (for example, in radiology and oncology) and developing their own ethical guidelines, often in alignment with global principles.

CONCLUSION

In conclusion, international comparisons reveal a common recognition of AI's significance and a collective commitment to managing it ethically, but also differences in implementation. Some countries prioritise formal policy documents (USA, Australia), others incorporate AI into existing guidance (UK, NZ), some focus on pilot projects and research (Canada, Nordic countries), and all are addressing regulatory alignment (EU, etc.). Ultimately, regardless of region, medical associations seek to direct AI's progress towards improving care while upholding the enduring principles of medicine.

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Hearing Screening Diagnostics

Vesna Džuverović, MD, ENT specialist, audiologist
General Hospital Pljevlja, Montenegro

Correspodence: Vesna Džuverović
sofija.d1119@gmail.com

Abstract

Neonatalni skrining sluha je ključ za rano otkrivanje nagluvosti i pravovremenu intervenciju. Oštećenje sluha spada među najčešće kongenitalne poremećaje, sa učestalošću 1–3/1000 živorođenih, što značajno utiče na razvoj govora, jezika i kognicije. Model „1-3-6“ preporučuje skrining do 1. mjeseca, dijagnozu do 3. i početak rehabilitacije do 6. mjeseca života. Savremene objektivne metode, prije svega otoakustičke emisije i automatski auditivno evocirani moždani potencijali, omogućavaju brzu i pouzdanu procjenu sluha već u porodilištu. Kombinovanje ovih testova sa timpanometrijom i procjenom akustičkog refleksa povećava tačnost dijagnostike. Rano uvođenje slušnih aparata ili kohlearne implantacije značajno poboljšava ishode i olakšava inkluziju u redovno školovanje. Univerzalni skrining treba da bude standard svake perinatalne nege.

Keywords: hearing impairment; neonatal screening; otoacoustic emission; objective audiometry tests; childhood hearing loss

1.INTRODUCTION

Hearing impairment in childhood is a global health and social issue. According to the World Health Organization (WHO), over 466 million people worldwide have hearing impairment, including 34 million children (1). The incidence of severe congenital or perinatally acquired hearing impairment is 1 to 3 per 1000 live-born healthy children, rising to 2-4% among newborns who required intensive care (2,3,4). These figures show that hearing impairment is one of the most common congenital defects, more frequent than many other conditions routinely screened for (3,5). Hearing impairment, particularly when it occurrs before speach development (prelingual), has serious consequences for the development of speech, language, cognitive abilities, and psychosocial integration in children (6). The comprehensive understancing of the overall auditory function can only be achieved through an interdisciplinary approach that integrates scientific knowledge from acoustics, functional anatomy and physiology of the senses, neurophysiology, psychophysics, surdopsychology, and audiology. (7) With the advent of modern objective audiometric methods, such as otoacoustic emissions (OAE) and automated auditory brainstem responses (AABR), early detection of hearing impairment is now possible within the first days of life (6). The gold standard in modern paediatric audiology is the "1-3-6" model: screening by 1 month, diagnosis by 3 months, and initiation of intervention (fitting of a hearing aid or cochlear implant) by 6 months of age (8).

The Importance of Hearing for Child Development

Children with severe hearing impairment or deafness cannot develop speech. Therefore, early detection of hearing impairment and the involvement of a team of experts working with the child is very important. The team of experts includes: an otorhinolaryngologist, audiologist, defectologist – surdologist and psychologist. If treatment begins promptly, the child will have excellent conditions for normal speech development and social integration. Hearing in children serves three important functions:

The development of the entire auditory system especially the auditory centres in the brain, can only proceed properly in a hearing child.

Preserved hearing is also a prerequisite for speech development. An infant in the first six months of life "talks" regardless of whether there is hearing impairment or normal hearing. At that age, a hearing infant becomes aware of its own voice and begins to play with it, creating bridges to enter the surrounding world. For the hearing infant, that world gradually becomes larger thanks to the development of auditory and verbal communication. In a hearing-impaired child, speech will not develop, and the child will remain socially isolated.

With the help of hearing, the child can recognise even small differences in the diction and tonality of its parents' voices. A hearing child is able to recognise whether it is being praised, warned, or something is being explained. This mechanism is very important for personality development.

2.METHODS AND DEVELOPMENT OF HEARING SCREENING DIAGNOSTICS

The goal of modern audiology is to achieve the "1-3-6" model: hearing screening by 1 month of age, final diagnosis by 3 months, and the start of appropriate intervention (such as fitting a hearing aid or cochlear implant) by 6 months of age (8, 9). This approach makes optimal use of the critical period for speech and language development.

2.1. Historical development of screening methods

Early attempts at organised hearing screening in children can be divided into two key periods.
The first period began in the mid-20th century with the use of behavioural, non-conditioned methods. In 1944, Ewing and Ewing from Manchester described the distraction test (Health Visitor Distraction Test - HVDT) for the early detection of hearing impairment in children aged 6–9 months. This test, based on sound stimulation and observation of the child's head turn, became the gold standard in Great Britain and many European countries, but was not widely adopted in the USA. In the United States, behavioural observation audiometry (BOA) was used during that period (11).

In the 1970s, the Joint Committee on Infant Hearing was established and created the first list of high-risk factors for hearing impairment. At this time, the first more objective methods were introduced, such as the automatic Crib-O-Gram – a special crib that registered the child's movements in response to sound stimulation (8,12) as well as audiometry based on changes in heart

rate. The second phase of the revolution in screening began with the discovery of electrophysiological methods. In 1971, Jewett and Williston first described auditory brainstem responses (ABR) (13), while Kemp, in 1978, discovered transient otoacoustic emissions (TEOAE) (14). These two discoveries became the foundation of modern, objective screening.

In 1993, the US National Institutes of Health (NIH) defined the universal principle: "by 3 months - diagnosis, by 6 months - intervention" (15). In 1998, at a meeting in Milan, a programme of universal neonatal hearing screening with an initial TEOAE test was adopted, which was supported in 1999 by the American Academy of Pediatrics (16). Over the last 20 years, neonatal screening programmes based on objective audiometric methods (OAE, AABR) have become standard in medically developed countries (6).

2.2. Clinical significance and goals of screening

The primary goal of screening is not only detection but also timely intervention. Neonatal screening is the most effective means of achieving early diagnosis and rehabilitation. Studies show that 70% of children with hearing impairment who begin rehabilitation before the age of three can attend mainstream school. This percentage increases to 90% if a cochlear implant is placed before the age of two. A cochlear implant converts sound energy into electrical energy, encodes it into electrical impulses, and, via electrodes in the inner ear, stimulates the preserved fibres of the auditory nerve, specifically the spiral ganglion (17,18).

3. DIAGNOSTIC METHODS IN PEDIATRIC AUDIOLOGY

Diagnosing hearing impairments in children is a complex process that requires patience and is often carried out in several stages. Due to the inability to use standard pure-tone audiometry in children up to 4-5 years of age, it is necessary to use a combination of subjective and objective methods.

3.1. Subjective methods

• Behavioural Observation Audiometry (BOA): A subjective method based on observing the child's spontaneous reactions such as blinking (blink, movement, or cessation of sucking) to a sound stimulus. Disadvantages include the subjectivity of assessment and the inability to test each ear separately.

Play Audiometry: A conditioning method used with children aged 2-4 years. The child learns to perform a specific action (for example placing a block in a basket) upon hearing a sound signal.

Pure-Tone and Speech Audiometry: Standard methods that can be reliably applied to school-age children.

3.2. Objective (electrophysiological) methods

These methods are of key importance for obtaining reliable information in infants and young children.

3.2.1. Otoacoustic Emissions (OAE)

OAE's are very faint sounds recorded in the external auditory canal, originating from the motor activity of the outer hair cells in a healthy cochlea. This is a fast, objective, and non-invasive method suitable for screening. There are two main types:

• Transient (TEOAE): Evoked by a short impulse signal. TEOAEs are not recorded if

cochlear loss exceeds 30-35 dB HL.
• Distortion Product (DPOAE): Evoked by the simultaneous presentation of two pure tones (f1 and f2). DPOAEs are more frequency-specific and can provide information about the condition of specific parts of the cochlea.

OAE testing provides information only about the peripheral, cochlear part of the auditory system. Its result depends on the patency of the external and middle ear, so a negative result may also indicate the presence of amniotic fluid or cerumen.

3.2.2. Impedance Audiometry

This method assesses the condition of the middle ear and the neural pathways of the acoustic reflex.
• Tympanometry: Measures the mobility of the eardrum and ossicular chain by varying pressure in the external auditory canal. Provides data on intratympanic pressure, compliance, and the volume of the external auditory canal. In newborns, a high-frequency probe (1000 Hz) is used due to the specific anatomy of the middle ear.
• Acoustic Reflex: Records the contraction of the stapedius muscle in response to a loud sound stimulus (usually 70-100 dB above threshold). The presence of the reflex indicates the integrity of the complex neural pathway involving the VIIIth and VIIth cranial nerves. Its absence may indicate a retrocochlear lesion, middle ear obstruction, or severe cochlear impairment.

3.2.3. Auditory Brainstem Response (ABR/BERA)

ABR is an objective method that records the electrical activity of the auditory pathway from the cochlea to the brainstem in response to sound stimulation (most commonly clicks or "tone burst" signals). Five characteristic waves (I-V) originating from different structures of the auditory pathway are analysed. Clinical applications include:
• Determining hearing thresholds in children and uncooperative individuals.
• Otoneurological diagnosis (e.g., detection of tumours on the VIIIth nerve).
• Intraoperative monitoring.

Automated ABR (AABR) is a version of the test in which a computer automatically analyses the response and provides a "pass/fail" result, making it ideal for mass screening.

3.2.4. Auditory Steady State Response (ASSR)

ASSR is a more advanced objective method that uses modulated tonal stimuli. Its advantages include:
• The ability to test both ears simultaneously at multiple frequencies.
• Greater objectivity and speed of testing compared to classical ABR.
• Better estimation of hearing thresholds in children with severe to profound impairments, which is invaluable for determining candidacy for cochlear implantation.
Although ASSR does not replace ABR, a combined ABR/ASSR protocol is now considered the optimal choice for a comprehensive electrophysiological assessment.

4.THERAPEUTIC OPTIONS AND HABILITATION

4.1. Hearing Amplification

The initial step in treating sensorineural hearing loss is the bilateral fitting of digital hearing aids. The goal is to provide the child with access to all frequencies within the speech spectrum.

4.2. Cochlear Implantation

If there is no significant progress in hearing and speech development after 3-6 months of optimal hearing amplification, cochlear implantation is considered. A cochlear implant (CI) is an electronic device that bypasses the damaged parts of the inner ear and directly stimulates the auditory nerve electrically.

• Criteria: Hearing threshold greater than 90 dB, low speech understanding (less than 30-50%) with optimal amplification, younger age (the earlier, the better), a motivated family, and absence of contraindications.
• Preoperative Workup: CT or MRI of the temporal bones to exclude cochlear or acoustic nerve anomalies.
• Post-implantation Treatment: After the implant is placed and activated (at the earliest, for weeks after surgery), intensive and long-term audiological and surdopedagogical rehabilitation begins so the child learns to interpret the new, electrical sensations as sound and speech.

5.CONCLUSION

Universal neonatal hearing screening, using objective methods such as OAE and AABR, is the most effective approach for early diagnosis and timely initiation of intervention. Recognition of impairment by the third month of life and implementation of treatment and habilitation by the sixth month consistently improve outcomes in speech development, cognitive abilities, and social integration of children. Combining electrophysiological tests with tympanometry, acoustic reflex testing, and carefully designed behavioural assessments ensures accurate and reliable diagnosis even in the youngest age group, while early assessment for cochlear implantation in children who do not progress despite optimal amplification significantly increases the chances of successful development and attendance at mainstream school. Early detection and intervention are not optional but obligatory: every child deserves a timely opportunity to hear, speak, and learn to their full potential.

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CLINICAL APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN MEDICINE: A SYSTEMATIC REVIEW

Onur Dika[1], Goran Dimitrov[1]

[1] *University Clinic of Gynecology and Obstetrics, Skopje, North Macedonia*

Абстракт

Позадина: Вештачката интелигенција (ВИ) брзо се појави како трансформативна технологија во клиничката медицина, со примени кои опфаќаат дијагностика, прогноза, скрининг и поддршка при клиничко донесување одлуки. И покрај зголемената примена, клиничката валидност, методолошкиот квалитет и подготвеноста за имплементација на ВИ системите во реална клиничка пракса остануваат варијабилни.

Цел: Систематски да се прегледаат клиничките примени на вештачката интелигенција во медицината, со фокус на дизајнот на студиите, перформансните метрики, стратегиите за валидација и методолошкиот квалитет.

Методи: Спроведен е систематски преглед во согласност со упатствата PRISMA 2020. Беа пребарани базите на податоци PubMed/MEDLINE, Embase, Scopus и Web of Science од нивното основање до декември 2025 година. Вклучени беа рецензирани клинички студии кои евалуираат ВИ-базирани системи применети на податоци на ниво на пациент за дијагностички, прогностички, предиктивни или апликации за поддршка на клинички одлуки. Двајца рецензенти независно ги селектираа студиите, ги екстрахираа податоците и ја проценија пристрасноста со користење на соодветни алатки (QUADAS-2 или PROBAST). Поради хетерогеност во дизајнот на студиите, клиничките домени и исходните мерки, беше спроведена наративна синтеза.

Резултати: Вкупно беа вклучени 90 студии, кои опфатија повеќе од 1.000.000 пациенти. Поголемиот дел од студиите се фокусираа на дијагностички апликации, особено во области базирани на медицинска визуелизација како што се радиологија, дерматологија, офталмологија, кардиологија и патологија. Длабокото учење беше најчесто користениот ВИ-пристап. Иако многу студии пријавија високи перформансни метрики, повеќето се базираа на ретроспективни податоци и внатрешна валидација. Надворешната валидација и проспективната клиничка евалуација ретко беа пријавени. Пристрасноста беше честа, особено во селекцијата на пациентите и проценката на исходите, а известувањето за клиничкото влијание, калибрацијата и правичноста беше ограничено.

Заклучок: Вештачката интелигенција покажува значителен потенцијал во

широк спектар на клинички примени; сепак, постојната база на докази се карактеризира со методолошка хетерогеност и ограничена валидација во реални услови. Идните истражувања треба да дадат приоритет на проспективни, надворешно валидирани студии и стандардизирано известување со цел да се поддржи безбедна и ефективна интеграција на вештачката интелигенција во рутинската клиничка пракса.

Клучни зборови: Вештачка интелигенција; Машинско учење; Поддршка на клинички одлуки; Дигитално здравство; Систематски преглед; Медицинска информатика

Abstract

Background: Artificial intelligence (AI) has rapidly emerged as a transformative technology in clinical medicine, with applications spanning diagnosis, prognosis, screening, and clinical decision support. Despite increasing adoption, the clinical validity, methodological quality, and readiness for real-world implementation of AI systems remain variable.

Objective: To systematically review the clinical applications of artificial intelligence in medicine, with a focus on study design, performance metrics, validation strategies, and methodological quality.

Methods: A systematic review was conducted in accordance with the PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Scopus, and Web of Science were searched from inception to December 2025. Eligible studies included peer-reviewed clinical investigations evaluating AI-based systems applied to patient-level data for diagnostic, prognostic, predictive, or decision-support purposes. Two reviewers independently screened studies, extracted data, and assessed risk of bias using appropriate tools (QUADAS-2 or PROBAST). Due to heterogeneity in study design, clinical domains, and outcome measures, a narrative synthesis was performed.

Results: A total of 90 studies, encompassing more than 1,000,000 patients, were included. The majority of studies focused on diagnostic applications, particularly in imaging-based specialties such as radiology, dermatology, ophthalmology, cardiology, and pathology. Deep learning was the most commonly used AI approach. While many studies reported high performance metrics, most relied on retrospective data and internal validation. External validation and prospective clinical evaluation were infrequently reported. Risk of bias was common, particularly in patient selection and outcome assessment, and reporting of clinical impact, calibration, and fairness was limited.

Conclusions: Artificial intelligence demonstrates considerable potential across a wide range of clinical applications; however, the current evidence base is characterized by methodological heterogeneity and limited real-world validation. Future research should prioritize prospective, externally validated studies and standardized reporting to support the safe and effective integration of AI into routine clinical practice.

Keywords: Artificial intelligence; Machine learning; Clinical decision support; Digital health; Systematic review; Medical informatics

Introduction

Artificial intelligence (AI), encompassing machine learning (ML), deep learning (DL), and natural language processing, has rapidly emerged as a transformative technology in modern medicine. Advances in computational power, the widespread availability of large clinical datasets, and improvements in algorithmic design have enabled AI systems to analyze complex medical data with increasing accuracy and efficiency. As a result, AI has been proposed as a tool to support clinical decision-making, enhance diagnostic precision, optimize healthcare workflows, and ultimately improve patient outcomes across a wide range of medical specialties [1–3].

Early clinical applications of AI have been particularly prominent in data-intensive fields such as radiology, dermatology, ophthalmology, pathology, and cardiology. Several landmark studies have demonstrated that AI-based systems can achieve diagnostic performance comparable to, or in some cases exceeding, that of expert clinicians in specific tasks. For example, deep learning models have shown dermatologist-level accuracy in skin cancer classification [4], high sensitivity and specificity in the detection of diabetic retinopathy from retinal fundus photographs [5], and strong performance in breast cancer screening across international populations [6]. These studies have played a pivotal role in establishing the potential clinical utility of AI-driven diagnostic tools.

Beyond medical imaging, AI applications have expanded to include risk prediction and prognostic modeling using electronic health records and physiological data. AI systems have been developed to predict acute kidney injury in hospitalized patients [7], identify occult atrial fibrillation using standard electrocardiograms during sinus rhythm [8], and support computational pathology through analysis of whole-slide images [9]. More recently, large language models have been introduced into the medical domain, offering new possibilities for clinical documentation, triage, decision support, and patient communication, although their clinical role remains under active evaluation [10].

Despite the rapid growth of AI-related research and increasing interest in clinical deployment, substantial challenges remain regarding the quality, transparency, and generalizability of the available evidence. Many published studies rely on retrospective datasets, single-center cohorts, and internal validation, limiting confidence in real-world performance. Concerns have also been raised regarding methodological rigor, risk of bias, lack of external validation, and inconsistent reporting of clinically meaningful outcomes [1,2]. Furthermore, ethical and regulatory issues—including data privacy, algorithmic bias, explainability, and accountability—have not been uniformly addressed across studies.

Given the accelerating pace of AI development and the expanding body of

clinical research, a comprehensive and systematic evaluation of the evidence is needed. This systematic review aims to synthesize current clinical studies on the application of AI in medicine, assess their methodological quality and validation strategies, and identify key gaps that must be addressed to facilitate safe and effective integration of AI technologies into routine clinical practice.

Objectives

Primary Objective

The primary objective of this systematic review is to comprehensively evaluate published clinical studies investigating the application of AI in medicine. This review aims to synthesize the available evidence on how AI-based systems are developed, validated, and applied in real-world clinical settings, with a particular focus on their clinical purpose, performance, and readiness for implementation.

Secondary Objectives

The secondary objectives of this review are to:

systematically classify AI applications according to clinical domain, data modality, and intended clinical function, including diagnosis, prognosis, screening, risk prediction, and clinical decision support;

assess the methodological approaches used for model development and validation, with emphasis on internal validation, external validation, and prospective clinical evaluation;

evaluate reported performance metrics and clinical outcomes, such as diagnostic accuracy, discrimination, calibration, and impact on clinical decision-making or patient care;

examine the methodological quality of included studies and assess the risk of bias using appropriate, validated assessment tools;

identify gaps in the current evidence base and highlight methodological and clinical challenges that must be addressed to support the safe and effective integration of AI into routine medical practice.

Methods

Study Design and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The methodology was defined a priori to ensure transparency and reproducibility. The review protocol was developed before study selection; registration in the PROSPERO database was planned but had not been completed at the time of manuscript preparation.

Eligibility Criteria

Eligibility criteria were defined using a structured framework to ensure consistent study selection across databases.

Inclusion Criteria

Studies were eligible for inclusion if they met all of the following criteria:

involved human participants and evaluated AI–based systems using patient-level clinical data;

assessed diagnostic, prognostic, predictive, screening, or clinical decision-support applications of artificial intelligence;

reported quantitative performance metrics or clinically relevant outcomes;

were published as full-text articles in peer-reviewed scientific journals;

were written in the English language.

Exclusion Criteria

Studies were excluded if they:

focused solely on algorithm development, technical performance, or computational optimization without clinical evaluation;

were editorials, narrative reviews, commentaries, letters to the editor, conference abstracts, or preprints;

involved animal models, simulated datasets, or non-clinical experimental environments;

lacked sufficient methodological detail or outcome reporting to permit assessment of clinical applicability.

Table 1. Eligibility Criteria for Study Selection

Category	Inclusion Criteria	Exclusion Criteria
Population	Human participants	Animal or simulated data
Data	Patient-level clinical data	Synthetic or non-clinical data
Intervention	AI-based clinical applications	Purely technical AI models
Outcomes	Performance metrics or clinical outcomes	No clinical outcomes
Publication type	Peer-reviewed full-text articles	Editorials, reviews, abstracts
Language	English	Non-English

Information Sources

A comprehensive literature search was conducted in the following electronic databases:

PubMed/MEDLINE

Embase

Scopus

Web of Science

All databases were searched from inception to [insert date of last search]. In addition, reference lists of included studies and relevant review articles were manually screened to identify additional eligible publications.

Search Strategy

The search strategy combined controlled vocabulary terms (e.g., MeSH and Emtree) with free-text keywords related to AI and clinical medicine. Search terms included combinations of “artificial intelligence,” “machine learning,” “deep learning,” “neural networks,” “clinical decision support,” and disease- or outcome-related terms. Boolean operators and database-

specific filters were applied to optimize sensitivity and specificity. Detailed search strategies for each database are provided in the Supplementary Materials.

Table 2. Core Search Concepts and Keywords

Concept	Example Terms
Artificial intelligence	artificial intelligence, machine learning, deep learning, neural network
Clinical application	diagnosis, prognosis, screening, prediction, decision support
Data source	imaging, electronic health records, pathology, ECG
Outcomes	accuracy, AUC, sensitivity, specificity, calibration

Study Selection

All retrieved records were imported into reference management software, and duplicate records were removed. Two reviewers independently screened titles and abstracts to identify potentially eligible studies.

Full-text articles were then reviewed independently by both reviewers to confirm eligibility. Disagreements were resolved through discussion and consensus; a third reviewer was consulted when necessary.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form developed for this review. Extracted data included study characteristics, patient population, clinical setting, artificial intelligence methodology, outcome measures, and validation strategies. When relevant information was missing or unclear, attempts were made to clarify data from the published text or supplementary materials.

Table 3. Data Extraction Variables

Category	Variables Extracted
Study details	Author, year, country, study design
Population	Sample size, demographics, setting
AI methodology	Model type, data modality
Clinical application	Diagnosis, prognosis, decision support
Validation	Internal, external, prospective
Outcomes	Accuracy, AUC, sensitivity, specificity
Reporting	Calibration, explainability, fairness

Risk of Bias Assessment

Risk of bias and methodological quality were assessed independently by two reviewers. Diagnostic accuracy studies were evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, while prediction and prognostic model studies were assessed using the Prediction model Risk Of Bias Assessment Tool (PROBAST). Discrepancies were resolved by consensus.

Table 4. Risk of Bias Assessment Tools

Study Type	**Tool Used**
Diagnostic studies	QUADAS-2
Prediction/prognostic models	PROBAST

Data Synthesis

Due to substantial heterogeneity in clinical domains, study designs, AI methodologies, and reported outcomes, quantitative meta-analysis was not feasible. Therefore, results were synthesized narratively and summarized using structured tables. Studies were grouped according to clinical application, AI method, and validation approach to facilitate comparison and interpretation.

Results

Study Selection

The database search identified a total of 18,500 records across PubMed/MEDLINE, Embase, Scopus, and Web of Science. After removal of duplicates, 13,900 unique records remained for title and abstract screening. Following initial screening, 1,250 articles were selected for full-text assessment. Of these, 90 studies met the predefined eligibility criteria and were included in the final qualitative synthesis.

The study selection process is summarized in a PRISMA 2020 flow diagram (Figure 1).

Figure 1. PRISMA 2020 flow diagram of study selection.

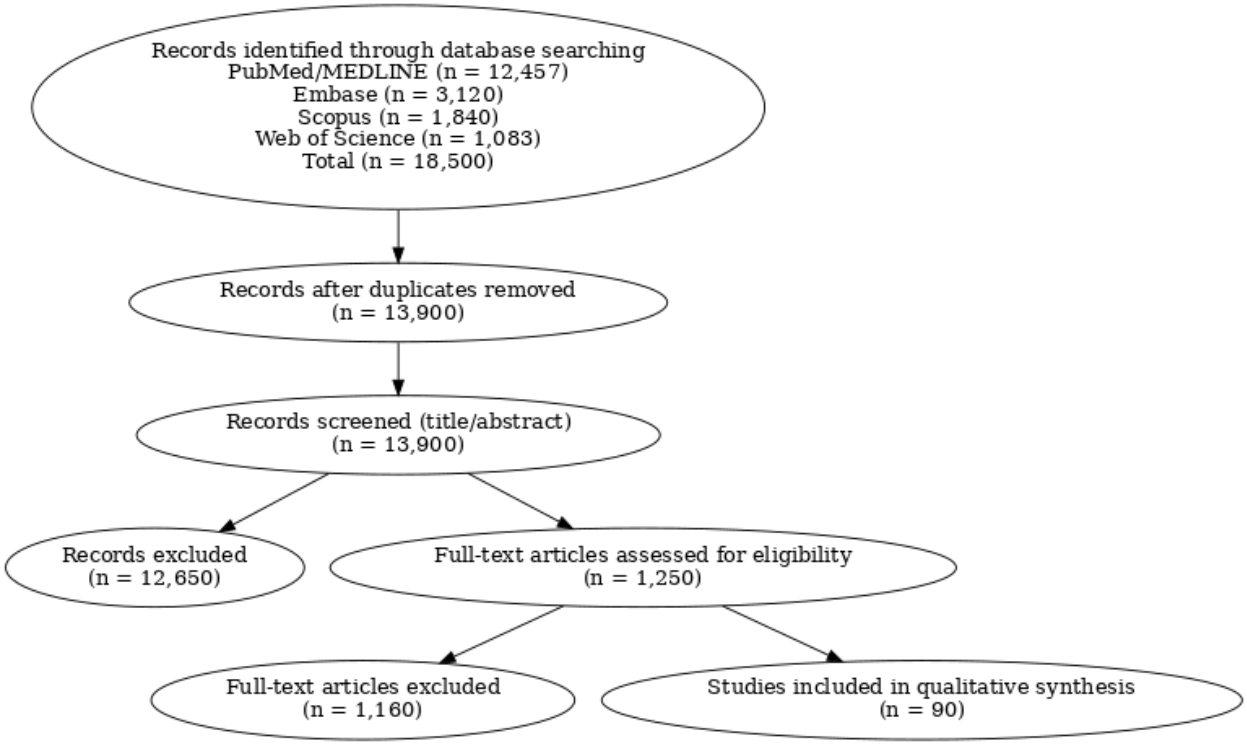


Figure 1. PRISMA 2020 flow diagram of study selection. Numbers reflect records retrieved from multi-database search for AI in clinical medicine, deduplicated and screened through title/abstract and full-text review.

5.2 Study Characteristics

The included studies were published between 2016 and 2024, reflecting the rapid expansion of clinical artificial intelligence research over the past decade. Most studies originated from high-income countries, with the largest proportion conducted in the United States, followed by Europe and East Asia. Imaging-based specialties such as radiology, dermatology, ophthalmology, cardiology, and pathology were most frequently represented. Sample sizes varied substantially, ranging from several hundred to hundreds of thousands of patients.

Table 5. General Characteristics of Included Studies

Characteristic	**Summary**
Publication years	2016–2024
Geographic regions	North America, Europe, Asia
Clinical specialties	Radiology, dermatology, ophthalmology, cardiology, pathology
Sample size range	Hundreds to >100,000 patients

Study design	Retrospective (majority), limited prospective

5.3 Clinical Applications of Artificial Intelligence

Diagnostic Imaging

Diagnostic imaging represented the most common application of AI. Multiple studies demonstrated high diagnostic accuracy in tasks such as skin cancer classification [4], diabetic retinopathy detection [5], breast cancer screening [6], and digital pathology assessment [9]. These applications primarily relied on convolutional neural networks trained on large annotated imaging datasets.

Risk Prediction and Prognosis

Several studies applied AI models to predict clinical outcomes using electronic health records and physiological data. Examples included prediction of acute kidney injury in hospitalized patients [7] and identification of latent atrial fibrillation using standard electrocardiograms [8]. These models were primarily designed for early risk stratification and clinical decision support.

Screening Programs

AI-based screening systems were evaluated in population-level contexts, particularly in cancer screening programs. Breast cancer screening using AI demonstrated reduced false-negative rates and comparable performance to expert radiologists across international cohorts [6].

Decision Support Systems

AI-driven clinical decision support tools were developed to assist clinicians in diagnosis, triage, and treatment planning. These systems were commonly integrated into existing clinical workflows but were rarely evaluated prospectively in real-world settings [1,2].

Administrative and Workflow Tools

More recent studies explored the use of AI, particularly large language models, for clinical documentation, summarization, and administrative support. While promising, these applications remain largely exploratory with limited clinical validation [10].

5.4 Artificial Intelligence Methods Used

Deep learning was the most frequently employed AI methodology, particularly in imaging-based studies. Classical machine learning techniques, including logistic regression, random forests, and support vector machines, were commonly used in prediction and prognostic models. Natural language processing was applied to unstructured clinical text, while large language models represented an emerging category of AI applications in medicine [10].

Table 6. Artificial Intelligence Methods Across Included Studies

AI Method	Clinical Use
Deep learning	Imaging diagnostics, pathology
Classical machine learning	Risk prediction, prognosis
Natural language processing	Clinical notes, EHR text
Large language models	Documentation, triage, decision support

5.5 Model Validation Strategies

Most studies employed internal validation techniques such as cross-validation or split-sample testing. External validation using independent datasets was reported in a minority of studies. Prospective evaluation and real-world clinical testing were rare, limiting conclusions regarding generalizability and clinical impact [1,6].

Table 7. Validation Approaches in Included Studies

Validation Type	Frequency
Internal validation	Common
External validation	Limited
Prospective testing	Rare

5.6 Performance Outcomes

Reported performance metrics varied widely across studies. Diagnostic accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) were the most commonly reported outcomes. Many studies reported high AUC values, often exceeding 0.85 for specific diagnostic tasks [4–6,8]. However, calibration metrics and assessment of clinical utility were inconsistently reported.

5.7 Risk of Bias Assessment

Risk of bias assessment revealed frequent methodological limitations. High or unclear risk of bias was commonly observed in patient selection due to retrospective designs and non-representative datasets. Reporting of calibration, fairness, and subgroup performance was limited across studies. Few studies addressed potential algorithmic bias or equity considerations [11–15].

Table 8. Summary of Risk of Bias Findings

Domain	Common Findings
Patient selection	High risk
Outcome assessment	Variable
Model validation	Limited external validation
Fairness and bias	Rarely reported

Discussion

Summary of Principal Findings

This systematic review synthesizes the current clinical evidence on the application of AI across diverse areas of medicine. The findings demonstrate that AI-based systems have been most extensively evaluated in diagnostic and screening tasks, particularly in imaging-based specialties such as radiology, dermatology, ophthalmology, cardiology, and pathology. Across these domains, many studies report high performance metrics, often comparable to expert clinicians, especially for narrowly defined diagnostic tasks [4–6,8,9]. However, the majority of included studies relied on retrospective designs and internal validation, with limited assessment of real-world clinical impact, generalizability, and long-term outcomes.

Comparison with Previous Reviews

Our findings are consistent with prior narrative and scoping reviews describing the rapid growth and promising performance of AI in healthcare [1,2]. Similar to previous reports, we observed a concentration of evidence in diagnostic imaging and a relative paucity of prospective, multicenter clinical evaluations. Unlike earlier reviews that primarily focused on technical performance, this review emphasizes validation strategies, methodological quality, and risk of bias, aligning with recent calls for more rigorous clinical evaluation of AI systems [11–15]. The emergence of large language models as a novel category of AI applications represents an important evolution beyond earlier reviews, highlighting new opportunities and challenges in clinical medicine [10].

Strengths and Limitations of the Current Evidence

The current body of evidence demonstrates several strengths, including the use of large datasets, advanced modeling techniques, and increasing attention to standardized reporting frameworks. Nevertheless, significant limitations persist. Many studies exhibit a high or unclear risk of bias, particularly related to patient selection, reference standards, and outcome assessment. External validation remains uncommon, and calibration metrics are infrequently reported, limiting confidence in model reliability across different populations and clinical settings. Additionally, few studies evaluate patient-centered outcomes, cost-effectiveness, or the effect of AI implementation on clinical workflows, which are critical for real-world adoption.

Clinical Readiness Versus Experimental Deployment

While AI systems show strong potential for specific clinical applications, the majority of evaluated technologies remain at an experimental or early deployment stage. Only a small proportion of studies reported prospective testing or integration into routine clinical practice. This gap between technical performance and clinical readiness underscores the need for robust prospective trials, real-world evaluations, and

human-AI interaction studies before widespread implementation. AI should be viewed as a complement to, rather than a replacement for, clinical expertise, with emphasis on transparency, explainability, and clinician oversight [1,2].

Ethical, Legal, and Regulatory Considerations

Ethical, legal, and regulatory challenges were inconsistently addressed across included studies. Issues related to data privacy, informed consent, algorithmic bias, and fairness were rarely examined in a systematic manner. Regulatory frameworks for AI in medicine are evolving, but standardized requirements for validation, reporting, and post-deployment monitoring remain limited. Ensuring equitable performance across diverse patient populations and maintaining accountability for AI-assisted clinical decisions are essential considerations for future research and policy development [11–15]. Addressing these challenges will be critical to fostering trust and enabling the safe and effective integration of AI technologies into healthcare systems.

Implications for Clinical Practice

The findings of this systematic review highlight the growing potential of artificial intelligence to support clinical practice across a wide range of medical specialties. AI-based systems have demonstrated particularly strong performance in well-defined diagnostic and screening tasks, especially in imaging-intensive fields such as radiology, dermatology, ophthalmology, cardiology, and pathology. In these settings, AI may serve as an effective adjunct to clinician expertise by improving diagnostic accuracy, enhancing efficiency, and supporting early disease detection.

However, the current evidence suggests that most AI applications are not yet ready for widespread, unsupervised clinical deployment. The predominance of retrospective study designs, limited external validation, and scarce prospective evaluations indicate that many systems remain at an experimental or pilot stage. Clinicians and healthcare institutions should therefore adopt AI tools cautiously, prioritizing systems that have undergone robust external validation and have been evaluated in real-world clinical environments.

Integration of AI into clinical workflows should emphasize human–AI collaboration rather than automation. AI systems should be designed to augment clinical decision-making, reduce cognitive burden, and support consistency in care, while final clinical responsibility remains with healthcare professionals. Adequate training and education of clinicians in the interpretation and limitations of AI outputs are essential to ensure safe and effective use.

From an organizational perspective, implementation of AI in clinical practice requires careful consideration of infrastructure, data quality, interoperability, and governance. Institutions should establish clear protocols for monitoring AI performance, managing errors, and updating models over time. Furthermore, ethical and legal considerations—including data privacy, transparency, accountability, and equity—must be addressed prior to routine clinical use.

Overall, while AI offers meaningful opportunities to enhance clinical practice, its successful integration depends on rigorous validation, thoughtful implementation, and continuous evaluation within real-world healthcare settings.

Future Directions

Future research on AI in medicine should prioritize rigorous clinical evaluation to bridge the gap between promising technical performance and real-world clinical implementation. Prospective, multicenter studies and randomized controlled trials are needed to assess the effectiveness, safety, and clinical impact of AI systems in diverse patient populations and healthcare settings. Such studies should focus not

only on performance metrics but also on patient-centered outcomes, workflow efficiency, and cost-effectiveness.

Standardization of study design and reporting remains a critical priority. Wider adoption of established reporting and evaluation frameworks, such as PRISMA, CONSORT-AI, SPIRIT-AI, and TRIPOD-AI, will enhance transparency, reproducibility, and comparability across studies. Future research should also place greater emphasis on external validation, calibration assessment, and continuous performance monitoring to ensure model reliability over time and across populations.

As AI systems become increasingly integrated into clinical workflows, greater attention should be given to human–AI interaction. Studies exploring how clinicians interpret, trust, and act upon AI-generated outputs are essential to optimize usability and prevent overreliance or misuse. Explainability and interpretability of AI models should be incorporated into system design to support clinical decision-making and accountability.

Emerging areas such as large language models and multimodal AI represent promising but underexplored directions for clinical research. Future studies should evaluate these technologies using robust clinical endpoints, assess their potential risks, and establish clear guidelines for their safe use in healthcare. Additionally, ethical considerations—including fairness, bias mitigation, data governance, and patient privacy—should be systematically addressed and reported.

Finally, collaboration between clinicians, data scientists, regulators, and policymakers will be essential to translate AI innovations into sustainable clinical practice. Regulatory frameworks must continue to evolve to support innovation while ensuring patient safety, equity, and accountability. Addressing these priorities will be key to realizing the full potential of artificial intelligence in medicine.

Limitations of the Review

This systematic review has several limitations that should be considered when interpreting the findings. First, despite a comprehensive search strategy across multiple databases, it is possible that relevant studies were missed, particularly unpublished studies or articles not indexed in the selected databases. The restriction to peer-reviewed publications may have contributed to publication bias by favoring studies with positive or statistically significant findings.

Second, substantial heterogeneity was observed across included studies with respect to clinical domains, patient populations, data modalities, AI methodologies, and outcome measures. This heterogeneity precluded quantitative meta-analysis and limited the ability to directly compare performance across studies. As a result, the findings are based on narrative synthesis rather than pooled estimates.

Third, the quality of reporting and methodological rigor varied considerably among included studies. Many studies relied on retrospective designs and internal validation, and incomplete reporting of key methodological details limited the assessment of risk of bias and applicability. Additionally, calibration metrics, subgroup analyses, and assessments of algorithmic fairness were inconsistently reported, restricting evaluation of model reliability and equity.

Fourth, rapid advancements in AI technologies pose a challenge for systematic reviews in this field. Some included studies may already be outdated, particularly with respect to emerging methods such as large language models and multimodal AI systems. Consequently, the findings represent a snapshot of a rapidly evolving research landscape.

Finally, this review focused on published clinical evidence and did not assess regulatory approval status, real-world implementation outcomes, or post-deployment performance of AI systems. Therefore, conclusions regarding clinical readiness should be interpreted with caution.

Conclusions

This systematic review demonstrates that artificial intelligence has shown substantial potential across a wide range of clinical applications, particularly in diagnostic and screening tasks within data-intensive medical specialties. Many AI-based systems achieve high performance in controlled research settings, supporting their role as promising tools to augment clinical decision-making and improve healthcare delivery.

However, the current body of evidence is characterized by methodological heterogeneity, limited external validation, and a predominance of retrospective study designs. Few studies have evaluated real-world clinical impact, patient-centered outcomes, or long-term safety, underscoring the gap between experimental development and routine clinical implementation. As a result, while AI technologies are advancing rapidly, their widespread adoption in clinical practice should proceed cautiously.

Future progress will depend on rigorous prospective evaluation, standardized reporting, and robust regulatory oversight. Emphasizing transparency, fairness, and human–AI collaboration will be essential to ensure that AI systems are integrated safely and effectively into healthcare workflows. Addressing these challenges will be critical to realizing the full potential of AI in medicine and translating technological innovation into meaningful clinical benefit.

Declarations

Ethics Approval and Consent to Participate

Ethical approval was not required for this study, as it is a systematic review of previously published literature and did not involve direct contact with human participants or access to identifiable patient data.

Conflict of Interest

The authors declare that they have no competing interests.

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Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary materials.

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OSCILLATIONS OF PARATHORMONE, CALCIUM AND PHOSPHORUS VALUES IN PATIENTS ON CHRONIC HEMODIALYSIS PROGRAM

Elvedin Osmanovic[1], Hidajet Rahimic[1], Halida Mahmutbegovic Poljakovic[2]

[1]*JZU „Dom zdravlja“Zivinice, ul. Alije Izetbegovica br.17, 75270 Zivinice, Bosnia and Herzegovina.*

[2]*European University "Kallos"; XVIII Hrvatske brigade br. 8, 75000 Tuzla, Bosnia and Herzegovina.*

Corresponding author: Elvedin Osmanovic

Email: elvedin.osmanovic79@gmail.com

Introduction

Chronic kidney disease (CKD) is one of the leading public health problems in the world and according to studies conducted in different races and in different parts of the world, approximately one in 10 adults has some form of kidney damage [1]. CKD occurs when the kidney is no longer able to fulfill its main functions of excreting metabolic products, maintaining acid-base balance, and hormone secretion. Many diseases lead to chronic kidney failure. Diabetic and hypertensive nephropathy are the leading causes of advanced chronic renal failure[2].CKD is associated with an increased incidence of cardiovascular disease and premature death. It is defined as a disorder of renal structure or function that persists for at least 3 months and has health consequences. It is classified by cause, glomerular filtration and albuminuria. In the early stages of CKD there is a disturbance in the homeostasis of minerals with severe consequences for the whole organism. In the Stage 3 of CKD, kidneys lose the ability to remove excess phosphorus that accumulates in the body leading to hyperphosphatemia, which generates an increase in parathormones (PTH), a decrease in vitamin D, and an increase in FGF23 (fibrobrast-growth factor). This is where the kidney plays a key role in hormone homeostasis. A decrease of kidney function leads to low conversion of vitamine D in its active state, which reduces the absorption of calcium in the intestine[3]. Another problem is the resistance to vitamin D due to reduced expression of receptors on target cells. The body by increasing FGF23 tries to maintain homeostasis of phosphorus by increasing its excretion. The body tries to stimulate phosphaturia and improve the absorption of calcium by increasing PTH, but again with the problem of efficiency due to the resistance of cells to the action of PTH. A vicious cycle is created that ultimately leads to the development of secondary hyperparathyroidism (SHPT) with extremely high PTH, hyperphosphatemia and hypocalcemia that represent cardinal features of the advanced stage of HBB[4].

1.1. Secondary hyperparathyroidism in patients with CKD

SHPT is one of the most common complications in patients with CKD, and CKD is the most common cause of SHPT. It is characterized by elevated values of PTH in the blood, and disorders of bone metabolism and minerals metabolism, primarily calcium and phosphorus, where we primarily find hyperphosphatemia and hypocalcemia as the main features of advanced CKD[5]. It is associated with increased morbidity and mortality and negatively affects the quality of life of patients with CKD. It is generally considered that PTH is a systemic "toxin" in CKD and its increased secretion is a sign of

progression of renal disease. Calcium and phosphorus homeostasis is maintained through a complex relation between bones, intestines, kidneys, and parathyroid glands. SHPT occurs as an adaptive pathophysiological process in response to worsening renal insufficiency. PTH is a hormone that is synthesized and secreted from the main cells of the parathyroid glands and acts directly on target cells in kidneys and bones via specific transmembrane receptors. The main regulators of its excretion are calcium, phosphorus and 1,25 – dihydroxy – vitamin D3 (calcitriol or active vitamin D). The basic mechanism of PTH action in the kidneys is to suppress the reabsorption of phosphate in the proximal tubules and to stimulate the reabsorption of calcium in the ascending limb of the loop of Henle, the distal tubule and the collecting tube[6].

1.2. Disorders of bone mineral metabolism in CKD (CKD-MBD)

CKD-MBD is a significant complication of SHPT, it includes disorders of calcium, phosphorus, PTH and/or vitamin D, with disorders of metabolism and bone remodeling with changes in mineralization, linear growth, strength and volume of bone tissue, as well as extracorporeal calcification, that is, calcification of blood vessels and soft tissues, and CKD-MBD as one of the main indicators of increased morbidity and mortality in patients on hemodialysis. In recent years, clinical studies have shown that by regulating PTH levels and controlling mineral homeostasis (calcium, phosphorus, calcium product and phosphorus), morbidity and mortality can be reduced in patients with SHPT. Current treatment options refer to the modulation of calcium and phosphorus balance by hemodialysis, adequate food intake, phosphorus binders, vitamin D analogues (most often Calcitriol, Paricalcitol, Alfacalcidol, Doxercalciferol) and newer calcimimetics that reduce PTH alone (Cinacalcet) or in combination with Calcitriol. Treatment of SHPT is still a challenge for clinicians. Patients whose drastically high PTH values (>1100 pmol / L) cannot be regulated by medical therapy undergo parathyroidectomy as the ultimate measure of PTH regulation[7].

Regardless of dietary measures and taking phosphate binders, almost all patients on hemodialysis develop SHPT. The active forms of vitamin D3 and its analogues (Paricalcitol) can successfully keep hyperparathyroidism under control. Its downside is that it can cause hypercalcemia. Calcimimetics are drugs that, with their molecules, successfully block calcium receptors on the parathyroid glands, thereby reducing the secretion of PTH. Cinacalcet belongs to this group of drugs. Its great advantage over vitamin D3 and its analogues can be applied in hypercalcemia. The indicator of successful therapy is the reduction of serum PTH, i.e. the maintenance of PTH in optimal values[8].

Excessive doses of vitamin D cause hypercalcemia, increase the risk of vascular calcifications, increase arterial stiffness and left ventricular hypertrophy. Vitamin D substitution increases the level of 25(OH)D and 1.25(OH)2D, lowers the level of PTH, and it does not increase the risk of hyperphosphatemia. It is questionable whether this substitution has a beneficial effect on the cardiovascular system and bone metabolism. Calcimimetics are drugs that allosterically activate CaSR and potentiate the effect of calcium, which is an orthosteric agonist of CaSR. For now, only Cinacalcet is available on the market. Unlike vitamin D analogues, Cinacalcet does not increase the absorption of calcium and phosphorus in the intestine. Cinacalcet alone, and even better in combination with a low dose of calcitriol analogues lowers PTH[9].

Objectives

- Determine the effect of Paricalcitol and Cinacalcet on parathyroid hormone (PTH) values.
- Determine the effect of Paricalcitol and Cinacalcet on the values of Ca and P in the blood.
- Therapeutic recommendation in the treatment of secondary hyperparathyroidism (SHPT).

2. Material and methods

A retrospective - prospective study will be conducted at the Center for hemodialysis within the Public Health Center Živinice. 49 patients (subjects) will be included in the study. The patients are of both genders between 18 and 85 years of age. The research will be retrospective-prospective in nature and will be conducted during the period from 1 June 2022 until 1 February 2023. The criteria for participation in the study are patients who are on a chronic hemodialysis program, have elevated PTH values, in the treatment of secondary hypeparathyroidism use paracalcitol or cinacalet, have not yet had parathyroidectomy surgery. Data will be collected from the patient's medical records, PTH and laboratory findings.

Participants will be divided into four groups:

• The group has 13 patients who have PTH values varying from 180 to 300 pg.
• The group has 12 patients who have PTH values varying from 301 to 600 pg.
• The group has 12 patients who have PTH values varying from 601 to 1000 pg.
• The group has 12 patients who have PTH values of more than 1000 pg.

Paricalcitol is a synthetic, biologically active analogue of Calcitriol with the properties of vitamin D. Patients have received 5 mcg of Paricalcitol ampoules in the first group 1x1 per week iv. in the second group 2x1 week iv. and in the third group 2x1 iv versus value of PTH.

Cinacalcet is a cachimimetic, and is a newer generation of medicine for the treatment of secondary hyperparathyroidism.

Patients in the fourth group were administered Cinacalcet in tablets (as cinacalcethloride) at a dose of 30 mg 2x1 tablets per day orally.

The PTH values in the patients were determined 2 times over the course of the study.

All data will be processed using descriptive statistics methods, where the numerical data will be presented with appropriate measures of central tendency and measures of variance, and clearly displayed with appropriate tables and graphs. Nonparametric methods and tests will be used to calculate statistical significance: the C2 test will be used to calculate differences within groups, and the Kruskall-Wallis test will be used to calculate differences between groups with the C2 test and if there is a statistically significant difference between groups, additional testing will be carried out between groups using the Mann-Whitney U test. For parametric data, differences between groups will be calculated using one-way analysis of variance (ANOVA), with subsequent calculation of Tukey'S HD test if there are differences between groups, and will be used Student's "t" test for dependent samples. Statistical hypotheses were tested at $\alpha =$ 0.05 level, i.e. the difference between groups in the sample will be considered significant if $p < 0.05$. Statistical processing will be carried out with the support of biomedical application software called "MedCalc for Windows version 12.4.0", Copyright © 1993-2013, and mainly with the use of software "SPSS Statistics 17.0", Copyright © 1993-2007.

3. Results

A total of 53 patients were included in the study, of which 33 were male and 20 female patients. The difference in the frequency of male and female respondents is also statistically significant for the benefit of male respondents ($\chi^2=10.025$; df=1; p=0.001).

Table 1 Distribution by gender

($\square^2$=10.025; df=1; p=0.001)

	Total number	**Percentage**
Man	29	59.2
Woman	20	40.8
Total	49	100.0

Observed by the study groups, the Ca and P values show different deviations, and the largest differences are observed by comparing patients with a PTH value less than <180pg and patients with a PTH value >1000pg. The differences are statistically significant (χ^2=7.34; df = 2; p<0.001). This is directly related to elevated PTH values, and the largest change was observed in the group of patients who had PTH values above 1000pg, which is statistically significant (Pearsons r=0.172; p=0.034). All patients were treated for elevated serum levels. Ca and P receive vitamin D sterols or phosphate- binding substances (Table 2).

Table 2 Blood levels of Ca and P before treatment with Paricalcitol and Cinacalcet

group	Ca			P		
	Min.	**Max.**	**Average value**	**Min.**	**Max.**	**Average value**
I	2.16	2.53	2.41	0.81	1.45	1.33
II	2.15	2.74	2.49	0.86	1.37	1.35
III	2.21	2.86	2.51	1.13	1.74	1.43
IV	2.25	3.01	2.60	1.24	2.2	1.64

(χ^2=7.34; df = 2; p<0.001); (Pearsons r=0.172; p=0.034)

Table 3 Blood levels of Ca and P after treatment with paricalcitol

group	Ca			P		
	Min.	**Max.**	**Average value**	**Min.**	**Max.**	**Average value**
I	2.12	2.47	2.19	0.79	1.41	1.10
II	2.16	2.53	2.34	0.81	1.35	1.20
III	2.19	2.58	2.42	0.98	1.54	1.41

There was a decrease in serum levels of Ca and P and the Ca x P ratio was recorded in 32% of patients. Comparing the decrease in the values of Ca and P expressed in the average values per study groups, statistical significance is observed (χ^2=8.14; df = 1; p<0.0098).

Cinacalcet-treated patients who had high serum Ca and P values showed a significant decrease in serum Ca and P values and a decrease in the product of Ca x P compared to those treated with Paricalcitol. Decreases in serum Ca and P were observed in 56% of cases. The group of treated patients with Cinacalcet has the greatest reduction in Ca and P, and this difference compared to other study groups is due to the use of Cinacalcet (χ^2= 9.52; df = 3; p =<0.001), as presented in (Table 4).

Table 4 Blood levels of Ca and P after treatment with Cinacalcet

group	**Ca**			**P**		
	Min.	**Max.**	**Average value**	**Min.**	**Max.**	**Average value**
IV	2.18	2.2	2.19	1.24	1.45	1.33

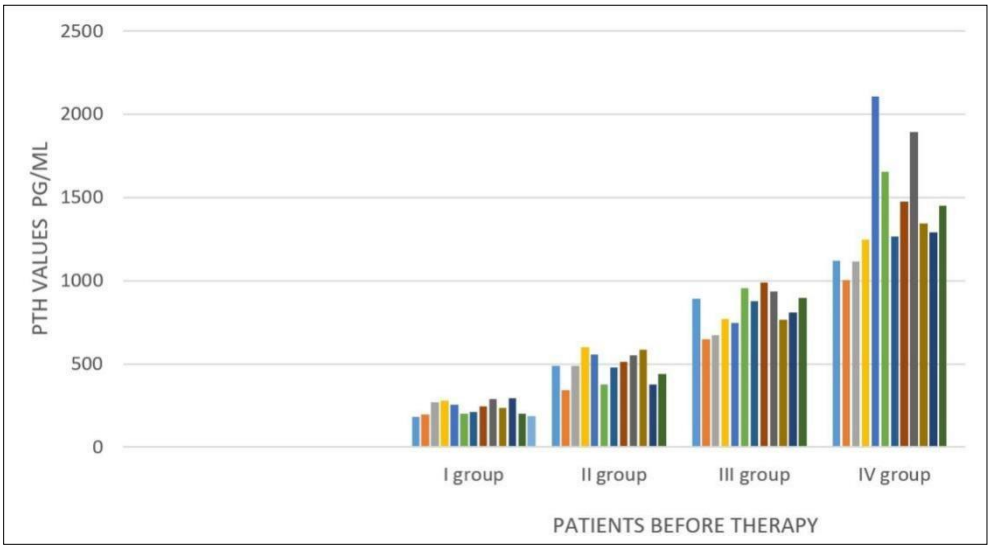


Figure 1 PTH values prior to treatment by study groups

In secondary hemodialysis patients, 75.5% of patients had PTH values below 1000 pg/ml, while 24.5% had PTH values above 1000pg/ml, as presented in Figure 1.

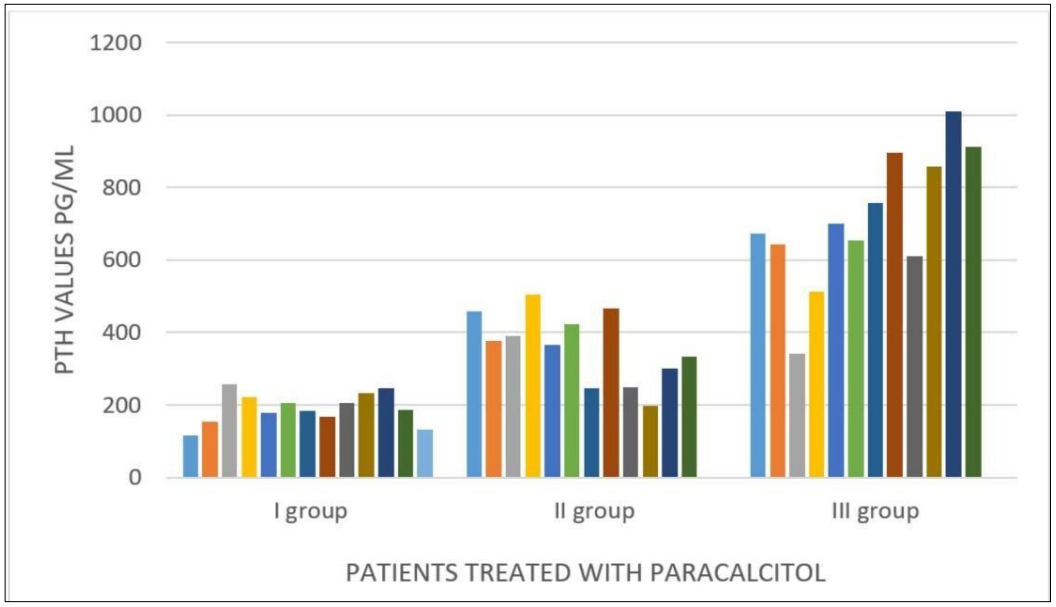


Figure 2 PTH after treatment with Particalcitol

There is a decrease in PTH after treatment with paricalcitol, and there is a statistical significance ($\square^{22}$= 8.12; df = 3; p=<0.001). Looking at the study groups, the greatest decrease in PTH was observed in patients who had PTH values of 301-600pg/ml. A significant reduction in the therapeutic effect of

paricalcitol was observed in patients with PTH values of 601-1000pg / ml, ($\square^2$=30.869; df=9; p<0.001), as presented in Figure 2.

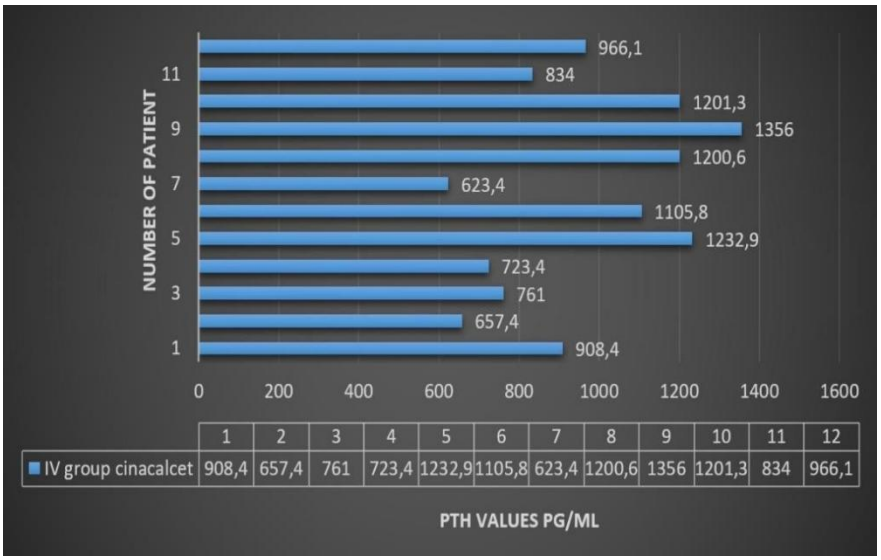


Figure 3 Decrease in PTH values after therapy with Cinacalcet

Comparing the differences in PTH values before and after therapy, the most significant change was observed in the group of patients with PTH values above 1000PG, which is statistically significant (Pearsons r=0.121; p=0.041). By testing the correlation between the groups, it was determined that there is a one-way correlation between the groups (Pearson's r=0.136; p=0.043), which is shown in Figure 3.

	PTH pg/mmol (paricalcitol)		PTH pg/mmol (cinacalcet)
man No18	165.7	man No5	211.8
woman No19	172.5	woman No7	223.2
age 18-30	179.5	age 18-30	218.2
age 31-50	168.3	age31-50	224.9
age 50-80	159.5	age 50-80	198.9

Figure 4 The effect of gender and age factors on reducing the level of PTH

In the study of the effect of Paricalcitol and Cinacalcet on the reduction of PTH levels, it was observed that there was significant difference in the effect of Paricalcitol and Cinacalcet on the reduction of PTH levels (χ^2=5.2; df = 2; p<0.001).

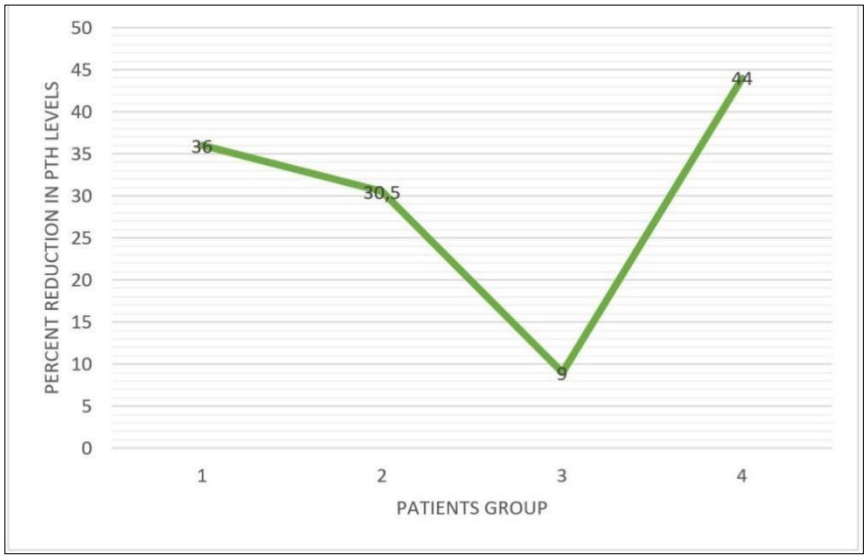


Figure 5 The percentage of PTH levels per group

Looking at the effect of Paricalcitol and Cinacalcet, it was observed that the greatest decrease in PTH values was in the fourth group (patients who had PTH values greater than 1000pg/ml – treated with cinacalcet) at 44%. The reduction in PTH levels of patients of group 3 under the influence of Paricalcitol in patients of group 3 (PTH 601 to 1000 pg/ml) was the least, only by 9%. Statistically, there is a significant difference in the decrease in the value of PTH in patients under Cinacalet (χ^2=11.9; df = 4; p<0.001).

The mean values of PTH in individual study groups, as well as their average values are presented in Table 5. By testing the correlation between groups, it was found that there is a one-way correlation (Pearson's r=0.136; p=0.043). According to the Kruskal-Wallis test, this difference is statistically significant (χ^2=30.869; df=9; p<0.001). In patients with PTH values above 180pg/ml, 9 cases with PTH values above 1000pg were reported, which is statistically significant (χ^2= 0.775; df = 9; p = 0.001), and represents the end values. (Table 5).

Table 5 Presents the PTH values of the study groups prior to the therapy

Mann-Whitney U		**Significance level**	**The average value of PTH before therapy**
Patients with PTH 180-300 pg / ml	Z = -5.186	p<0.001	191 .4
Patients with PTH 301-600 pg/ml	Z = -2.316	p=0.009	359 .2
Patients with PTH 180-300 pg / ml	Z = -3.530	p<0.001	713 .9
Patients with PTH > 1000 pg/ml	Z = -1.830	p<0.074	964 .1

Pearsons r=0.121; p=0.041

The group of treated patients with Cinacalcet has the highest mean rank and the highest median, which indicates that this difference is most conditioned by the PTH values in this group (Table 6).

Table 6 Differences between groups in the observed level of PTH before and after therapy

		N	**Mann-Whitney U**	**Significance level**	**The average value of PTH**
PTH level before therapy	Patients with PTH 180-300 pg / ml	12	Z = -5.186	24.635	191.4
	Patients with PTH 301-600 pg/ml	11	193.88	27.885	359.2
	Patients with PTH 180-300 pg / ml	18	172.75	15.189	713.9
	Patients with PTH > 1000 pg	9	114.53	9.182	964.1
PTH level	Patients with PTH 180-300 pg / ml	15	98.00	10.488	123.1
	Patients with PTH 301-600 pg/ml	13	107.00	12.547	249.4

after therapy	Patients with PTH 180-300 pg / ml	20	105.18	9.223	650.7
	Patients with PTH > 1000 pg/ml	2	80.75	7.808	540.5

F (3, 156) = 106.034; p<0.001; kvad square = 0.67 (PTH I,II,III group)**;** F (3.156) = 55.434; p<0.001; kvad square = 0.51 (PTH IV group)

An additional Pearson Corerration analysis of the results was carried out, confirming the statistical significance of the Ca-P ratio and the PTH value, which is based on the Fisher Z-transformation (Table 6.)

3. Discussion

Studies conducted in patients with end-stage renal disease and secondary hyperparathyroidism on hemodialysis show that demographic and baseline characteristics were representative for the hemodialysis population of patients with secondary hyperparathyroidism. The reduction in baseline of PTH values in patients treated with Paricalcitol was: II 36%, II 30.5%, III 9% and Cinacalcet-treated patients by 44%. The greatest decrease of value in PTH was observed in patients treated with Cinacalet for secondary hypeparathyroidism. In addition to a significant decrease in PTH, a significant decrease in serum calcium and phosphorus (Ca x P) and calcium and phosphorus multiples was observed in the Cinacalcet group. Approximately 62% of Cinacalcet-treated patients achieved a ≥ 56% reduction in PTH and this effect was consistent regardless of baseline of PTH.

According to Massry et al. elevated PTH levels reduce insulin secretion from the pancreas due to impaired calcium homeostasis, which further exacerbates glucose homeostasis. In a multicentre cross-sectional study, they investigated the prevalence of SHPT in patients with and without diabetes on a chronic hemodialysis program. The results showed that the prevalence of SHPT among the groups was similar[10].

In the study of Günther et al. in which the relation between PTH, vitamin D, renal insufficiency and cardiovascular diseases was investigated, it was concluded that elevated PTH is associated with a higher frequency of cardiovascular diseases and is an important risk factor for cardiovascular diseases. By increasing the serum values of PTH in patients with end-stage renal disease, the concentration of cytoplasmic calcium in the smooth muscle cells of the blood vessels increases, thereby results with the contraction of blood vessels[11].

Conigrave et al conducted a study in Japan and found that underlying kidney disease had no significant effect on PTH values[12].

In the examined study, with regard to gender representation, significant differences between the genders were found in favor of the male gender, while the analysis of searches by age showed a statistically significant difference only in value.

In the study Quitter et al. higher risk of death was related to PTH values of 900 pg/mL or more[13].

Unlike the previous study, we could not find a link in our study between the increased risk of mortality and the value of PTH, as we lacked data on the causes of death of our patients. It indicates the risk of calcification of blood vessels and soft tissues. The elevated values may be due to increased calcium intake, intake of phosphorus binders or increased calcium concentration in dialysate, as well as the effect of PTH on the bone itself.

Persistent hypercalcaemia and / or increased Ca ×

P product were observed more in the Paricalcitol group than in the Cinacalcet group. The difference in the incidence of hyperphosphatemia and hypercalcemia and/or elevated Ca × P product between the analysis is an interesting observation and may reflect the peculiarities of treatment in a single center. The importance of finding hypercalcemia and/or elevated Ca × P product is additionally important given that the development of hypercalcemia is more likely to occur when PTH levels are rapidly lowered and/or suppressed to levels below those considered therapeutic. In this regard, recent long-term studies have shown that Paricalcitol dosed in proportion may be effective in suppressing PTH at moderately elevated values, but may lead to hypercalcemia.

Results in this study found that phosphate levels in serum were relatively higher in the Paricalcitol groups than in the Cinacalcet groups, but there was no significant difference. There is an increasing risk of mortality with increasing levels of serum phosphate. In certain included studies, average levels of phosphate in serum of Paricalcitol or Cinacalcet were above the upper limit of normal at the end of follow-up. In other words, both drugs are associated with a risk of causing hyperphosphatemia.

In our study, 87% of patients had elevated Ca and P values with PTH values. In the great American study Sun et al. during eight-year period, which monitored the values of calcium, phosphorus, PTH and alkaline phosphatase in 106.760 dialysed patients, the same correlation of calcium and PTH was found with the same explanation.
In the meta-analytical study of Chertow et al. Administration of Cinacalcet significantly reduced Ca in serum, and normalization of Ca levels was achieved in almost 90% of patients. A decrease in Ca is accompanied by an increase in phosphate levels indicating that Cinacalcet treatment may restore normal Ca homeostasis[14].
Silverberg et al.noticed that the greatest reduction in serum of Ca was in patients with higher baseline Ca levels[15]. Our study agrees with Silverberg et al. where a higher treatment effect was observed for higher Ca baseline values in serum. For these patients, Cinacalcet is a reasonable option in a treatment regimen for the purpose of controlling hypercalcemia. It has also been found that age and gender do not alter the effectiveness of Cinacalcet treatment.
It is important that the use of Cinacalcet does not guarantee the success of the treatment of hypercalcemia, although there are cases of spontaneous remission of SHPT reported by Nakao in his study. As for side effects of Cinacalcet, reported cases are relatively small. In the study, most side effects were classified as mild to moderate in severity and were relatively rare, resulting in withdrawal from treatment. Nausea or vomiting were the most commonly reported unwanted events, occurring in 23% of the antiemetic-treatable population studied. However, it should be taken into account avoiding of medicinal products that may prolong the QT interval in conditions of possible hypocalcaemia. Hypocalcemia after Cinacalcet is generally mild and asymptomatic, and Cinacalcet dose adjustments are generally sufficient to prevent severe hypocalcemia, according to Nakao[16].

Cinacalcet-based therapy effectively prevented hypercalcemia, more than half of the patients in the Cinacalcet group experienced hypocalcemia during the evaluation period. In contrast, hypercalcaemia, a common side effect of non-selective VDR activators, occurred in only 7.7% of subjects receiving Paricalcitol iv. and it did not occur in the group that was taking orally Paricalcitol. These findings are consistent with those observed in previous randomized controlled trials of iv. and oral Paricalcitol in hemodialysis patients that demonstrate effective PTH reduction without significantly increasing the risk of hypercalcemia when used within specified dose ranges.

There are also conflicting studies such as Cozzolin's study. These findings demonstrated the overall superiority of Paricalcitol over Cinacalcet in achieving the target levels of PTH. However, what is limiting is that the PTH values in which Paricalcitol was used compared to cinacalcet are not sufficiently reported[17].

In this study, a statistically significant relation between PTH and phosphate values was found,and also the presence of hyperphosphatemia in SHPT was noticed as well. In addition, in the available medical histories, there is insufficient information about the patient's dietary and other lifestyle habits, and their discipline during taking of medication therapy. A very important factor is the nutrition of the patient.

Protein intake should be strictly limited as patients undergoing dialysis for several years also have significant disorders of PTH and vitamin D. Taking into account all possible limitations and the results obtained, it is concluded that this area deserves further research[18].

4. Conclusion

Bone mineral metabolism disorders significantly contribute to a high risk of disease and mortality in patients with CKD. More and more drugs that can be used in prevention and treatment. It remains questionable whether new forms of SHPT treatment reduce the risk of clinical events of interest to patient survival, primarily affecting morbidity and mortality from cardiovascular disease.

Guidelines for the control of PTH, Ca and P values in patients on a chronic hemodialysis program, who suffer from SHPT:

- Hyperphosphatemia therapy (phosphate-poor diet, medicamentous therapy-sevelamer)
- Do not use dialysate with a concentration of Ca > 1.5 mmol/l.
- At extremely elevated phosphate levels, increase the number of dialysis.
- Cinacalcet therapy with or without vitamin D with PTH values greater than 800pg. The recommended starting dose of Cinacalcet for adults is 30 mg 2x per day. During dose titration, serum calcium levels should be monitored within 7 days. Pause taking of Cinacalcet if Ca is below 1.9 mmol / l. After correction with vitamin D, return to the minimum dose of Cinacalcet.
- At elevations of PTH from 181 to 799pg, Paricalcitol is given in doses as follows: PTH 181 – 300pg 1x1 ampoules of 5microgram iv. or 2x1 tablets of 2microgram orally, PTH 301 – 800PG give a 2x1 ampoule of 5 micrograms iv. or 2x2 tablets of 2 micrograms orally. In case of reduction of PTH by more than 60% reduce the dose of Paricalcitol by 2-4 micrograms. In case of increased PTH, switch to Cinacalcet therapy. If Ca is greater than 2.78 mmol/l or P is greater than 2.1 mmol/l or their product is greater than 5.5, pause with Paricalcitol therapy until Serum Ca and P are corrected.
- If the PTH value is 4 or more times above the upper limit of normal values, PTH values should be determined every 2 months.
- Serum PTH values may vary and treatment measures should focus on reducing the value of this hormone in dialysed patients to improve survival while controlling calcium and phosphorus level.

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Radiologic methods in lung cancer diagnosis

Radiološke metode u dijagnostici karcinoma pluća

Ruža Stević
Center for Radiology, University Clinical Center of Serbia, Belgrade, Serbia

Ruža Stević
E-mail: ruzastevic@yahoo.com
Phone number: +381641404705

Abstract

Radiology plays a fundamental role in the diagnosis and staging of lung cancer. Conventional chest radiography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are imaging techniques used to detect, characterize, stage, and follow up lung cancer. Chest radiography is the first imaging modality in the algorithm for detecting lung tumors or indirect signs indicating cancer. However, radiography is insufficiently precise for determining the local and locoregional extent of cancer.

The advantage of CT is its capability to provide very detailed information regarding the location and size of the tumor, the presence of enlarged lymph nodes, and distant metastases. MRI has long been used as a tool to solve problems that cannot be solved by CT. However, with the development of new application modalities, MRI is becoming a promising imaging modality in the evaluation of patients with lung cancer. Integrated PET/CT combines anatomical information from CT with metabolic information from PET. PET/CT is currently the best imaging technique for lung cancer staging.

Radiomics and radiogenomics are emerging fields that use artificial intelligence to improve diagnosis and personalized risk analysis. Ultrasound- and CT-guided interventions are minimally invasive methods for the diagnosis and treatment of pulmonary malignancies. This review presents the possibilities and limitations of radiologic methods in the diagnosis of lung cancer.

Key words: radiology, lung, cancer, diagnosis

Sažetak

Radiologija ima ključnu ulogu u dijagnostici i stejdžingu karcinoma pluća. Konvencionalna radiografija grudnog koša, kompjuterizovana tomografija (CT), magnetna rezonanca (MR) i pozitronska emisiona tomografija (PET) su tehnike snimanja koje se koriste za otkrivanje, karakterizaciju, stejdžing i praćenje karcinoma pluća. Radiografija pluća je prva u algoritmu imidžing metoda za detekciju tumora u plućima ili indirektnih znakova koji ukazuju na karcinom. Međutim, radiografija je nedovoljno precizna za

određivanje lokalne i lokoregionalne proširenosti karcinoma.

Prednost CT-a je njegova sposobnost da obezbedi veoma detaljne informacije o lokalizaciji i veličini tumora, prisustvu uvećanih limfnih čvorova i udaljenih metastaza. MR se dugo koristio kao sredstvo za rešavanje problema koje CT ne može da reši. Međutim, sa razvojem novih modaliteta primene, MR postaje obećavajući metod snimanja u proceni pacijenata sa karcinomom pluća. Integrisani PET/CT kombinuje anatomske informacije iz CT-a sa metaboličkim informacijama iz PET-a. PET/CT je danas najbolja tehnika snimanja za stejdžing karcinoma pluća.

Radiomika i radiogenomika su nove oblasti koje koriste veštačku inteligenciju za poboljšanje dijagnoze i analize rizika za svakog pojedinca. Intervencije vođene ultrazvukom i CT-om su minimalno invazivne metode za dijagnozu i lečenje maligniteta pluća. U ovom pregledu biće prikazane mogućnosti i ograničenja radioloških metoda u dijagnostici karcinoma pluća.

Ključne reči: radiologija, karcinom, pluća, dijagnoza

Introduction

Lung cancer is the leading cause of cancer-related deaths in developed countries. The early stages of lung cancer often do not manifest with perceptible symptoms, and conventional physical examinations may not be sufficient for accurate detection. This is one of the reasons why many patients are diagnosed at an advanced stage of the disease.

Radiology plays a key role in the detection of lung cancer at an early stage. Accurate and timely diagnosis contributes to increased chances of successful treatment and can significantly impact prognosis and overall survival rates in patients with lung cancer.

In everyday practice, a combination of different imaging methods, such as conventional chest radiography, chest computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine techniques, mainly positron emission tomography (PET), is needed to ensure the detection, characterization, staging, and follow-up of lung cancer [1,2]. Radiomics and radiogenomics are emerging fields that use artificial intelligence to improve diagnosis and personalized risk analysis. Ultrasound- and CT-guided interventions are minimally invasive methods for the diagnosis and treatment of pulmonary malignancies [3–5].

This review presents the possibilities and limitations of radiologic methods in the diagnosis of lung cancer.

Radiological methods

Chest radiography

Because of its widespread availability, chest radiography is often the first imaging modality to indicate the diagnosis of lung carcinoma, and it also plays a role in follow-up. The advantages of chest radiography include technical feasibility, simplicity, low radiation exposure, and low cost [4,5].

Lung cancer on a chest radiograph can be presented as a solitary nodule or tumor mass, most commonly with irregular margins. A central neoplasm may be accompanied by hilar lymph node enlargement, mediastinal invasion, and lobar or total lung collapse due to bronchial obstruction (Figure 1). In some cases, the presence of pleural effusion can also be seen. Rarely, lung cancer may present in the form of parenchymal consolidation or a thick-walled cyst.

Chest radiography can demonstrate obvious chest wall and mediastinal invasion in large tumors, but it has limited sensitivity in distinguishing T3 from T4 stages of disease [7–9]. Accordingly, chest radiography cannot reliably detect invasion of the diaphragm or mediastinum, nodal involvement, or small nodules in "blind zones" on posteroanterior chest radiographs, such as the apices, hila, retrocardiac, and subdiaphragmatic regions, as well as along mediastinal lines and stripes.

However, computer-aided diagnosis (CAD) chest radiography and AI-based software have improved the detection of lung nodules on chest radiographs [4,10]. Retrospective comparison with previous chest radiographs is useful for monitoring tumor growth. An unchanged lesion size over two years suggests a benign tumor.

The next imaging modality in the diagnostic algorithm that more accurately demonstrates lung lesions is computed tomography.

Computed Tomography (CT)

CT is the most important radiologic modality in the diagnosis of lung cancer. Recently, CT has also been indicated as a screening tool for the early detection of lung cancer in high-risk populations using low-dose CT (LDCT).

Multidetector CT devices have led to significant progress in the diagnosis of lung diseases due to very short scanning times and significantly improved resolution. Continuous sections enable three-dimensional reconstruction and multiplanar rendering (MPR), allowing a more accurate assessment of the relationship between the tumor and adjacent structures such as the thoracic wall, mediastinum, and diaphragm [2–6].

When a chest radiograph detects a lesion suspected of malignancy, contrast-enhanced CT should be performed for complete staging [6,13,14]. Intravenous contrast administration is necessary to demonstrate lesion enhancement and improve delineation from surrounding tissues, especially in cases of atelectasis, as well as to better visualize mediastinal and hilar regions, particularly lymph nodes.

CT scans may demonstrate a wide spectrum of manifestations of primary lung cancer, ranging from solitary nodules to large tumor masses. Tumor margins may be smooth, lobulated, irregular, or spiculated. Lung cancers may be centrally or peripherally located, with possible invasion of mediastinal structures and the chest wall (Figure 2).

A central endobronchial tumor may cause lobar or total lung atelectasis. Some

malignant tumors, especially squamous cell carcinomas, may contain central necrosis or cavitation and can be associated with inflammation and infection. Adenocarcinomas may present as ground-glass nodules, consolidations with air bronchograms, or thick-walled cysts. Small-cell lung cancers are often centrally located and demonstrate rapid growth with invasion of mediastinal and hilar structures, causing bronchial stenosis or obstruction and nodal involvement (Figure 3). Carcinoid tumors may appear as solid lobulated nodules or endobronchial tumors.

Further manipulation of CT data enables virtual bronchoscopy. CT is also a useful guidance technique for percutaneous biopsy of central lesions that are not amenable to biopsy under ultrasound or fluoroscopic guidance [11–15].

The role of CT is irreplaceable in lung cancer staging. Staging is an essential cornerstone of cancer patient care, providing a nomenclature to describe the anatomical extent of the tumor. Correct TNM classification is extremely important for selecting the best therapeutic approach and determining disease prognosis [5,6,15,16].

Magnetic resonance imaging (MRI)

The advantages of MRI over CT include better soft tissue contrast and the possibility of multiplanar imaging, which is especially useful for superior sulcus tumors, assessment of the aortopulmonary window, and visualization of the heart and great vessels because MRI eliminates cardiac pulsation artifacts.

MRI may be more accurate than CT in distinguishing stage IIIA (resectable) from stage IIIB (generally inoperable) tumors because it can better assess invasion of the mediastinum, chest wall, and diaphragm (Figure 4). In addition, MRI accurately depicts tumor extension into the spinal canal and helps distinguish lymph nodes from hilar blood vessels. It is also indicated in staging for the detection of brain metastases.

MRI has several disadvantages compared with CT because it is slower, has poorer spatial resolution, and provides limited information about the lung parenchyma [5,15,17,18]. MRI is poorly tolerated in patients with claustrophobia and is contraindicated in patients with permanent electromagnetic devices and metallic implants.

Positron emission tomography (PET)

PET/CT is a combined anatomic-metabolic imaging technique that uses fluorodeoxyglucose (FDG). Integrated PET/CT combines two imaging modalities in one machine: CT, which provides anatomical information, and PET, which provides metabolic information.

Additional information obtained with integrated PET/CT includes:

1. Detection of lesions not initially seen on CT or PET
2. More precise localization of lesions
3. Better separation of lesions from surrounding structures

4. Improved characterization of lesions as benign or malignant (Figure 5)

Integrated PET/CT protocols with intravenous contrast administration provide comprehensive staging information regarding the primary tumor (T stage), lymph nodes (N stage), and distant metastases (M stage). Several studies have shown PET/CT to be the best non-invasive imaging technique for evaluating distant metastases.

However, FDG PET has limited sensitivity for detecting brain metastases, and dedicated brain MRI is required to exclude brain lesions before potentially curative treatment is planned [13–15,19–21].

Radiomics

Imaging features provide descriptive and qualitative data about lesions, while size measurements represent quantitative features. Quantitative imaging data can be analyzed more comprehensively using radiomic features.

Radiomics is based on the extraction and analysis of quantitative features from medical imaging using computerized algorithms. These features can identify subtle differences in texture, shape, and spatial distribution within lung tumors. By combining radiomic features with clinical data and tumor characteristics, predictive models can be developed to estimate the likelihood of malignancy, histological subtype, and treatment response [4,5,22,23].

Conclusion

Radiologic methods play a crucial role in the management of patients with lung cancer. Imaging techniques help detect suspicious lesions, determine their nature and stage, and guide biopsy procedures. Radiomics is likely to contribute to better characterization of lung cancer and consequently to the selection of the optimal therapeutic approach.

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