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World Patient Safety Day (WPSD) has been observed on 17 September since 2019, with the aim of raising awareness about patient vulnerability and encouraging joint action toward safer healthcare. This year's focus is on safe healthcare for patients with noncommunicable diseases (cardiovascular, malignant, chronic respiratory, and diabetes), which account for as much as 74% of deaths globally. Patients suffering from noncommunicable diseases are exposed to risks of delayed diagnosis, medication errors, healthcare-associated infections, and unsafe use of medical devices. Therefore, WPSD 2026 is celebrated under the slogan "Safe care for noncommunicable diseases".

Svetski Dan bezbednosti pacijenata (DBP), obeležava se 17. septembra od 2019. godine, s ciljem podizanja svesti o ranjivosti pacijenata i podsticanja zajedničkog delovanja za bezbedniju zdravstvenu zaštitu. Ove godine u fokusu je bezbedna zdravstvena zaštita obolelih od nezaraznih bolesti (kardiovaskularnih, malignih, hroničnih respiratornih, dijabetesa) koje su uzrok čak 74% smrtnih slučajeva na globalnom nivou. Oboleli od nezaraznih bolesti izloženi su riziku od kašnjenja u postavljanju dijagnoze, grešaka u primeni lekova, infekcija povezanih sa zdravstvenom zaštitom i nebezbedne upotrebe medicinskih aparata. Zbog toga se svetski DBP 2026. obeležava pod sloganom „Bezbedna zdravstvena zaštita za nezarazne bolesti“.



More than a century of pathology at the Military Medical Academy: from the prosector's department to the academic medical specialty

Više od veka patologije na Vojnomedicinskoj akademiji: od prosekture do akademske medicinske grane

Snežana Cerović

Military Medical Academy, Institute of Pathology and Forensic Medicine, Belgrade, Serbia; University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia

Important years in the development of pathology at the Military Medical Academy (MMA) were shaped by global historical events, especially in the turbulent Balkans. The period from 1904 to 2024 in pathology at the MMA is not only chronologically impressive. Many individual and collective professional destinies are woven into pathology's scientific research mission, which today bridges fundamental sciences and clinical medicine. This editorial serves as a humble tribute to all the educators who laid the foundations and inspired numerous generations of pathologists over more than a century of the MMA's history. The pathology service at the MMA was organized as a Prosector's Service, Center, Department, and Institute. For the longest period, it has been mostly recognized as the core component of the Institute of Pathology and Forensic Medicine (IPFM) at the MMA^{1, 2}. While presenting historically significant data in parts of the text that occasionally resemble a sentimental journey through pathology, I was guided by the wisdom of Pythagoras (6th century BC): "Do not talk a little about a lot of topics. Talk a lot about a few." In this endeavor, I was aided by decades of experience and motivation as a pathologist and professor, as well as by my long-term leadership of the IPFM.

Pathology of the Military Medical Academy: from Prosector's Office to Institute 1904–1949

The development of pathology at the MMA overlaps with the worldwide acceptance and reconceptualization of pathology as a distinct medical specialty. It was only in the 1940s that pathology evolved into more than a medical practice in both Europe and North America³. In preserved

historical articles and rare publications in national journals, the beginnings of pathology and forensic medicine at the present MMA are most often linked to 1904 and the formation of the Prosector of the Main Military Hospital (MMH) in Belgrade. The prosector, which in Latin means to cut off or to divide, refers to a pathological-anatomical department where autopsies are performed. The first medical examiners – prosectors at the Prosector's Department were not pathologists or forensic medicine specialists, but rather physicians from the clinical wards where the patients had passed away. In a country exhausted by wars and conflicts from 1904 to 1920, the MMA, as well as the entire healthcare system in Serbia, was still waiting for its first specialists in pathology^{4–6}. With the establishment of the Faculty of Medicine at the University of Belgrade in 1920 and its Institute of Pathology, prominent pathologists and professors of the Faculty of Medicine in Belgrade were engaged as part-time prosectors at the military hospital and within the army. The most famous among them were Professor Đorđe Joannović, Academician, Professor Ksenofor Šahović, and Professor Živojin Ignjačev. Professor Đorđe Joannović was the first pathologist in both the civilian and military health services of Serbia to perform autopsies and the first head of the Prosector's Department at the MMH from 1921 to 1932⁴. In some works, the year 1922 is linked to the beginnings of pathology at the MMA precisely because of a significant improvement of the Prosector's Department. The protocol of the very first official autopsy at the MMH is preserved within the IPFM Archive; it is signed by Professor Joannović and other professors from the Faculty of Medicine of the University of Belgrade^{4–6}. Colonel

Roman Fedina, Doctor of Medicine (MD), was officially the first head of the MMH Prosecutor's Department from 1935 to 1940⁴. Following the end of the Second World War, pathology at the MMA became recognized as pathological anatomy, driven by a steadily increasing volume of clinical autopsies. The histopathologic aspect of the work, involving biopsies, operative tissue, and organ samples, became notably more prominent when, in 1949, the MMH was renamed the MMA.

Heads of the Institute of Pathology and Forensic Medicine at the Military Medical Academy: pathologists and forensic medicine specialists (1949–2024)

In this period, there were a total of 10 heads: 6 pathologists and 4 forensic medicine specialists managed the IPFM (including temporary renamings of the Institute to Department and Center). From 1945 to 1957, the head of the Prosecutor's Department and then the first head of the IPFM was Colonel Professor of Forensic Medicine Miodrag Bučić, MD, Doctor of Philosophy (PhD). From 1957 to 1975, the head of the IPFM was Colonel Professor of Pathology Konstantin Brankovan, MD, PhD. Forensic medicine specialist Colonel Professor Aleksandar Ćeramilac, MD, PhD, managed the IPFM from 1975 to 1986. Colonel Professor of Pathology Nikola Bojanić, MD, PhD, led the IPFM from 1986 to 1990. Forensic medicine specialist Colonel Professor Petar Spasić, MD, PhD, was the director of the IPFM from 1990 to 1999, and then from 1999 to 2000, the position was held by pathologist Colonel Professor Vujadin Tatić, MD, PhD. Forensic medicine specialist Major General Assistant Professor Zoran Stanković, MD, PhD, was the head in 2000. Pathologist Colonel Professor Jovan Dimitrijević, MD, PhD, was the head from 2002 to 2005, and pathologist Colonel Professor Srbislav Ilić, MD, PhD, was the director from 2005 to the end of 2007. From 2008 to 2024, the head of the IPFM was the first civilian pathologist, Professor Snežana Cerović, MD, PhD. In 2024, as an Assistant Professor, Lieutenant Colonel, specialist of forensic medicine, Ivan Aleksić, MD, PhD, was appointed head of the IPFM.

Milestones at the Military Medical Academy pathology: technological and laboratory innovations, popularization of the profession (1957–2024)

Pathology institutions worldwide and leading international pathologists have always been our role models. For decades, a special place belonged to the leading institution in global pathology: the Armed Forces Institute of Pathology (AFIP) of the United States of America – USA⁷. Following a study visit to this largest pathology institution, Professor Brankovan improved histopathologic diagnostics and implemented administrative and spatial frameworks inspired by the AFIP model. In 1957, IPFM was the first in the country (former Yugoslavia) to introduce the intraoperative or *ex tempore* method. At the end of 1989,

immunohistochemical and enzyme-chemical analyses, as well as a computer program for archiving biopsy registries and autopsy documentation, were introduced. Furthermore, a strong institutional connection was forged between the IPFM pathology service and the clinics and institutes of the MMA, as well as with other pathology institutions nationwide and internationally. We gained a wealth of knowledge in pathology not only through the implementation of modern diagnostic procedures and literature updates, but also through invaluable master lectures by leading visiting pathologists. In the period 1986–1989, the IPFM hosted the largest number of internal seminars, clinical-pathological confrontations, and thanatological analyses in its history. Unforgettable lectures were delivered by Professor Vojislav Vuzevski (head of the Department of Diagnostic Electron Microscopy at the Institute of Clinical Pathology of the Erasmus University in Rotterdam, Netherlands) and Professor Dojčin Dojčinov. "I learned the most by teaching others" – this guiding philosophy encapsulates the professional creed of Professor Dojčinov, who selflessly imparted his knowledge to students and aspiring pathologists at the Faculties of Medicine in Niš and Belgrade, as well as to pathologists at the IPFM. In 1971, electron microscopy was introduced at the IPFM, followed by telepathology at the end of the last century^{8, 9}. The Institute's cytology laboratory was established in 1990, while cytogenetic analysis and human tissue culture techniques were introduced in the last decade of the 20th century¹.

Military Medical Academy pathology as an academic medical branch: student and resident perspectives (2009–2024)

The number of pathologists and residents from other healthcare institutions who completed their specialization, or part of it, at the IPFM over the past decades, as well as the number of master's and doctoral theses based on the results of histopathologic diagnostics, is immeasurable. Two golden periods when 13–17 pathology residents were trained at the IPFM at the same time occurred between 1986 and 1989, and from 2008 to 2017. Since the establishment of the integrated academic studies of medicine at the MMA of the University of Defense in 2009, and later the Faculty of Medicine of the MMA in 2011, pathology has become a true academic branch, as in other medical faculties in the country. The IPFM recorded by far the largest number of PhDs across various fields: pathology, molecular biology, and forensic medicine, totaling 13 between 2008 and 2024. Although very low, the number of pathology teachers during the same period ranged from 1 to 3: Professor Snežana Cerović, Assistant Professor Vesna Škuletić, and Lieutenant Colonel Assistant Professor Božidar Kovačević. Due to his retirement, Lieutenant Colonel Assistant Professor Miloš Kostov, Head of the Department of Pathology at the Niš Military Hospital, briefly participated in classes at the Faculty of Medicine of the MMA. Nevertheless, we managed to establish our optimal teaching, scientific, and research portfolio and contributed to the spread of medical knowledge¹⁰. A total of 221



Fig. 1 – The sixth class of the Faculty of Medicine of the Military Medical Academy cadets at the Institute of Pathology and Forensic Medicine laboratory (personal photo).

cadets/students completed their education between 2009 and 2024¹¹. Although their medical education in pathology was extensive, sometimes turbulent, it remained consistently interactive and engaging. The IPFM pathology faculty, as well as the teaching program, were rated with the highest marks by the Faculty of Medicine of the MMA cadets and students, confirming that their understanding of medicine had become increasingly comprehensive. We deeply appreciate their ambition and cherish their smiles after our shared successes (Figure 1).

Four of our cadets chose pathology as their specialization, two of whom are currently in their final year of PhD studies. A great success for us as educators is the scientific and research “awakening” of future pathologists – challenging, yet beautiful and promising in its complexity and perspective. This represents not only the pride and satisfaction we share, but also an aspiration toward professional excellence as the basis for the continued progress of pathology at the MMA.

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Effects of ionizing radiation on the thyroid gland and systemic inflammatory response in occupationally exposed nuclear medicine personnel

Efekti jonizujućeg zračenja na štitastu žlezdu i sistemski inflamacijski odgovor kod profesionalno izloženog osoblja na nuklearnoj medicini

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Abstract

Background/Aim. Low-dose ionizing radiation (IR) can cause subtle biological effects with clinical implications after chronic occupational exposure. The aim of the study was to examine the effect of low-dose IR occupational exposure on female nuclear medicine personnel (NMP). **Methods.** The study was conducted by analyzing medical data from mandatory periodic health examinations of 45 female NMP exposed to IR for an average of 14 years (exposed group – EG) and 43 age-matched female healthcare workers who were not occupationally exposed to IR (control group – CG). Based on peripheral blood count values, systemic inflammatory indices were calculated: neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic-immune-inflammation index (SII), systemic inflammation response index (SIRI), along with platelet indices, such as mean platelet volume (MPV). Thyroid function was assessed using free thyroxine (fT4) and thyroid-stimulating hormone (TSH). Ultrasonographic thyroid gland anatomy was classified as normal or abnormal (nodules, cysts, or diminished echogenicity). **Results.** Compared with

CG, a significantly higher absolute number of monocytes ($p = 0.006$) and higher values of the SIRI ($p = 0.046$) were found in EG. SIRI had a borderline negative association ($p = 0.057$) with IR exposure duration, while LMR had a substantial positive correlation ($p = 0.026$). EG had significantly decreased fT4 values ($p < 0.001$), with no significant difference in TSH values ($p = 0.858$) compared with CG. EG had more abnormal thyroid ultrasonography findings, and occupational IR exposure significantly enhanced the risk of abnormal findings in several logistic regression models ($p < 0.05$). **Conclusion.** Chronic occupational exposure to low-dose IR in female NMP is associated with parallel effects—both systemic and thyroid-related—including altered inflammatory response indices, lower fT4 values within the reference range, and higher structural thyroid abnormalities. These findings imply that radiation-related thyroid abnormalities are accompanied by systemic immunological alterations; however, they should be interpreted as associative and hypothesis-generating.

Keywords:

health personnel; nuclear medicine; radiation, ionizing; women; workplace.

Apstrakt

Uvod/Cilj. Niske doze jonizujućeg zračenja (*ionizing radiation* – IR) mogu izazvati suptilne biološke efekte sa kliničkim implikacijama nakon hronične profesionalne izloženosti. Cilj rada bio je da se ispita efekat profesionalne izloženosti niskim dozama IR kod žena zaposlenih na poslovima iz oblasti nuklearne medicine (*nuclear medicine personnel* – NMP). **Metode.** Istraživanje je sprovedeno analizom medicinskih podataka iz obaveznih periodičnih zdravstvenih pregleda 45 žena NMP izloženih IR u proseku 14 godina (*exposed group* – EG) i 43 zdravstvene radnice, usklađene po starosti, koje nisu bile izložene IR (*control group*

– CG). Na osnovu vrednosti parametara periferne krvi, izračunati su indeksi sistemske inflamacije: odnos neutrofila i limfocita (*neutrophil-to-lymphocyte ratio* – NLR), izvedeni (*derived*) NLR (dNLR), odnos trombocita i limfocita (*platelet-to-lymphocyte ratio* – PLR), odnos limfocita i monocita (*lymphocyte-to-monocyte ratio* – LMR), sistemski imunsko-inflamacijski indeks (*systemic-immune-inflammation index* – SII), indeks sistemskog inflamacijskog odgovora (*systemic inflammation response index* – SIRI), zajedno sa indeksom trombocita, kao što je srednja zapremina trombocita (*mean platelet volume* – MPV). Funkcija štitaste žlezde procenjena je određivanjem slobodnog tiroksina (*free thyroxine* – fT4) i tireostimulirajućeg hormona (TSH). Ultrazvučna anatomija

štitaste žlezde klasifikovana je kao normalna ili abnormalna (nodusi, ciste ili smanjena ehogenost). **Rezultati.** U poređenju sa CG, u EG je utvrđen statistički značajno viši apsolutni broj monocita ($p = 0,006$), kao i viši SIRI ($p = 0,046$). SIRI je pokazao granično negativnu povezanost ($p = 0,057$) sa trajanjem izloženosti IR, dok je LMR imao značajnu pozitivnu korelaciju ($p = 0,026$). U EG su nađene značajno niže vrednosti fT4 ($p < 0,001$), bez značajne razlike u vrednostima TSH ($p = 0,858$) u poređenju sa CG. U EG broj abnormalnih ultrazvučnih nalaza štitaste žlezde bio je veći, a profesionalna izloženost IR značajno je povećala rizik od abnormalnih nalaza u više modela logističke regresije ($p < 0,05$). **Zaključak.** Hronična

profesionalna izloženost niskim dozama IR kod NMP žena, povezana je sa paralelnim dejstvima – sistemskim i onim vezanim za štitastu žlezdu – uključujući izmenjene indekse inflamacijskog odgovora, niže nivoe fT4 u okviru referentnog opsega i više strukturne abnormalnosti štitaste žlezde. Ovi nalazi ukazuju na to da su abnormalnosti štitaste žlezde indukovane zračenjem praćene sistemskim imunološkim promenama, ali treba ih tumačiti kao asocijativne i hipotetičke.

Ključne reči:

zdravstveno osoblje; medicina, nuklearna; zračenje, jonizujuće; žene; radno mesto.

Introduction

The medical application of ionizing radiation (IR) has increased continuously over recent decades, with healthcare personnel representing the largest occupational group exposed to artificial radiation sources. Nuclear medicine, in particular, employs a variety of unsealed radionuclides (alpha, beta, and gamma emitters) for both diagnostic and therapeutic purposes. According to the current estimates, approximately 200,000 individuals are engaged in this discipline, with women comprising nearly 70% of the workforce¹. The same demographic structure applies to the Serbian nuclear medicine personnel (NMP) system. The expansion of clinical nuclear medicine has consequently increased the potential occupational radiation risk. Nevertheless, data indicate a general trend toward decreasing occupational exposure (OE) levels among NMP in recent decades. Reported values of the average annual effective dose vary considerably, ranging between 0.2 mSv and 1.8 mSv¹. The predominant sources of exposure are associated with the preparation and administration of radiopharmaceuticals, as well as imaging procedures. Personnel are subjected to IR while handling radioactive substances, administering them to patients, and performing diagnostic investigations. The extent of exposure is determined by factors such as the type of radionuclide used, the nature and frequency of procedures, and the workload of the department. Furthermore, personnel working with radioiodine may accidentally inhale or ingest some of it, leading to thyroidal radiation burden^{1, 2}. Studies from Poland^{3, 4} and China⁵, using a whole-body spectrometer and sodium iodide scintillation detector, have shown that NMP may have unavoidably absorbed different doses of radioiodine in the thyroid depending on their job.

NMP in Serbia who are occupationally exposed to IR are subject to mandatory periodic medical examinations, as regulated by the law^{6, 7}. Such occupational health and safety procedures represent not only a preventive measure, but also a clinically validated approach for the early detection of chronic radiation effects. These examinations include routine evaluation of overall health, hematological parameters, and, among other aspects, a comprehensive assessment of the thyroid gland (TG).

TG is among the most radiosensitive organs, and exposure to IR can induce a spectrum of functional and structural alterations⁸. A substantial body of epidemiological and experimental evidence has established a strong association between high-dose radiation exposure and thyroid injury. The adverse effects of high-dose IR on thyroid tissue have been thoroughly investigated since the atomic bomb detonations in Japan⁹ and the nuclear accidents in Chernobyl¹⁰ and Fukushima¹¹. In contrast, radiation levels experienced by occupationally exposed workers are considerably lower, and recent studies have sought to elucidate the potential consequences of chronic low-dose IR exposure on thyroid morphology and function^{12, 13}. However, the available literature remains inconclusive, presenting conflicting findings regarding the relationship between occupational radiation exposure and thyroid burden^{8, 14, 15}. Namely, radiation can impair iodine uptake and hormone synthesis by thyroid tissue. Moreover, radiation-induced damage to the hypothalamic–pituitary–thyroid regulatory axis may further exacerbate thyroid dysfunction^{8, 14, 16–18}. Thyroid hormone testing, including free thyroxine (T4) – fT4 and thyroid-stimulating hormone (TSH) assessments, is frequently used to evaluate thyroid function¹⁹. In addition, ultrasound surveillance has been instrumental in detecting thyroid morphological changes, especially in assessing the presence and nature of the thyroid nodules (TNs), accurately determining their number and size, as well as potential accompanying lymphadenopathy²⁰. Although many nodules are benign, the risk of malignancy is also elevated in radiation-exposed groups^{13, 15}.

Given the radiosensitivity of the TG and its highly oxidative metabolic environment, chronic OE to low-dose IR may contribute to structural and functional thyroid alterations through redox imbalance, deoxyribonucleic acid – DNA damage responses, and low-grade inflammatory signaling, highlighting the need for integrated biomarker-based monitoring in exposed workers^{8, 18, 21–23}. Of note, thyroid nodular changes in occupationally exposed workers may originate from redox-inflammatory interplay, shaped by chronic low-dose IR, with systemic inflammatory markers providing complementary insight into this particular biological response. Several studies have demonstrated that such systemic inflammatory markers are associated with the presence and biological behavior of TNs^{24, 25}. Data de-

rived from mandatory periodic health examinations of NMP provide an opportunity to assess the systemic inflammatory response by analyzing accessible and low-cost biomarkers, such as systemic inflammatory indices (SyII) [neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic-immune-inflammation index (SII), systemic inflammation response index (SIRI), along with platelet indices, such as mean platelet volume (MPV)]. These indices are readily available to occupational health specialists through the routine complete blood count analysis and can be easily calculated. Nevertheless, the clinical value of most proposed indices remains inconclusive, particularly in the context of radiation-related thyroid changes and their potential relevance to future malignant risk^{24–29}.

Therefore, the aim of our study was to investigate the possible effects of occupational low-dose IR exposure on TG function and morphology, as well as on systemic inflammatory response indices, using medical data from mandatory periodic health examinations in female NMP.

Methods

Study design

This case-control study enrolled 88 female healthcare workers who underwent mandatory periodic health surveillance at the Serbian Institute of Occupational Health, Belgrade, Serbia, from June 2024 to September 2025. The study was conducted according to the Declaration of Helsinki, as the study protocol was approved by the Ethics Committee of the Serbian Institute of Occupational Health (No. 06-3602, from September 04, 2025, and No. 06-674, from February 20, 2026). Informed and written consent was obtained from all participants.

Study participants

Inclusion criteria were female sex and employment in healthcare, with no reported personal or family history of diagnosed thyroid disease or thyroid surgery, and no current therapy for hyperthyroidism or hypothyroidism. In addition, individuals with self-reported hematological and systemic diseases, diabetes mellitus, and recent history of infectious diseases were not eligible. However, the Charlson Comorbidity Index (CCI) was calculated using the standardized scoring algorithm and incorporates patients' age and 19 pre-defined comorbid conditions, including cardiovascular, pulmonary, renal, hepatic, malignant, and other chronic diseases, each assigned a weighted score. It was used as a standardized measure of patients' baseline health status and overall comorbidity burden³⁰. Of note, pregnant women were excluded from the study. The study participants were dichotomized into non-exposed (control group – CG) and exposed group (EG). CG comprised 43 age-matched female healthcare workers who had never been occupationally exposed to IR. The control subjects were selected according to exposure to similar occupational hazards in their workplace (biological hazards and psychological burden). On the other hand, EG included 45 NMP employed in different jobs and occupationally exposed to IR through a variety of unsealed radionuclides used for diagnostic purposes only (I-131, I-123, and mTc-99). IR exposure intensity was estimated based on personal dosimetric control data. Data on annual effective dose were obtained from the nuclear medicine service department. All employees working in controlled areas with exposure to IR were required to wear appropriate personal protective equipment, including lead aprons, thyroid shields, and lead glasses, in accordance with radiation protection regulations. The flowchart of the individual enrollment process in EG is shown in Figure 1. Information on demographic data, total work experience, duration of exposure to IR,

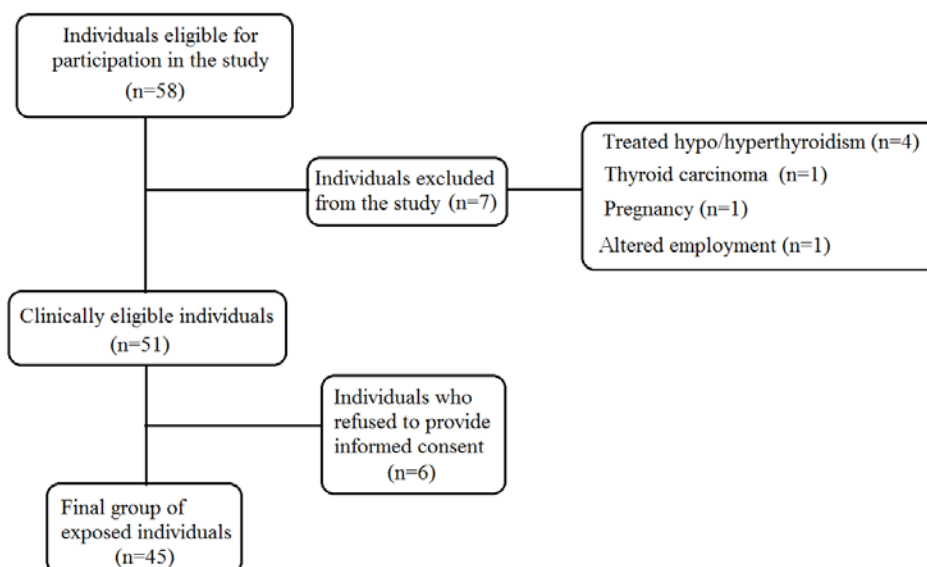


Fig. 1 – The flowchart of the individual enrollment process in the exposed group.
n – number of subjects.

and medical history, including complete blood count parameters obtained during routine periodic examinations, was extracted from the medical records. All respondents were divided into smokers, non-smokers, and ex-smokers, with respect to their cigarette smoking habits. A non-smoker was defined as a person who has never smoked or has smoked less than 100 cigarettes in his lifetime. An ex-smoker is a person who has abstained from smoking for more than 12 months. All participants declared no history of abuse of alcohol or other psychoactive substances. Smoking exposure was expressed as pack-years. By selecting control subjects from the same geographically defined population as the exposed subjects, the confounding effects of geographic factors or ethnic background were limited. This approach is particularly important where mild iodine deficiency has historically been present and is currently addressed through a nationwide iodine permanent preventive measure by fortifying table salt with iodine in Serbia³¹.

Data collection

The annual effective dose limit recommended by the International Commission on Radiological Protection (ICRP) for members of the public is 1 mSv. In addition to public exposure to IR, NMP may be occupationally exposed to IR at their workplace. In accordance with the Serbian law⁶, exposure monitoring to IR is performed with thermoluminescent dosimeters (TLDs). This study used data on external individual doses based on occupational radiation exposure absorbed from the time of placement of TLDs on the body of a worker, at a 10 mm depth [personal deep dose equivalent – Hp(10)]. The annual effective dose limit for OE recommended by the ICRP is 20 mSv, averaged over five consecutive years, with no single year exceeding 50 mSv. Of note, the thyroid has a tissue weighting factor of 0.04, which corresponds to approximately 4% of the total stochastic risk from whole-body exposure³². However, this study did not estimate the thyroid equivalent dose.

Complete blood count parameters obtained during routine periodic examinations were extracted from the medical records. Reference values were based on the specifications of the testing instruments and assay kits used within the Serbian Institute of Occupational Health, and were as follows: white blood cells – WBC ($3.4\text{--}9.7 \times 10^9/\text{L}$), neutrophil count – NC ($2.1\text{--}6.5 \times 10^9/\text{L}$), lymphocyte count – LyC ($1.2\text{--}3.4 \times 10^9/\text{L}$), monocyte count – MoC ($0.1\text{--}0.8 \times 10^9/\text{L}$), platelet count – PIC ($150\text{--}450 \times 10^9/\text{L}$) and MPV (6.2–12.1 fL). The values of SyII were calculated using the formula: SII – peripheral blood (PB) NC x PIC / LyC; SIRI – PB NC x MoC / LyC; LMR – PB LyC / MoC; NLR – PB NC / LyC; dNLR – PB NC / (WBC count- NC); PLR – PB PIC / LyC. Serum levels of fT4 and TSH were determined using a chemiluminescence immunoassay analyzer AutoLumo A1000 (Autobio, China) with appropriate assays. Reference values were based on the specifications of the testing instruments and assay kits used within the Serbian Institute of Occupational Health, and were as follows: TSH (0.35–4.75 mU/L) and fT4 (10.0–22.0 pmol/L). All obtained results were reviewed and confirmed by a professional biochemist.

Thyroid ultrasonography was performed using DC-80A ultrasound equipment (Mindray, China) with a 4.4–13.5 MHz linear array transducer L12-3E and by one dedicated radiologist. The ultrasonographic evaluation of the TG was categorized as normal or abnormal based on the finding of nodules, cysts, or reduced echogenicity. Thus, the study used a Thyroid Imaging Reporting and Data System (TIRADS) proposed by the European Thyroid Association. The total points determined the nodules' European TIRADS – EU-TIRADS level, which ranges from thyroid risk 1 – TR1 (no nodule) to TR5 (high suspicion of malignancy)²⁰.

Statistical analysis

While categorical variables were presented using frequency counts (numbers, percentages), continuous variable data were expressed as mean $\pm$ standard deviation or median (minimum–maximum) in this study. Data distribution was tested using the Kolmogorov–Smirnov test. Consequently, differences in the investigated parameters were assessed using a *t*-test for continuous data with a normal distribution and the Mann-Whitney rank-sum test for continuous data with a non-normal distribution. Lastly, for categorical variables, the χ^2 test was employed. The correlation was analyzed using Spearman's coefficient of linear correlation. Using logistic regression analysis, odds ratio (OR) and 95% confidence interval (CI) were used to calculate the odds of abnormal ultrasonography findings (UFs) development in those chronically exposed to low-dose IR. In addition, we calculated several logistic regression models (OR2-OR5) adjusted for age, as well as selected hematological parameters and SyII. All analyses were conducted using SPSS version 22 (IBM Corp., Armonk, NY, USA).

Results

Demographic, occupational, and clinical characteristics of 45 subjects in EG and 43 subjects in CG are shown in Table 1. Female NMP have been exposed to IR for a median of 14 years (range: 1–40 years) with a median annual effective dose of 0.22 mSv (range: 0.08–0.76 mSv). Although the frequency of smoking did not differ between groups ($p = 0.795$), smokers and ex-smokers in the CG had a significantly higher smoking exposure, expressed as pack-years index, compared with those in EG ($p = 0.022$). Of note, CCI did not differ significantly between groups ($p > 0.05$), supporting comparable overall comorbidity burden between exposed and non-exposed participants ($p > 0.05$).

The hematological parameters obtained from mandatory periodic medical examinations and blood count-derived SyII are presented in Table 2. Our results indicate that the absolute number of monocytes was significantly higher in EG compared to CG ($U = 647.50$, $p = 0.006$), whereas no significant difference was observed for other analyzed hematological parameters. In addition, no significant difference was observed for the majority of SyII, except SIRI, which exhibited higher values in EG ($U = 729.00$, $p = 0.046$).

Table 1**Demographic and occupational characteristics of nuclear medicine personnel and controls**

Variable	EG (n = 45)	CG (n = 43)	p-value
Age, years	47.0 ± 11.8	47.8 ± 12.5	0.517 [†]
Smoking habit			
non-smokers	23 (51)	23 (54)	
smokers	17 (38)	17 (39)	0.795 [‡]
ex-smokers	5 (11)	3 (7)	
Pack-years index	9.9 (0.5–27.0)	15.0 (1.5–40.0)	0.022 [§]
CCI	0 (0–2)	1 (0–2)	0.177 [§]
Total work experience, years	23.0 (1–40)	19.0 (1–41)	0.773 [§]
Duration of exposure to radiation, years	14 (1–40)	NA	NA
Annual effective dose, mSv	0.22 (0.08–0.76)	NA	NA

EG – exposed group; n – number of subjects; CG – control group; CCI – Charlson Comorbidity Index; NA – not applicable.

Values are given as mean ± standard deviation for normally distributed continuous variables, median (minimum–maximum) for non-normally distributed continuous variables, and numbers (percentages) for other analyzed variables.

Note: [†]p-value for t-test; [‡]p-value for χ^2 test; [§]p-value for Mann-Whitney U test.

The pack-year index is calculated as: (cigarettes smoked per day × years of smoking) / 20.

Table 2**Hematological parameters and systemic inflammatory indices of female nuclear medicine personnel and non-exposed controls**

Variable	EG (n = 45)	CG (n = 43)	p-value [†]
Hematological parameters			
WBC, 10 ⁹ /L	6.60 (4.10–11.40)	6.10 (2.90–12.00)	0.053
neutrophiles, 10 ⁹ /L	3.60 (1.60–8.10)	3.40 (1.40–7.50)	0.096
lymphocytes, 10 ⁹ /L	2.10 (1.00–4.10)	1.90 (1.00–4.10)	0.216
monocytes, 10 ⁹ /L	0.50 (0.30–0.90)	0.40 (0.30–1.00)	0.006
platelets, 10 ⁹ /L	265.00 (167.00–381.00)	241.00 (126.00–392.00)	0.141
Systemic inflammatory indices			
SIRI	0.97 (0.24–3.17)	0.76 (0.30–2.50)	0.046
SII	475.33 (179.20–1,714.50)	432.50 (203.00–880.00)	0.194
LMR	4.16 (2.14–7.50)	4.50 (2.17–7.50)	0.167
NLR	1.73 (0.80–4.53)	1.76 (0.82–3.60)	0.496
dNLR	1.36 (0.64–3.12)	1.28 (0.67–2.42)	0.341
PLR	122.77 (57.59–211.67)	120.00 (58.29–234.00)	0.838
MPV	7.80 (6.80–9.80)	7.90 (6.80–10.40)	0.339

EG – exposed group; n – number of subjects; CG – control group; WBC – white blood cells; SIRI – systemic inflammation response index; SII – systemic-immune-inflammation index; LMR – lymphocyte-to-monocyte ratio; NLR – neutrophil-to-lymphocyte ratio; dNLR – derived NLR; PLR – platelet-to-lymphocyte ratio; MPV – mean platelet volume.

Values are given as median (minimum–maximum) for non-normally distributed continuous variables.

Note: [†]p-value for Mann-Whitney U test. Statistically significant values are bolded. Reference values for laboratory parameters are shown in the Methods section of the manuscript.

Table 3**The correlation between systemic inflammatory indices, the duration of exposure, and the annual effective dose of female nuclear medicine personnel**

Systemic inflammatory indices	Duration of IR exposure, years	Annual effective dose, mSv
SIRI	- 0.285	- 0.032
SII	- 0.187	0.065
LMR	0.333*	0.077
NLR	- 0.279	- 0.018
dNLR	- 0.187	0.004
PLR	- 0.221	0.026
MPV	- 0.059	- 0.023

IR – ionizing radiation; SIRI – systemic inflammation response index; SII – systemic-immune-inflammation index; LMR – lymphocyte-to-monocyte ratio; NLR – neutrophil-to-lymphocyte ratio; dNLR – derived NLR; PLR – platelet-to-lymphocyte ratio; MPV – mean platelet volume.

Note: *The statistically significant value is bolded ($p < 0.05$). Spearman's correlation coefficient (ρ) was used.

Furthermore, the duration of IR exposure on female workers correlated positively with LMR ($\rho = 0.333$, $p = 0.026$) and showed a borderline negative correlation with

SIRI ($\rho = -0.285$, $p = 0.057$). No significant correlation was found between the annual effective dose and assessed values of SyII ($p > 0.05$) (Table 3).

Functional thyroid parameters in female NMP from EG and those from CG are shown in Table 4 and Figure 2. The mean fT4 values were significantly lower in EG compared to CG ($t = -4.612$, $p < 0.001$), whereas no significant difference was observed in TSH values ($U = 946.0$, $p = 0.858$). Although the assessed values for TSH and fT4 were within the reference ranges determined for the laboratory center at the Serbian Institute for Occupational Health, high normal values for TSH and low normal values for fT4 were observed within EG.

A weak, yet insignificant correlation was found between the annual effective dose and assessed levels of hormones (for TSH: $\rho = -0.083$, $p = 0.589$; for fT4: $\rho = -0.062$, $p = 0.684$), as well as the duration of exposure to IR and assessed levels of hormones (for TSH: $\rho = 0.133$, $p = 0.383$; for fT4: $\rho = 0.076$, $p = 0.620$). The respective scatter/dot plots are shown in Figure 3.

Regarding morphological UFs, abnormal findings (nodules, cysts, hypoechogenicity) were more prevalent in

Table 4

Functional thyroid parameters in female nuclear medicine personnel occupationally exposed to IR and non-exposed controls

Hormonal status	EG (n = 45)	CG (n = 43)	p-value
TSH, mIU/L	2.11 (0.58–5.30)	2.14 (0.60–4.09)	0.858 [†]
intervals			
< 0.35	/	/	
0.35–4.75	44 (98)	43 (100)	
> 4.75	1 (2)	/	NA
fT4, pmol/L	15.83 ± 2.84	18.43 ± 2.41	<0.001[‡]
intervals			
< 10.0	/	/	
10.0–22.0	45 (100)	42 (98)	
> 22.0	/	1 (2)	NA

IR – ionizing radiation; EG – exposed group; n – number of subjects; CG – control group; TSH – thyroid-stimulating hormone; fT4 – free thyroxine; NA – not applicable.

Values are given as: median (minimum–maximum) for non-normally distributed continuous variables, mean ± standard deviation for normally distributed continuous variables, and numbers (percentages) for intervals.

Note: [†] p-value for Mann-Whitney U test; [‡] p-value for t-test. The statistically significant value is bolded. Reference values for thyroid hormones are shown in the Methods section of the manuscript.

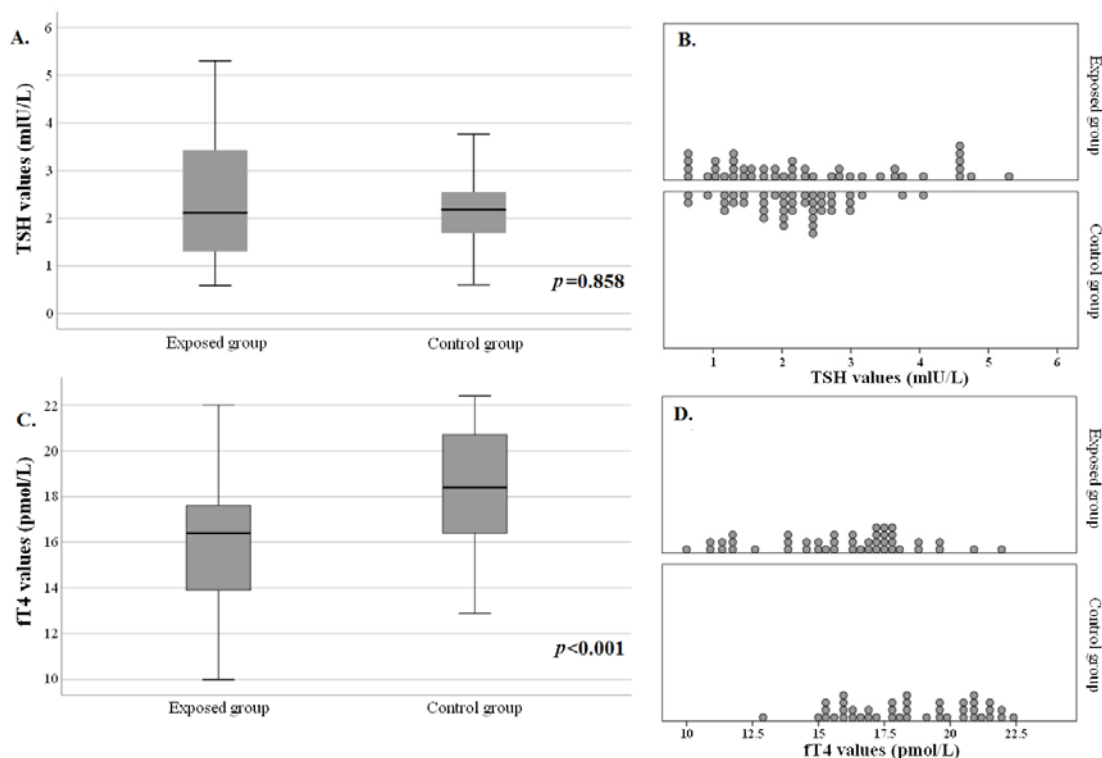
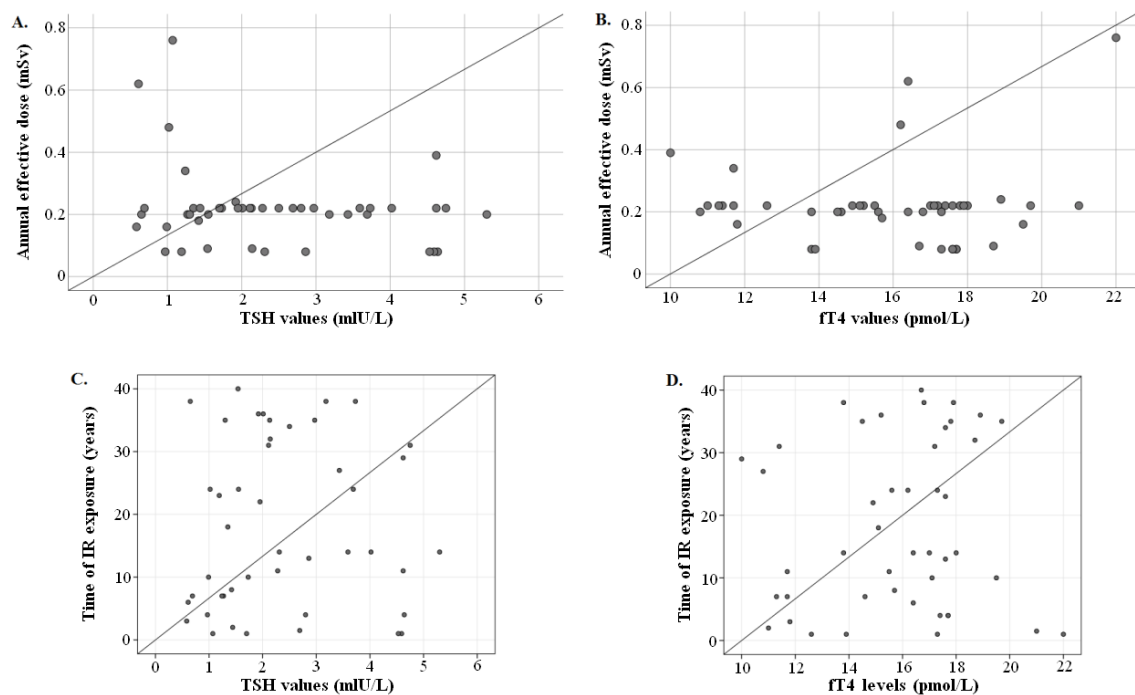


Fig. 2 – Comparison of TSH values (A, B) and fT4 values (C, D) between exposed and control groups.

TSH – thyroid-stimulating hormone; fT4 – free thyroxine.

Note: Dot plots show individual measurements. High-normal TSH and low-normal fT4 values were observed in the exposed group (B, D).



**Fig. 3 – The correlation between annual effective dose (A, B) and duration of IR exposure (C, D) with hormonal status in female nuclear medicine personnel occupationally exposed to ionizing radiation ($p > 0.05$).
IR – ionizing radiation; TSH – thyroid-stimulating hormone; fT4 – free thyroxine.**

Table 5

Morphological thyroid parameters in female nuclear medicine personnel occupationally exposed to IR and non-exposed controls

Variable	EG (n = 45)	CG (n = 43)	p -value [†]
Ultrasonography findings			
normal	20 (44)	33 (77)	
nodules	19 (42)	8 (19)	
cysts	3 (7)	1 (2)	
hypoechoogenicity	3 (7)	1 (2)	0.022
TIRADS level			
TR1	23 (51)	34 (79)	
TR2	15 (33)	5 (12)	
TR3	4 (9)	3 (7)	
TR4	2 (4)	1 (3)	
TR5	1 (3)	0 (0)	0.073

IR – ionizing radiation; EG – exposed group; n – number of subjects; CG – control group; TIRADS – Thyroid Imaging, Reporting, and Data System; TR – thyroid risk. Data are presented as numbers (percentages) of subjects (for categorical variables).

Note: [†] p -value for χ^2 test.

EG compared to CG ($\chi^2 = 9.630$, $p = 0.022$), whereas the frequency of TIRADS levels exhibited no significant difference between the groups ($\chi^2 = 8.558$, $p = 0.073$). As shown, the most frequent TIRADS level we found to be TIRADS1 and TIRADS2 (Table 5). Interestingly, among participants with abnormal thyroid UFs, smoking exposure, expressed as pack-years index, was higher in CG than in EG [30.0 (7.5–40.0) vs. 10.2 (0.5–27.0), respectively].

The estimated odds of abnormal UFs development in female NMP due to OE to IR are shown in Figure 4. As demonstrated, five risk models were calculated: Model 1 (crude OR1) without any adjustments, Model 2 (OR2) with

age as a confounding factor, and Models 3 to 5 (OR3–5) adjusted for covariates from Model 2, hematological parameters, and SyII that were found to be significant. Indeed, exposure to IR significantly increased the odds of abnormal UFs development (OR1 = 4.12, 95% CI: 1.64–10.35, $p = 0.003$; OR2 = 4.83, 95% CI: 1.82–12.83, $p = 0.002$), which was even more pronounced in Model 3, adjusted to absolute MoC (OR3 = 5.31, 95% CI: 1.89–14.85, $p = 0.001$). Moreover, increased risk was observed in Models 4 and 5, adjusted for the values of SyII, comprising absolute MoC (OR4 = 4.81, 95% CI: 1.82–13.05, $p = 0.002$; OR5 = 4.53, 95% CI: 1.68–12.16, $p = 0.003$).

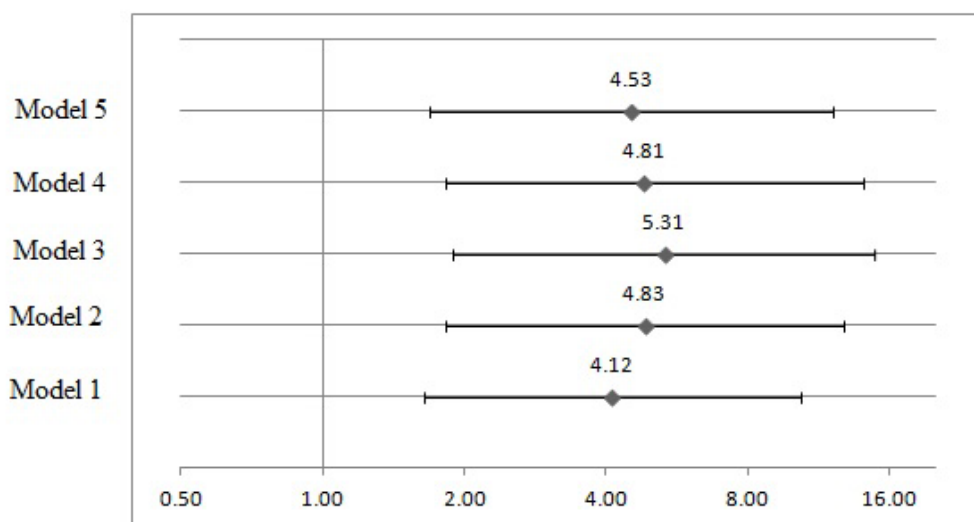


Fig. 4 – The estimated risk of abnormal ultrasonography findings development in female nuclear medicine personnel due to occupational exposure to IR ($p < 0.05$). Model 1 – crude odds ratio; Model 2 – adjusted for age as a covariate; Model 3 – adjusted for absolute monocyte number as a covariate; Model 4 – adjusted for LMR as a covariate; Model 5 – adjusted for SIRI as a covariate. Bolded lines represent the 95% confidence interval. IR – ionizing radiation; LMR – lymphocyte-to-monocyte ratio; SIRI – systemic inflammation response index.

Discussion

In this study, chronic exposure to low-dose IR in female NMP was associated with adverse effects on TG and altered systemic inflammatory response.

Our findings suggest systemic inflammatory response alteration in occupationally exposed female workers, reflected by higher MoC and elevated SIRI, an index integrating neutrophils, monocytes, and lymphocytes. Indeed, IR exposure can cause various biological effects in cells and tissues^{33, 34}. These effects can be direct, involving the damage of molecular components, and indirect, primarily through the generation of reactive oxygen species. In the early phase, reactive oxygen species can induce tissue damage events, even causing changes in cellular signaling pathways^{13, 21–23, 33, 34}. Plausibly, IR can result in damage-associated molecular patterns – DAMPs release, contributing to bone marrow activation through cytokine-dependent enhancement of bone marrow myelopoiesis, resulting in mobilization of circulating monocytes, reflected as monocytosis^{22, 23, 26, 35}. In the chronic phase, IR exposure associated with low-grade chronic inflammation might be reflected by LMR positively correlating with exposure duration^{21, 22, 36}. On the other hand, the observed positive correlation between LMR and duration of IR exposure, together with a negative correlation of SIRI, suggests a possible adaptive shift in systemic inflammatory responses^{36, 37}. Moreover, the established correlation with exposure duration may reflect a “healthy worker survivor” effect, resulting in a relatively healthier long-term exposed population. Interestingly, although smoking prevalence was similar between assessed groups and cumulative smoking history (expressed as pack-years index) was higher among smokers and ex-smokers in CG, MoC and SIRI values were higher in EG. This finding suggests that

smoking exposure alone does not fully account for the observed differences in SyII.

The TG is recognized as a radiosensitive organ susceptible to radiation-induced damage, both directly and through an oxidative environment. Its heightened vulnerability is largely attributed to the intrinsic sensitivity of thyroid tissue to repeated micro-injuries along with repair cycles, particularly under prolonged exposure^{8, 14, 18}. Even low-dose exposure may affect thyroid hormone synthesis¹⁴. Our findings indicated that ft4 values were significantly lower in EG than in CG, whereas no significant difference was observed in TSH values. A weak correlation was found between duration of IR exposure and the investigated hormones, as well as between the annual effective dose and those hormones. Only several studies have evaluated the effects of low-dose IR on thyroid function. The reported findings are inconsistent, partly because different thyroid parameters were assessed [triiodothyronine (T3), T4, free T3, or ft4], and because most investigations included heterogeneous groups of occupationally exposed medical workers rather than specifically NMP^{14, 38, 39}. Of note, NMP are among the occupational groups receiving the highest dose of IR. However, we observed an increase in TSH and a decline in ft4—both remaining within reference ranges—possibly due to the negative feedback regulation mechanism of the hypothalamus-pituitary-thyroid axis. This observation surely requires further monitoring to evaluate the risk of developing hypothyroidism in such individuals.

The prevalence of TNs in EG and CG was 42% and 19%, respectively. The majority of participants in both groups exhibited TIRADS 1 and 2 findings, with no significant difference in TIRADS category distribution between groups. TNs are more frequently detected in the female population and are clinically important for several reasons⁴⁰. They may cause thyroid dysfunction and compressive symp-

toms, but they are primarily important because of the need to exclude thyroid cancer. Although more than 90% of detected nodules are clinically benign, TNs are clinically important as they may represent thyroid cancer in approximately 4.0 to 6.5% of cases ⁴¹. However, we observed no significant association between ultrasonographic abnormalities and either annual effective dose or the duration of exposure to IR. Indeed, the results of multiple studies investigating the association between occupational IR exposure and TNs vary significantly due to differences in study design, work characteristics, radiation doses, and iodine status ^{14, 39, 42–48}.

In our study, the chronic IR exposure, specifically in female NMP, significantly increased the risk of ultrasonographic changes. Furthermore, after model adjustment to MoC, the association between OE and abnormal thyroid UFs was even more pronounced. Finally, we observed the lack of additional increase in OR in models adjusted for SIRI or LMR. Overall, our results suggest that selected hematological parameters and SyII reflect parallel effects of exposure rather than mediating thyroid structural changes in this cross-sectional setting. Indeed, PB MoC and derived indices cannot reliably capture a possible local macrophage infiltration, differentiation, and polarization within thyroid tissue. Therefore, we could not directly link systemic inflammatory markers to macrophage-driven fibrotic or angiogenic remodeling in the thyroid, which may require tissue-level profiling or longitudinal biomarker assessment. However, parallel systemic and thyroid-specific effects may reflect a shared biological background: the interplay of chronic oxidative and inflammatory stress ^{18, 21–23}. In perspective, future mechanistic research could comprise the assessment of systemic oxidative stress markers in order to explore the redox component of this response, provide complementary biological context, and accompany inflammatory indices.

Limitations of the study

Some limitations of this study should be addressed. Firstly, the study was conducted in a female population only, mainly due to the frequency of female workers in the nuclear personnel system. The relatively small sample size limited detailed stratification according to specific job tasks in nuclear medicine. External TLD data indicate low effective doses, but internal exposure was not measured; therefore, the total thyroid dose may be underestimated. Moreover, the level of antibodies relevant for thyroid pathophysiology was not taken into account in this study. Therefore, although participants with a self-reported personal history of thyroid disease were excluded, subclinical or previously unrecognized autoimmune thyroiditis might contribute to structural and functional thyroid abnormalities. Moreover, the level of relevant hormones and hematological parameters was analyzed only once, without any periodic follow-up. Diurnal rhythm has a pronounced effect that is impossible to control, and individual variation in lymphocyte radiosensitivity is also large.

Conclusion

Chronic occupational exposure to low-dose ionizing radiation in female nuclear medicine personnel is linked to both systemic and thyroid effects, including altered inflammatory response indices, lower free thyroxine values within the reference range, and an increased prevalence of structural thyroid abnormalities. The findings of this study provide additional evidence in the area of occupational exposure to low doses of ionizing radiation and are therefore interpreted as associative and hypothesis-generating.

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Effect of adding chair-based group exercises to conventional rehabilitation on fear of falling after stroke: a systematically allocated controlled study

Uticaj dodavanja grupa vežbi sa stolicom konvencionalnoj rehabilitaciji na strah od pada posle moždanog udara: kontrolisana studija sa sistematskom raspodelom ispitanika

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Abstract

Background/Aim. Most patients who survive a stroke develop a fear of falling (FoF). The aim of this study was to evaluate the effects of conventional rehabilitation (CR) alone as well as of CR combined with chair-based group exercises on FoF in patients after a stroke. **Methods.** A total of 86 post-stroke patients were systematically allocated to two groups: a control group (CG) and a treatment group (TG); both underwent 3 weeks of inpatient rehabilitation. While CG received CR only, TG, in addition to CR, also participated in a program of chair-based group exercises. The Fall Efficacy Scale – International (FES-I) was used to measure FoF. Functional mobility was assessed using the Timed Up and Go (TUG) test. To evaluate the impact of therapeutic interventions on patients' functionality, their independence in activities of daily living (ADLs) was examined. The evaluations were performed at baseline and after rehabilitation, on discharge. **Results.** Following 3 weeks of interventions,

both groups showed significant improvement, suggesting that the interventions were effective. According to the FES-I, FoF decreased in both groups: by 4.63 ± 1.98 [95% confidence interval (CI): 1.81–7.44; $t = 3.316$; $p = 0.002$] in CG, and by 10.07 ± 1.08 (95% CI: 6.97–13.17; $t = 6.550$; $p = 0.001$) in TG. Post-rehabilitation, both groups showed significant improvements in the time of the TUG test: CG improved by 2.83 ± 1.23 s (95% CI: 1.53–4.14; $t = 4.391$; $p = 0.001$), while TG had a greater improvement of 4.95 ± 1.86 s (95% CI: 3.14–6.75; $t = 5.534$; $p = 0.001$). Furthermore, a more significant improvement in ADLs was observed in TG than in CG. **Conclusion.** Chair-based group exercises, as an addition to CR, are effective in decreasing FoF, improving functional mobility, and increasing patient independence in ADLs.

Keywords:

accidental falls; fear; postural balance; rehabilitation; stroke; treatment outcome.

Apstrakt

Uvod/Cilj. Većina preživelih bolesnika posle moždanog udara razvije strah od pada (*fear of falling* – FoF). Cilj rada bio je da se procene efekti same konvencionalne rehabilitacije (*conventional rehabilitation* – CR), kao i CR kombinovane sa grupnim vežbama sa stolicom, na FoF kod bolesnika nakon moždanog udara. **Metode.** Ukupno 86 bolesnika posle moždanog udara sistematski je raspoređeno u dve grupe: kontrolnu grupu (KG) i terapijsku grupu (TG); bolesnici obe grupe bili su podvrgnuti stacionarnoj rehabilitaciji tokom 3 nedelje. Dok je KG bila podvrgnuta samo CR, TG je, pored CR, učestvovala i u programu grupa vežbi sa stolicama. Za merenje FoF korišćena je skala *Fall Efficacy Scale – International* (FES-I). Funkcionalna mobilnost procenjena je pomoću testa *Timed Up and Go* (TUG). Da

bi se procenio uticaj terapijskih intervencija na funkcionalnost bolesnika, ispitana je njihova nezavisnost u svakodnevnom aktivnostima (*activities of daily living* – ADLs). Procene su sprovedene na početku rehabilitacije i posle nje, pri otpustu. **Rezultati.** Nakon 3 nedelje intervencija, nađeno je značajno poboljšanje u obe grupe, što ukazuje na to da su intervencije bile efikasne. Prema FES-I, FoF je bio smanjen u obe grupe: za $4,63 \pm 1,98$ [95% *confidence interval* (CI): 1,81–7,44; $t = 3,316$; $p = 0,002$] u KG i za $10,07 \pm 1,08$ (95% CI: 6,97–13,17; $t = 6,550$; $p = 0,001$) u TG. Posle rehabilitacije, značajno poboljšanje u vremenu TUG testa nađeno je u obe grupe: u KG za $2,83 \pm 1,23$ s (95% CI: 1,53–4,14; $t = 4,391$; $p = 0,001$), dok je u TG nađeno značajnije poboljšanje od $4,95 \pm 1,86$ s (95% CI: 3,14–6,75; $t = 5,534$; $p = 0,001$). Takođe, primećeno je značajnije poboljšanje u ADLs u TG u poređenju sa KG. **Zaključak.**

Program grupa vežbi sa stolicama je, kao dodatak CR, efikasan u smanjenju FoF, poboljšanju funkcionalne mobilnosti i povećanju samostalnosti bolesnika u ADLs.

Ključne reči:

nesrećni padovi; strah; ravnoteža; rehabilitacija; moždani udar; lečenje, ishod.

Introduction

Stroke is one of the leading causes of death and disability worldwide, resulting in numerous long-term consequences in the form of neurological and motor impairments¹. In addition to motor deficits, many survivors develop a fear of falling (FoF) after stroke. FoF is a multi-faceted health and psychological issue characterized by reduced confidence in maintaining balance during activities of daily living (ADLs), as well as by excessive concern about falling². Numerous factors contribute to the development of FoF after a stroke, including poor balance, physical inactivity, muscular weakness, spasticity, a history of previous falls, perceptual and visual deficits, medication side effects, and reliance on assistive devices³. Several studies have shown that FoF is directly associated with baseline balance disorders, impaired functional mobility, and restricted community reintegration⁴. Furthermore, FoF has been identified as a critical risk factor for future falls in neurological patients and is negatively correlated with health-related quality of life after stroke^{5,6}.

Research indicates that nearly 90% of individuals develop FoF following a fall. This psychological barrier often leads to a self-imposed restriction of physical activity as a protective measure. However, this reduction in movement paradoxically results in physical deconditioning, which ultimately increases the objective risk of future falls. Consequently, FoF is strongly linked to progressive activity limitation, a decline in physical and cognitive functions, and reduced overall quality of life⁷.

Targeted physical exercise that improves balance and walking capacity has been shown to successfully reduce FoF in stroke survivors⁴. For instance, circuit-based training consisting of a combination of walking, balance, and strengthening exercises, as well as structured walking programs, effectively reduces FoF and improves self-confidence in post-stroke patients⁸. Group exercises (GE), particularly task-oriented balance training combined with cognitive behavioral therapy, simultaneously reduce FoF and enhance long-term balance confidence after stroke⁴.

The aim of this study was to evaluate the effects of combined treatment on FoF in patients after stroke. The treatment included a program of GE with chairs in addition to conventional rehabilitation (CR), as well as CR alone.

Methods

Study design

This single-blinded, systematically allocated controlled study was conducted between November 2020 and July 2021 at the Institute for Physical Medicine, Rehabilitation, and Rheumatology "Dr. Simo Milošević", Igalo, Montenegro.

The healthcare system of Montenegro provides patients with a three-week inpatient rehabilitation program following a stroke. All patients admitted for their first rehabilitation after a stroke during the study period, who met the inclusion criteria, were included in the study. The time elapsed since the stroke was registered, but it was not used as an inclusion criterion.

Ethics approval

The study protocol was approved by the Ethics Committee of the Faculty of Health Studies at the University of Sarajevo, Sarajevo, Bosnia and Herzegovina (No. 04-7-99/20, from July 27, 2020) and conducted in accordance with the principles of the Declaration of Helsinki. Following the approval of the University of Sarajevo Senate by decision 01-23-123/20 on October 28, 2020, institutional consent (No. 01/1-2915) was granted on November 3, 2020, to conduct the research at the Institute for Physical Medicine, Rehabilitation, and Rheumatology "Dr. Simo Milošević" in Igalo. Written informed consent was obtained from each patient.

Participants and group allocation

A total of 86 stroke patients were allocated into two equal groups: control group (CG) and treatment group (TG). Patients in CG (n = 43) underwent CR, while patients in TG (n = 43) underwent a program of chair-based GE in addition to CR. This study utilized a pseudo-randomized, parallel-group design with a 1 : 1 allocation ratio. Group assignments were determined systematically based on patients' chronological sequence of admission and clinical examination by the physiatrist. To manage this process, an independent assistant prepared ten numbered envelopes in advance. Following the medical evaluation and formal enrollment of a batch of new patients, the physiatrist provided the assistant with the sequential list of examined participants. The assistant then sorted the patients into the envelopes on an alternating basis, allocating odd-numbered admission sequences to TG and even-numbered sequences to CG. While allocation was concealed from the primary researcher until enrollment was complete, the nature of the physical therapy interventions prevented the blinding of patients and the treating physiotherapist after the baseline assessment.

Inclusion criteria

The study enrolled patients of both genders with a clinical diagnosis of stroke who met specific physical and cognitive criteria. To participate, patients had to be enrolled in an inpatient stroke rehabilitation program and mobile: able to walk at least 10 m with or without a walking aid and able to

stand for 10 min independently or hold onto the back of a chair. They also had to be able to perform exercises in a standing position (with or without holding onto the back of a chair), answer questionnaires, and provide informed consent⁹.

Exclusion criteria

Patients were excluded if they were not enrolled in inpatient rehabilitation, were unable to walk 10 m (with or without aids), were unable to stand independently or with support for 10 min, were unable to perform exercises in a standing position, or were unable to complete the questionnaire or provide informed consent. Additionally, patients with severe cognitive impairment and major comorbidities were excluded. Conditions with International Classification of Diseases, 10th Revision (ICD-10) codes F06 (Mental disorders due to brain damage and dysfunction and physical disease) and F03 (Dementia) were considered serious cognitive impairments. The presence of unstable cardiovascular disease was considered a major comorbidity. The decision to exclude or include patients in the research was made by attending psychiatrists after the initial medical assessment but before the start of the rehabilitation program. The only evaluation tool used in the decision was a medical examination.

The sample size was determined by the timeline of the author's PhD program and was also influenced by the epidemiological situation of the coronavirus disease 2019 (COVID-19) pandemic. Sample size was not formally calculated. This pseudo-randomized trial was not prospectively registered in a public repository.

Assessment and data collection

The medical history and demographic information of all patients were collected from facility medical records and *via* self-report (with permission from the department and informed consent from the participants).

The Falls Efficacy Scale – International (FES-I), a 16-item questionnaire, was used to assess perceived confidence in performing various domestic and social activities. The FES-I questionnaire has not yet been linguistically or cross-culturally validated for stroke patients within the participants' specific speaking area. However, the FES-I has demonstrated a good discriminatory ability to differentiate fallers from non-fallers in chronic and subacute post-stroke patients^{10, 11}. Participants rate their concern on a scale of 1–4, yielding total scores ranging from 16 to 64, with higher scores indicating lower self-efficacy. In this study, the questionnaires were administered to patients as structured interviews.

Given that concern about falling and the risk of falling are closely associated with parameters of balance and functional mobility in stroke survivors, we used the Timed Up and Go (TUG) test for evaluation. The TUG test is a brief assessment tool for functional mobility and falls risk in elderly or post-stroke patients. It requires the subject to stand up from the chair, walk 3 m, turn around, return, and sit back

down on the chair. Activities such as standing, walking, and sitting are among the most affected in stroke patients and are critical for daily life. The test is reliable and valid for quantifying functional mobility, making it useful for monitoring changes in the subject's condition over time¹². For testing, we used a stopwatch, a chair with a standard backrest, and a 3-m-long path marked on the floor. The test was performed twice, and we registered the second result. This test has been applied in several studies to assess balance, functional mobility, and the risk of falling after a stroke^{13, 14}.

Questions about ADLs are valid and reliable tools for screening stroke patients for functional dependency. Specific ADLs, such as walking, bathing, and dressing, have shown good sensitivity and specificity in identifying different levels of dependency in older adults¹⁵. We classified the basic ADLs (feeding, continence, transferring, toileting, dressing, and bathing), which are numerically assessed by the Katz Index of Independence, into three categories: "independent", "dependent only with bathing", or "dependent in all activities"¹⁶.

The use of a cane when walking on a flat surface—both before and after rehabilitation in a hospital environment—was registered by observation. Patients were classified into one of the three categories: "does not use a cane", "uses a cane", or "uses a cane with a wide base of support".

Exercise program

Both CG and TG participated in an inpatient CR program consisting of four components: individual exercise sessions (45 min) focusing on strengthening, flexibility, and walking; manual massage; occupational therapy (30 min); and physical modalities. The standard rehabilitation program was applied 5 times a week on weekdays. On those same days, TG received an additional 30-min chair exercise program. During the first 20 min of this program, patients performed exercises while sitting in chairs. During the final 10 min, patients performed exercises in a standing position, with safety measures provided by standing between chairs and the wall. This program included a combination of flexibility, bodyweight resistance strengthening, coordination, and static and dynamic balance exercises.

The chair exercise program was individually adapted to each patient. For example, the chair stand-up exercise was performed with or without arm support, according to the subjects' abilities. If a patient was unable to fully stand up and sit down, it was sufficient to simply separate their buttocks from the chair, using their hands. Some patients practiced maintaining balance in a unipodal stance, while others practiced maintaining more stable positions. The patients repeated each exercise a maximum of 10 times. In case of insufficient endurance, the patients repeated the exercise as many times as they could.

Exercises were performed daily with increased repetitions, longer standing times, and increased reach or stride length, based on individual tolerance. Chairs were arranged in a semicircle to allow therapists to easily demonstrate, monitor, and correct the participants' performance.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 20.0. Descriptive statistics were used to express data in arithmetic mean $\pm$ standard deviation for two groups. Analysis of categorical variables was performed using Pearson's χ^2 -test. A one-way analysis of variance test (ANOVA) was utilized to evaluate the homogeneity of the groups at baseline and to compare the post-intervention means between the two examined groups. A paired *t*-test was used to compare scores for each group before and after rehabilitation. A mixed-design ANOVA was used to evaluate the interaction effect between time (before and after rehabilitation) and the groups (CG and TG) to determine whether TG achieved a significantly greater magnitude of improvement than CG. To evaluate the influence of baseline independent variables on the primary outcome measure (FES-I and TUG test scores) at discharge, separate multiple linear regression analyses were conducted for both CG and TG. Statistical significance for the individual predictors was assessed using

t-tests, reporting both unstandardized coefficients (B) with 95% confidence intervals (CI) and standardized coefficients (β). The threshold for statistical significance was set *a priori* at $\alpha = 0.05$.

Results

In our research, we included 86 patients enrolled in stroke rehabilitation. The period that passed from the last stroke to arrival at the rehabilitation was registered. In CG, 4.30 ± 2.13 months had elapsed since stroke onset, compared to 4.67 ± 2.50 months in TG. Applying the ANOVA test, no statistically significant difference was found between the examined groups in the length of the period from the last stroke to the beginning of rehabilitation ($F = 0.541$; $p = 0.464$) (Table 1).

Data analysis found no statistically significant differences between CG and TG in terms of age, gender, employment status, cause of stroke, living arrangement, and number of strokes (Tables 1 and 2).

Table 1

Age of respondents and time elapsed since last stroke according to the group

Parameters	Mean $\pm$ SD	SEM	95% CI	Min–Max	<i>F</i>	<i>p</i> -value
Age of respondents, years						
CG	64.79 $\pm$ 9.21	1.40	61.95–67.62	38.00–79.00	1.371	0.245
TG	66.97 $\pm$ 8.96	1.23	64.49–69.45	45.00–81.00		
Time elapsed since last stroke, months						
CG	4.30 $\pm$ 2.13	0.32	3.65–4.96	1.50–10.00	0.541	0.464
TG	4.67 $\pm$ 2.50	0.38	3.90–5.45	0.80–12.00		

SD – standard deviation; SEM – standard error of the mean; CI – confidence interval; Min – minimum; Max – maximum; CG – control group; TG – treatment group.

Note: Both groups had equal respondents (number of respondents = 43).

Table 2

Demographic characteristics and stroke-related characteristics of respondents according to group (CG vs. TG)

Characteristics	Groups		Total	χ^2	<i>p</i> -value
	CG	TG			
Gender					
male	23 (53.5)	22 (51.2)	45 (52.3)	0.047	0.500
female	20 (46.5)	21 (48.8)	41 (47.7)		
Strokes, number					
one	40 (93.0)	38 (88.4)	78 (90.7)	0.545	0.356
two	3 (7.0)	5 (11.6)	8 (9.3)		
Stroke, cause					
ischemia	38 (88.4)	35 (81.4)	73 (84.9)	0.806	0.274
hemorrhage	5 (11.6)	8 (18.6)	13 (15.1)		
Employment status					
employed	7 (16.3)	5 (11.6)	12 (14.0)	0.544	0.461
unemployed	9 (20.9)	8 (18.6)	17 (19.8)		
retired	27 (62.8)	30 (69.8)	57 (66.3)		
Living arrangement					
alone	11 (25.6)	7 (16.3)	18 (20.9)	1.132	0.214
with family	32 (74.4)	36 (83.7)	68 (79.1)		

CG – control group; TG – treatment group.

All values are given as numbers (percentages).

Note: Both groups had equal respondents (number of respondents = 43).

The average FES-I score at admission was 33.51 ± 14.21 for CG and 38.00 ± 15.13 for TG. The one-way ANOVA test showed no statistically significant difference between the two groups at admission ($F = 2.010$, $p = 0.160$). On discharge, the average FES-I score was 28.88 ± 11.78 for CG and 27.93 ± 12.51 for TG. The one-way ANOVA test found no statistically significant difference between the discharge scores of the two groups ($F = 0.132$, $p = 0.717$). Following rehabilitation, a significant within-group reduction in FoF was observed in both cohorts. FES-I scores decreased by a mean of 4.63 points in CG ($t = 3.316$, $p = 0.002$; 95% CI: 1.81–7.44) and by a mean of 10.07 points in TG ($t = 6.550$, $p = 0.001$; 95% CI: 6.97–13.17). The mixed-design ANOVA revealed a statistically significant group-time interaction effect [$F(1.84) = 7.15$, $p = 0.009$]. While both groups demonstrated significant individual progress, TG achieved a significantly greater magnitude of improvement over time compared to CG (mean difference in change scores = 5.44; 95% CI: 1.30–9.58; $p = 0.009$) (Table 3).

The average TUG score at admission was 15.55 ± 10.11 s for CG and 15.96 ± 10.21 s for TG. The one-way ANOVA test showed no statistically significant difference between the two groups at admission ($F = 0.034$, $p = 0.855$). On discharge, the average TUG score for CG was 12.72 ± 7.71 s, and for TG, it was 11.00 ± 6.01 s. The one-way ANOVA test found no statistically significant difference between the discharge scores of the two groups ($F = 1.320$, $p = 0.254$). Following rehabilitation, a significant within-group improvement in functional mobility was observed in both cohorts. TUG scores decreased by a mean of 2.83 s in CG ($t = 4.391$; $p = 0.001$; 95% CI: 1.53–4.14) and by a mean of 4.95 s in TG ($t = 5.534$; $p = 0.001$; 95% CI: 3.14–6.75). The mixed-design ANOVA revealed a statistically significant group-time interaction effect [$F(1.84) = 6.74$, $p = 0.011$]. While both groups demonstrated significant individual recovery, TG achieved a significantly greater magnitude of functional mobility improvement over time compared to CG (mean difference in change scores = 2.12 s; 95% CI: 0.49–3.75; $p = 0.011$) (Table 4).

Table 3**Comparison of average values of the FES-I score before and after rehabilitation between examined groups**

Variable	Mean $\pm$ SD	SEM	95% CI	Min–Max	<i>F</i>	<i>p</i> -value
FES-I						
before rehabilitation						
CG	33.51 ± 14.21	2.17	29.14–37.89	16–64	2.010	0.160
TG	38.00 ± 15.13	2.31	33.34–42.66	16–62		
after rehabilitation						
CG	28.88 ± 11.78	1.80	25.26–32.51	16–58	0.132	0.717
TG	27.93 ± 12.51	1.91	24.08–31.78	16–57		
	Mean $\pm$ SD	SEM	95% CI	<i>t</i> -test*	<i>df</i>	<i>p</i> -value
FES-I before–after						
CG	4.63 ± 1.98	1.40	1.81–7.44	3.316	42	0.002
TG	10.07 ± 1.08	1.54	6.97–13.17	6.550	42	0.001
Group-time interaction (mixed ANOVA)				$F = 7.15$	1.84	0.009

FES-I – Fall Efficacy Scale – International; SD – standard deviation; SEM – standard error of the mean; CI – confidence interval; Min – minimum; Max – maximum; CG – control group; TG – treatment group; *df* – degrees of freedom; ANOVA – analysis of variance.

Note: * Paired *t*-test. Both groups had equal respondents (number of respondents = 43).

Table 4**Comparisons of average values of the TUG score before and after rehabilitation between examined groups**

Variable	Mean $\pm$ SD	SEM	95% CI	Min–Max	<i>F</i>	<i>p</i> -value
TUG, s						
before rehabilitation						
CG	15.55 ± 10.11	1.54	12.44–18.67	6.40–52.20	0.034	0.855
TG	15.96 ± 10.21	1.56	12.81–19.10	6.30–62.20		
after rehabilitation						
CG	12.72 ± 7.71	1.18	10.34–15.09	6.00–38.70	1.320	0.254
TG	11.00 ± 6.01	0.92	9.16–12.85	4.50–40.10		
	Mean $\pm$ SD	SEM	95% CI	<i>t</i> -test*	<i>df</i>	<i>p</i> -value
TUG, s; before–after						
CG	2.83 ± 1.23	0.64	1.53–4.14	4.391	42	0.001
TG	4.95 ± 1.86	0.89	3.14–6.75	5.534	42	0.001
Group-time interaction (mixed ANOVA)				$F = 6.74$	1.84	0.0011

TUG – Timed Up and Go; CG – control group; TG – treatment group; SD – standard deviation; SEM – standard error of the mean; CI – confidence interval; *df* – degrees of freedom; ANOVA – analysis of variance.

Note: * Paired *t*-test. Both groups had equal respondents (number of respondents = 43).

A multiple linear regression analysis was conducted to evaluate the influence of demographic and clinical variables (gender, age, stroke number, time, diagnosis, and cause) on the outcome measure for both CG and TG at discharge. Statistical significance was assessed using the *t*-test for unstandardized coefficients (B) and standardized coefficients (β), with a 95% CI. Apart from the rehabilitation therapy, no other independent variables significantly influenced the discharge FES-I scores in either CG or TG (Table 5). In CG, the regression model revealed that patient age was a statistically significant predictor of post-rehabilitation TUG times ($\beta = 0.340$; $t = 2.26$; $p = 0.030$). The positive coefficient ($B = 0.284$) indicates that older age was significantly associated with longer TUG execution times after rehabilitation. The regression model for TG yielded no statistically significant

predictors of post-rehabilitation functional mobility (Table 6).

Following rehabilitation, both groups experienced enhanced independence in performing ADLs. In CG, the number of subjects independent in all activities increased from 27 to 31. In TG, the number of subjects independent in all activities increased from 26 to 34 (Table 7). The improvement in TG was statistically significant compared to CG ($\chi^2 = 5.743$; $p = 0.048$).

We analyzed the impact of interventions on the use of a walking cane. The use of a walking cane in CG remained unchanged, with 29 participants. In TG, the number of participants walking independently without a cane increased significantly from 21 to 26 participants after rehabilitation (Table 7). The improvement in TG was statistically significantly better than in CG ($\chi^2 = 6.516$; $p = 0.038$).

Table 5

The influence of the independent research variables on the dependent variable FES-I in the examined groups after rehabilitation

Groups/Variable	B	SE	β	<i>t</i> -test	<i>p</i> -value	95% CI for B
CG						
(constant)	25.600	17.343	–	1.476	0.149	-9.574–60.77
gender	0.102	3.834	0.004	0.027	0.979	-7.675–7.878
age	-0.212	0.208	-0.166	-1.02	0.314	-0.635–0.210
stroke number	10.377	7.620	0.227	1.362	0.182	-5.077–25.83
time	1.162	0.894	0.211	1.299	0.202	-0.652–2.976
diagnosis	-0.633	2.870	-0.036	-0.221	0.827	-6.454–5.187
cause	1.589	5.813	0.044	0.273	0.786	-10.20–13.37
TG						
(constant)	14.154	27.204	–	0.520	0.606	-41.01–69.32
gender	-0.816	4.144	-0.033	-0.197	0.845	-9.220–7.588
age	0.154	0.292	0.099	0.529	0.600	-0.437–0.746
stroke number	5.594	6.639	0.145	0.843	0.405	-7.870–19.05
time	-0.904	0.878	-0.181	-1.03	0.310	-2.685–0.877
diagnosis	1.682	3.367	0.087	0.500	0.620	-5.146–8.510
cause	-0.276	6.063	-0.009	0.045	0.964	-12.57–12.02

FES-I – Falls Efficacy Scale – International; SE – standard error; CI – confidence interval; CG – control group; TG – treatment group.

Table 6

The influence of the independent research variables on the dependent variable TUG test score in the examined groups after rehabilitation

Groups/Variable	B	SE	β	<i>t</i> -test	<i>p</i> -value	95% CI for B
CG						
(constant)	19.172	10.462	–	1.832	0.075	-2.047–40.39
gender	2.802	2.313	0.184	1.211	0.234	-1.889–7.493
age	0.284	0.126	0.340	2.26	0.030	0.539–0.030
stroke number	1.381	4.597	0.046	0.301	0.766	-7.941–10.70
time	0.594	0.540	0.165	1.100	0.278	-0.501–1.688
diagnosis	-0.780	1.731	-0.067	-0.450	0.655	-4.291–2.732
cause	4.517	3.507	0.190	1.288	0.206	-2.594–11.62
TG						
(constant)	20.368	13.020	–	1.564	0.126	-6.038–46.77
gender	-0.350	1.983	-0.029	-0.176	0.861	-4.372–3.672
age	-0.034	0.140	-0.045	-0.024	0.811	-0.317–0.249
stroke number	-1.422	3.178	-0.077	-0.448	0.657	-7.867–5.022
time	0.237	0.420	-0.099	0.564	0.576	-1.089–0.616
diagnosis	0.146	1.611	-0.016	-0.090	0.928	-3.414–3.122
cause	-3.067	2.902	-0.201	-1.05	0.298	-8.953–2.818

TUG – Timed Up and Go; SE – standard error; CI – confidence interval; CG – control group; TG – treatment group.

Table 7

**Ability to perform ADLs and use of walking aids
among examined groups before and after rehabilitation**

Variable	CG (n = 43)		TG (n = 43)	
	before	after	before	after
ADLs				
independent	27	31	26	34
dependent only with bathing	12	8	12	9
dependent in all activities	4	4	5	0
Use of walking aids				
does not use a cane	29	29	21	26
uses a cane	3	3	16	11
uses a cane with a wide base of support	11	11	6	6

ADLs – activities of daily living; CG – control group; n – number of respondents; TG – treatment group.

All values are given as numbers.

Discussion

The current study investigated the efficacy of adding chair-based GE to CR in reducing FoF among stroke patients. The chair-based balance exercises introduced a novel group methodology to stroke rehabilitation. Based on current research, expert opinions, and established guidelines, the program promoted a range of activities in sitting, standing, and upright positions necessary for daily functioning^{17–19}.

The findings of this study may indicate that integrating chair-based GE into CR protocols significantly enhances the reduction of FoF in stroke patients. While both groups showed improvement, the reduction in FES-I scores in TG (10.07 ± 1.08) was more than double that observed in CG (4.63 ± 1.98). This suggests that chair-based GE may significantly reduce FoF. These results align with previous research indicating that multidimensional interventions are more effective for managing post-stroke FoF than physical therapy alone^{20, 21}. Combining body weight-supported treadmill training with CR yielded significantly better outcomes than either treatment in isolation²². Similarly, a randomized controlled clinical trial by Gunduz et al.²³ concluded that combined treatments in subacute and chronic stroke rehabilitation enhance balance and reduce FoF more effectively than isolated approaches, specifically when comparing robot-assisted gait training plus traditional balance training against traditional training alone. Hung et al.²⁴ compared the effects of video games vs. conventional weight-bearing training and found that both groups showed improved FoF outcomes at a three-month follow-up. In contrast to these high-tech interventions, our research highlights the benefits of chair-based GE, which are cost-effective, easy to implement, and require minimal resources.

A primary limitation of this study is the heterogeneity of the patient sample regarding time since stroke onset. Our study included patients in both subacute and chronic phases, which may have influenced the magnitude of the observed effects. Literature consistently emphasizes that the most significant gains in functional recovery typically occur during the subacute phase^{1, 25, 26}. By including a broader demographic, our study avoids creating an “artificial” environ-

ment, ensuring the findings apply to a more complex, clinical population. This approach may enhance the external validity of our findings, demonstrating that chair-based GE remain a viable intervention for reducing FoF, even in the later stages of recovery. However, because the participants were at vastly different points in their recovery trajectories, these results cannot be generalized to a specific post-stroke population without further stratified research.

Functional mobility was measured using the TUG test. The non-significant baseline differences in both FES-I and TUG scores indicate that groups were well-matched in terms of both subjective FoF and objective functional mobility, ensuring that any subsequent improvements can be attributed to the intervention rather than initial disparities. While both groups improved with rehabilitation, results demonstrated that the combined treatment protocol yielded a significantly greater reduction in TUG time (4.95 ± 1.86 s) than the standard rehabilitation (2.83 ± 1.23 s). While both improvements were statistically significant, their clinical relevance is best interpreted through the Minimal Clinically Important Difference (MCID) typically cited as 2–3 s for the TUG test in similar populations^{27, 28}.

The significant between-group difference (0.011) is not merely a statistical artifact; the 2.12 s advantage in TG is roughly equivalent to a full MCID unit. Notably, the 95% CI for TG (3.14–6.75) remains entirely above the 3-s MCID ceiling, whereas the lower bound for CG (1.53) falls below the 2-s floor. Clinically, the 4.95-s reduction in TG represents a more robust improvement in functional mobility. These results suggest that a combined approach more effectively moves patients toward functional mobility.

While CR remains the most practical and accessible option for stroke recovery²⁹, our findings align with current trends emphasizing multimodal post-stroke rehabilitation³⁰. Recent studies indicate that mobility and functional recovery are most effectively enhanced through a combination of diverse treatment components³¹, including specialized vestibular and dual-task training³² and advanced technology such as exoskeleton robot-assisted walking³³. The superior results in our TG suggest that chair-based GE may serve as a safe and effective addition to standard rehabilitation. This integrated

approach likely addresses functional mobility more comprehensively than standard rehabilitation alone.

Our data may suggest that the quality and effectiveness of rehabilitation interventions contribute meaningfully to improvements in balance confidence and functional mobility, irrespective of individual demographic or clinical factors such as age, diagnosis, or stroke history. Exploratory multiple linear regression models revealed that baseline demographic and clinical covariates generally did not predict post-rehabilitation outcomes, suggesting that the benefits of the intervention operate independently of factors like gender, stroke frequency, or injury etiology. Notably, advanced age was significantly linked to slower mobility recovery within CG ($p = 0.030$), whereas this negative age effect was entirely absent in TG ($p = 0.811$). This may indicate that the treatment protocol effectively mitigates standard age-related barriers to neurological and functional recovery. However, given the statistical constraints of the regression models ($n = 86$ total; $n = 43$ per group), these predictive insights must be interpreted with strict caution due to the localized risk of overfitting. While the treatment framework stands out as a highly effective intervention for accelerating motor confidence and gait speed, multi-center trials with larger sample populations are required to definitively validate these exploratory predictive pathways.

The results of this study confirmed that combined treatment significantly boosts ADLs performance and reduces reliance on walking aids, aligning with previous findings by Bjälkefur et al.³⁴ and Kaźmierczak et al.³⁵. The success observed in TG may be attributed to the functional design of chair-based exercises. By practicing simulated ADLs (reaching, bending, and weight transfer), patients enhance the skills essential for regaining independence in daily life.

Addressing the psychological barrier, FoF is crucial as physical rehabilitation for stroke survivors. Chair-based GE offer a practical, resource-efficient, and scalable solution for busy inpatient wards, serving to bridge the gap between intensive therapy and functional self-reliance. While these interventions show significant immediate promise in boosting patient confidence and safety, further longitudinal research is essential to confirm the long-term durability of these gains and their impact on permanent functional independence.

A primary strength of this research lies in the implementation of a chair-based GE program, which provided a safe and inclusive framework for the participants. Furthermore, despite sample-related methodological constraints, systematic group allocation achieved baseline homogeneity

across key variables—such as initial physical function—supporting internal comparability between the examined groups.

Limitations of the study

Although the study design and data analysis were planned prior to data collection, a limitation of our research is the lack of prospective trial registration. Furthermore, the findings of this study should be interpreted with regard to several additional limitations. First, the sample size was relatively small and was not determined through formal power calculations, which may affect the generalizability of the results. Second, the study lacked investigator blinding; the primary author delivered the intervention and conducted all assessments. While this was necessitated by resource constraints, it introduces potential for performance and detection bias. Third, while the FES-I questionnaire is a widely recognized tool, it has not yet undergone formal linguistic or cross-cultural validation for stroke survivors in this specific regional context. Finally, the intervention period was relatively brief, and the absence of long-term follow-up precludes conclusions regarding the durability of the improvements observed.

Conclusion

The results of our study indicate that adding a chair-based group exercise program may significantly improve standard rehabilitation for patients in the subacute and chronic phases post-stroke. The intervention yielded measurable improvements in the fear of falling and functional mobility, while also leading to more favorable classifications of activities of daily living dependence and reduced reliance on walking aids. These findings suggest that the targeted nature of chair-based exercises, specifically their focus on balance, may be an important factor in improving functional independence and self-confidence during activities of daily living. Integrating such programs into clinical practice offers an effective, low-risk strategy to optimize recovery outcomes. Future research should prioritize larger cohorts and longitudinal designs to validate these preliminary findings.

Conflict of interest

The authors declare no conflict of interest concerning the authorship and/or publication of this article.

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Epidemiological characteristics of tuberculosis in the Autonomous Province of Vojvodina, Serbia (1998–2025): a population-based study

Epidemiološke karakteristike tuberkuloze u Autonomnoj Pokrajini Vojvodini, Srbija (1998–2025): populaciona studija

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Abstract

Background/Aim. Tuberculosis (TB) incidence has declined substantially in Europe over recent decades. However, demographic shifts and health disruptions such as the coronavirus disease-19 – COVID-19 pandemic continue to influence TB epidemiology. In the Republic of Serbia, long-term subnational analyses remain limited. The aim of the study was to analyze trends in TB incidence, mortality, demographic characteristics, and seasonality in the Autonomous Province (AP) of Vojvodina, Serbia, over 28 years. **Methods.** A descriptive, population-based study was conducted using routinely collected surveillance data from 1998 to 2025. TB cases were identified according to national case definitions aligned with World Health Organization and European Center for Disease Prevention and Control standards. Occupational data for TB cases among workers were available for the period 2015–2025. **Results.** A total of 9,511 TB cases were reported (mean 339.7 annually). Joinpoint regression analysis demonstrated a significant overall decline in TB incidence (average annual percent change – AAPC = -5.73%; 95% confidence interval: -7.31 to -4.02; $p < 0.001$), primarily driven by a marked annual decrease between 2002 and 2021, followed by a non-

significant increase in incidence during the final study period. A total of 226 deaths were recorded. Mortality remained low (0.00–0.98 *per* 100,000), with no deaths recorded in 2020–2021. TB incidence and mortality showed a pronounced age gradient, with the highest rates in individuals aged ≥ 60 years, while pediatric TB was nearly eliminated. The proportions of older patients, laboratory-confirmed cases, and fatal outcomes compared to survivors were all significantly higher in 2012–2025 than in 1998–2011. A consistent seasonal pattern was observed, with peak case notifications in January (22% of all reported cases). A total of 21 sporadic TB cases were identified among workers during 2015–2025, distributed across various occupational groups, mainly among middle-aged males. **Conclusion.** TB burden in the AP of Vojvodina has declined markedly, but an increasing proportion of TB cases among older adults was recorded. Although rare, TB cases among workers occurred across diverse occupational groups, underscoring the need for continued occupational surveillance.

Keywords: epidemiology; incidence; mortality; serbia; tuberculosis.

Apstrakt

Uvod/Cilj. Učestalost tuberkuloze (TB) u Evropi je značajno opala tokom poslednjih decenija. Međutim, demografske promene i zdravstvene krize poput pandemije izazvane korona virusom 2019. (*coronavirus disease-19* – COVID-19) i dalje utiču na epidemiologiju TB. U Republici Srbiji, analize dugogodišnjih trendova na subnacionalnom nivou su i dalje ograničene. Cilj rada bio je da se analiziraju trendovi stopa incidencije i mortaliteta od TB, demografske

karakteristike i sezonalnost u Autonomnoj Pokrajini (AP) Vojvodini, Srbija, tokom perioda od 28 godina. **Metode.** Korišćenjem rutinski prikupljenih podataka iz sistema nadzora, sprovedena je deskriptivna populaciona studija za period 1998–2025 godine. Slučajevi TB definisani su prema nacionalnim definicijama slučaja, usklađenim sa standardima Svetske zdravstvene organizacije i Evropskog centra za prevenciju i kontrolu bolesti. Podaci o zanimanju obolelih od TB među zaposlenima bili su dostupni za period 2015–2025. **Rezultati.** Prijavljeno je ukupno 9 511 slučajeva TB

(prosečno 339,7 godišnje). Regresiona analiza tačaka spajanja (*joinpoint*) pokazala je statistički značajan ukupni pad incidencije tuberkuloze (*average annual percent change* – AAPC = -5,73%; 95% *confidence interval*: -7,31 do -4,02; $p < 0,001$), prvenstveno uslovljen izraženim godišnjim padom stope incidencije u periodu 2002–2021, praćen porastom incidencije, koji nije bio statistički značajan, u finalnom periodu studije. Registrovano je ukupno 226 smrtnih ishoda. Mortalitet je bio nizak (0,00–0,98 na 100 000), bez registrovanih smrtnih slučajeva u periodu 2020–2021. Učestalost obolevanja i smrtnost od TB zavisili su od životnog doba obolelih, sa najvišim stopama registrovanim kod osoba starosti ≥ 60 godina, dok je TB kod dece bila gotovo eliminisana. Udeo starijih obolelih, procenat laboratorijski potvrđenih slučajeva, kao i procenat smrtnih ishoda u odnosu na preživjele, bio je statistički značajno viši

u periodu 2012–2025. u odnosu na period 1998–2011. Uočen je dosledan sezonski obrazac, sa maksimalnim brojem obolelih u januaru (22% svih registrovanih slučajeva). U periodu 2015–2025 utvrđeno je ukupno 21 sporadično obolelih od TB među radnicima svrstanim u različite profesionalne grupe, uglavnom među muškarcima srednjeg životnog doba. **Zaključak.** Opterećenje TB u AP Vojvodini značajno je smanjeno, ali je zabeležen veći udeo TB među starijim osobama. Mada retki, slučajevi TB među radnicima javljali su se u različitim profesionalnim grupama, što naglašava potrebu za kontinuiranim nadzorom u oblasti medicine rada.

Ključne reči:
epidemiologija; incidencija; mortalitet; srbija;
tuberkuloza.

Introduction

Tuberculosis (TB) remains a major global public health challenge, with substantial incidence and mortality despite considerable progress in prevention, diagnosis, and treatment¹. According to the World Health Organization (WHO), an estimated 10.7 million people developed TB globally in 2024, with approximately 1.3 million deaths (including 150,000 among people with human immunodeficiency virus – HIV), highlighting the persistent global burden of the disease². Approximately one-quarter of the global population is estimated to be infected with TB. The risk of progressing to active disease is highest within the first 2 years after infection (around 5%), and declines substantially thereafter^{1,3}. Although TB incidence has been declining over the past two decades, the rate of decrease remains insufficient to meet the targets set by the End TB Strategy^{1,2}. Urgent action is needed to end the global TB epidemic by 2030, a goal endorsed by WHO and all Member States of the United Nations^{1,4}.

In low-incidence regions, including Europe, TB epidemiology is characterized by heterogeneous trends, with higher burdens observed in specific subpopulations such as older adults, migrants, and socioeconomically vulnerable groups. In 2024, an estimated 204,000 people developed TB in the WHO European Region, corresponding to 22 cases *per* 100,000 population. The overall reduction in TB incidence between 2015 and 2024 was 39%, falling short of the WHO End TB milestone of a 50% reduction by 2025. In 2023, a total of 38,993 TB cases were reported across 29 European Union (EU) and European Economic Area (EEA) – EU/EEA countries, corresponding to a notification rate of 8.6 *per* 100,000 population. This reflects a continued slight increase observed in most countries since 2022, although the overall trend over the past 5 years remains downward⁵.

In 2023, the United States reported 9,633 TB cases, corresponding to an incidence rate (IR) of 2.9 *per* 100,000 population. This represents an increase of 15% compared with 2022 and 6.2% compared with 2019 (the year preceding the coronavirus disease 2019 – COVID-19 pandemic). While

these data indicate overall effective TB control, they also highlight persistent disparities among high-risk groups⁶.

In South-Eastern Europe, including Serbia, TB incidence has shown a sustained downward trend over recent decades, largely driven by strengthened national control programs, improved diagnostics, and the widespread implementation of directly observed therapy (DOT)⁵. According to national surveillance data, Serbia has transitioned to a low-incidence setting, with notification rates declining from over 30 *per* 100,000 population in the late 1990s to below 10 *per* 100,000 in recent years. A substantial reduction was observed between 2005 and 2019, with an approximately 80% decrease in notification rates, reaching 9 *per* 100,000 population. In 2020 and 2021, rates further declined to 5.0 and 3.75 *per* 100,000, respectively, most likely reflecting underreporting during the COVID-19 pandemic. This was followed by an increase to 7.2 *per* 100,000 in 2023, and a slight decrease to 6.8 *per* 100,000 in 2024, representing a 6% reduction compared with the previous year. Despite this overall progress, ongoing challenges remain, including population ageing, the growing burden of comorbidities, and potential disruptions to TB services, particularly during the COVID-19 pandemic⁷.

Understanding long-term epidemiological trends at the subnational level is essential for tailoring public health interventions and identifying residual transmission patterns. The Autonomous Province (AP) of Vojvodina, Serbia, represents a specific epidemiological setting within Serbia, characterized by demographic ageing, urban–rural diversity, and varying socioeconomic conditions that may influence TB dynamics. TB surveillance in the AP of Vojvodina has been conducted since 1949; however, until 1998 it was under the jurisdiction of the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia, after which responsibility was transferred to the epidemiological service of the Institute of Public Health of Vojvodina (IPHV), Novi Sad, Serbia⁸.

The aim of this study was to analyze long-term trends in TB incidence, mortality, demographic characteristics, and seasonal patterns over 28 years (1998–2025), and to describe

the occupational profile of workers diagnosed with TB during routine medical examinations (2015–2025) in the AP of Vojvodina.

Methods

Study design and setting and data sources

This descriptive study was conducted in the AP of Vojvodina, Serbia, a northern region of Serbia with approximately 1.7 million inhabitants⁹.

Data were obtained from the regional communicable disease surveillance system, coordinated by the IPHV. From 1998 onwards, data on registered active TB cases were retrospectively entered into the communicable diseases' registry in collaboration with the Institute for Pulmonary Diseases of Vojvodina. Since 2000, dispensaries for pulmonary diseases and TB in the AP of Vojvodina have routinely reported newly diagnosed TB cases to the IPHV, as well as to the regional public health institutes across the province⁸. TB notification is mandatory in Serbia, and cases are reported in accordance with national legislation and aligned with international standards defined by the WHO and the European Center for Disease Prevention and Control (ECDC)^{7, 10, 11}. All active TB cases (both clinically- and laboratory-confirmed) reported between 1 January 1998 and 31 December 2025 were included in the comprehensive analysis.

Case definition, variables, and population data

An active TB case was defined as either a laboratory-confirmed case (by bacteriological methods, including smear microscopy, culture, or molecular diagnostics) or a clinically diagnosed case based on radiological, histopathological, and clinical findings in the absence of laboratory confirmation – signs, symptoms and/or radiological findings consistent with active TB in any site and a clinician's decision to treat the person with a full course of anti-TB therapy^{10, 11}.

The following variables were analyzed: year/month of notification, age, gender, place of residence (urban/rural), district of residence, diagnostic category (laboratory-confirmed vs. clinically diagnosed), and treatment outcome (including death). Age was categorized into four groups: 0–14, 15–39, 40–59, and ≥ 60 years.

Occupational data for active TB cases among workers were obtained from the Institute of Occupational Health of Novi Sad. Data were collected for the period 2015–2025 and classified according to the International Standard Classification of Occupations 2008 (ISCO-08) of the International Labor Organization (ILO)¹².

Statistical analysis

Descriptive epidemiological methods were used to summarize TB incidence, mortality, and demographic characteristics of TB cases. Population denominators were obtained from official statistics of the Statistical Office of the

Republic of Serbia⁹. Mid-year population estimates were used to calculate incidence and mortality rates (MRs) *per* 100,000 inhabitants. Trends in TB IRs over the period under study were assessed using joinpoint regression analysis (JRA), which characterized temporal trends by estimating their magnitude and direction from models fitted to the observed data. Changes in TB incidence trends were presented graphically. The average annual percent change (AAPC) and corresponding 95% confidence intervals (CIs) were estimated to summarize trends over the entire study period. Trends were considered statistically significant when the slope differed from zero at $\alpha = 0.05$ (indicated by an AAPC that differed significantly from zero) and were classified as increasing or decreasing. JRA was performed using Joinpoint Regression Software, version 6.0.1 (National Cancer Institute, Bethesda, MD, USA)¹³. The value of $p < 0.05$ was considered statistically significant across the analyses. Incidence and MRs were calculated annually and stratified by age groups. Seasonality was assessed by analyzing the monthly distribution of TB notifications over the entire study period and across age groups.

The demographic (gender, age), geographic (place of residence, district), temporal (quarter of the year), and clinical characteristics (diagnostic confirmation and outcome) of active TB cases were compared between the two study periods (1998–2011 vs. 2012–2025). The study period was stratified into two equal intervals based on the average annual number of reported cases, with case numbers close to or above the overall average in 1998–2011 and below the average in 2012–2025 in the AP of Vojvodina. Comparisons between the two study periods were performed using the χ^2 test for categorical variables and the *t*-test for continuous variables. The results were presented as numbers and percentages or means $\pm$ standard deviation (SD), with statistical significance set at $p < 0.05$. All statistical analyses were conducted using SPSS software, version 21 (IBM Corp., Armonk, NY, USA).

Ethical considerations

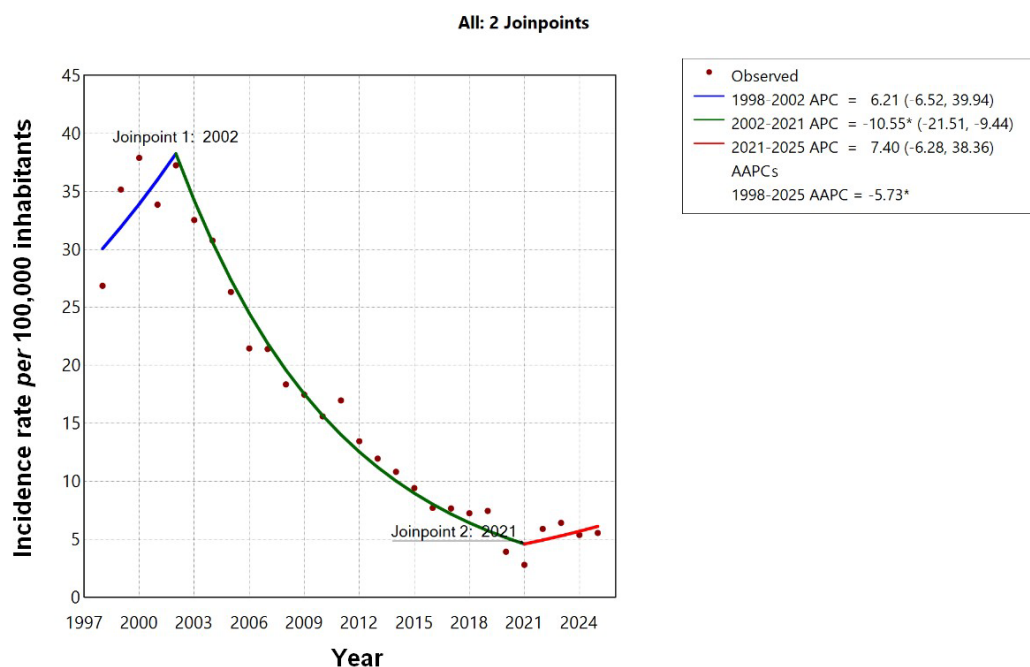
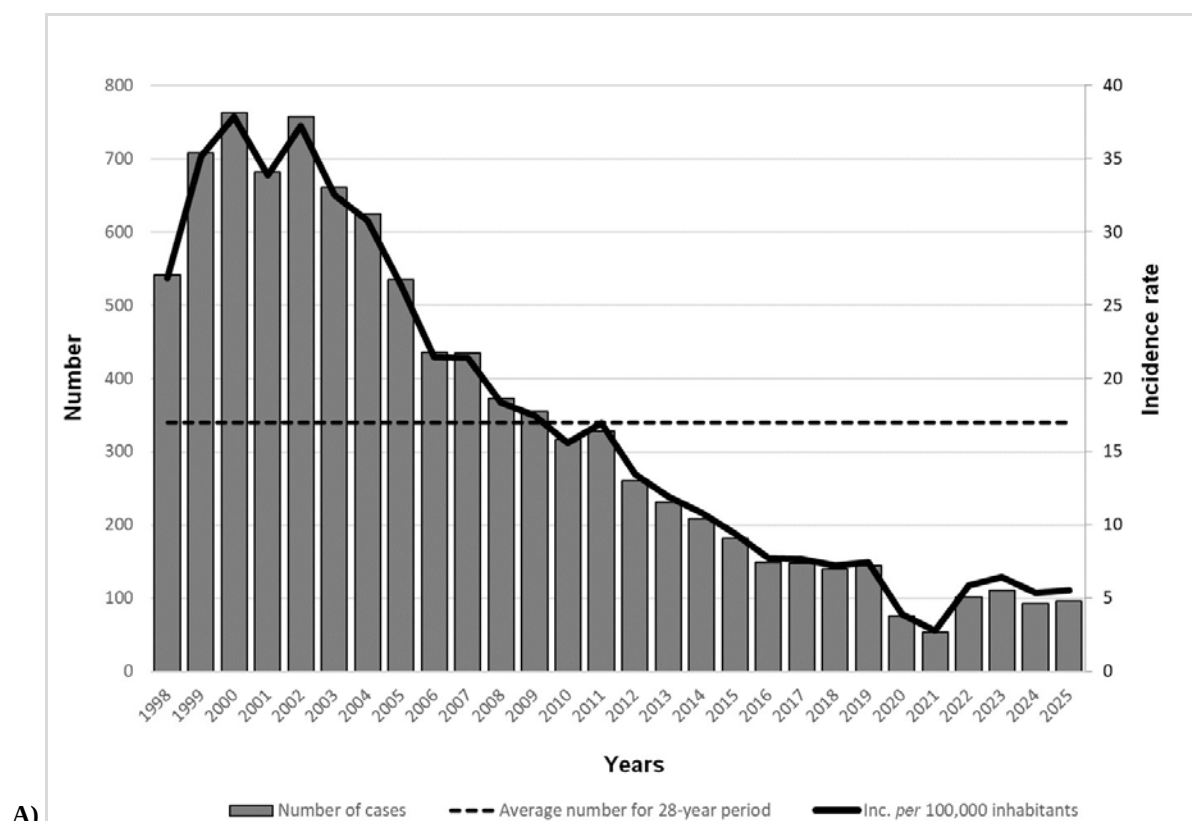
The study was based on anonymized surveillance data routinely collected for public health purposes. Therefore, approval from an Ethics Committee was not required under Serbian regulations. All analyses were conducted using anonymized and aggregated surveillance data.

Results

Between 1998 and 2025, a total of 9,511 active TB cases were reported in the AP of Vojvodina. Over the 28-year observation period, the mean annual number of reported TB cases was 339.7. According to JRA, the TB IR in the AP of Vojvodina showed a statistically significant decreasing trend over the study period (AAPC = -5.73%; 95% CI: -7.31 to -4.02; $p < 0.001$). Two joinpoints were identified, resulting in three distinct temporal trends in TB incidence. Between 1998 and 2002, IR increased non-significantly by an average of 6.21% *per* year (APC = 6.21%; 95% CI: -6.52

to 39.94; $p = 0.343$). This was followed by a statistically significant annual decline of 10.55% between 2002 and 2021 (APC = -10.55%; 95% CI: -21.51 to -9.44; $p = 0.001$).

During the final period (2021–2025), IR showed a non-significant annual increase of 7.40% (APC = 7.40%; 95% CI: -6.28 to 38.36; $p = 0.324$) (Figure 1A, B).



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the $\alpha = 0.05$ level.

Final Selected Model: 2 Joinpoints.

Fig. 1 – A, B) Joinpoint regression analysis plot of tuberculosis incidence rate trends in the Autonomous Province of Vojvodina, Serbia (1998–2025).
Inc. – incidence; AAPC – average APC.

Over the study period, a total of 226 fatal cases were recorded. The annual number of TB-related deaths ranged from 0 to 19, corresponding to MRs between 0.00 and 0.98 *per 100,000* population. During the late 1990s and early 2000s (1998–2001), mortality remained relatively stable, with 11–13 fatal cases annually and MRs of 0.55–0.65 *per 100,000*. This was followed by a moderate decline between 2002 and 2004, when the number of TB deaths decreased to 7–9 cases *per year*, with MRs between 0.34 and 0.44 *per 100,000*. From 2005 to 2010, mortality fluctuated without a clear trend, ranging from 6 to 12 deaths annually and corresponding rates of 0.30–0.59 *per 100,000* inhabitants. A pronounced peak was observed in 2011, with 19 fatal cases, representing the highest recorded MR (0.98 *per 100,000*) during the study period. In the subsequent years (2012–2014), mortality declined again (MRs 0.41–0.62 *per 100,000*). A sustained low-mortality phase was evident from 2015 to 2019, with 4–5 fatal cases annually. Notably, no fatal cases were recorded in 2020 and 2021. After this period, mortality re-emerged, with 4 deaths in 2022 (0.23 *per 100,000*) and a transient increase in 2023 to 10 fatal cases (0.58 *per 100,000*), followed by a decline in 2024–2025, when mortality ranged from 0.29 to 0.46 *per 100,000* inhabitants (Figure 2).

From 1998 to 2025, TB incidence showed a marked decline across all age groups, with a persistent age-related gradient. The highest incidence was consistently observed in individuals aged ≥ 60 years, followed by those aged 40–59 years, while substantially lower rates were recorded in the 15–39-year and 0–14-year age groups.

During the early study period (1998–2002), incidence was highest among older adults, reaching 66.0 *per 100,000* in those aged ≥ 60 years and 57.9 *per 100,000* in the 40–59-year age group. Thereafter, a sustained decline was observed across both age groups. In the 15–39-year age group, the highest TB IRs were also recorded in the early study period, followed by a continuous decline until 2021; however, an increasing trend was observed between 2022 and 2025. Among children aged 0–14 years, incidence declined to below 1.0 *per 100,000* by 2007 and reached zero from 2021 onwards (Figure 3).

From 1998 to 2025, TB mortality showed a pronounced age gradient, with fatal outcomes occurring almost exclusively among adults, particularly in the ≥ 60 -year age group.

Throughout the entire study period, no TB-related deaths were recorded among children aged 0–14 years, except for a single low-rate observation in 1998. Mortality among individuals aged 15–39 years remained very low and sporadic, with annual rates generally below 0.32 *per 100,000*, and isolated increases observed in 2000–2001, 2013–2014, and 2025. In contrast, mortality in the 40–59-year age group and especially among those aged ≥ 60 years was consistently higher. The highest age-specific MRs were observed in 2011, reaching 1.41 *per 100,000* in the 40–59-year group and 2.19 *per 100,000* in individuals aged ≥ 60 years. Elevated mortality in the oldest age group was also recorded in 2000 (2.39 *per 100,000*) and 2005 (2.48 *per 100,000*) (Figure 4).

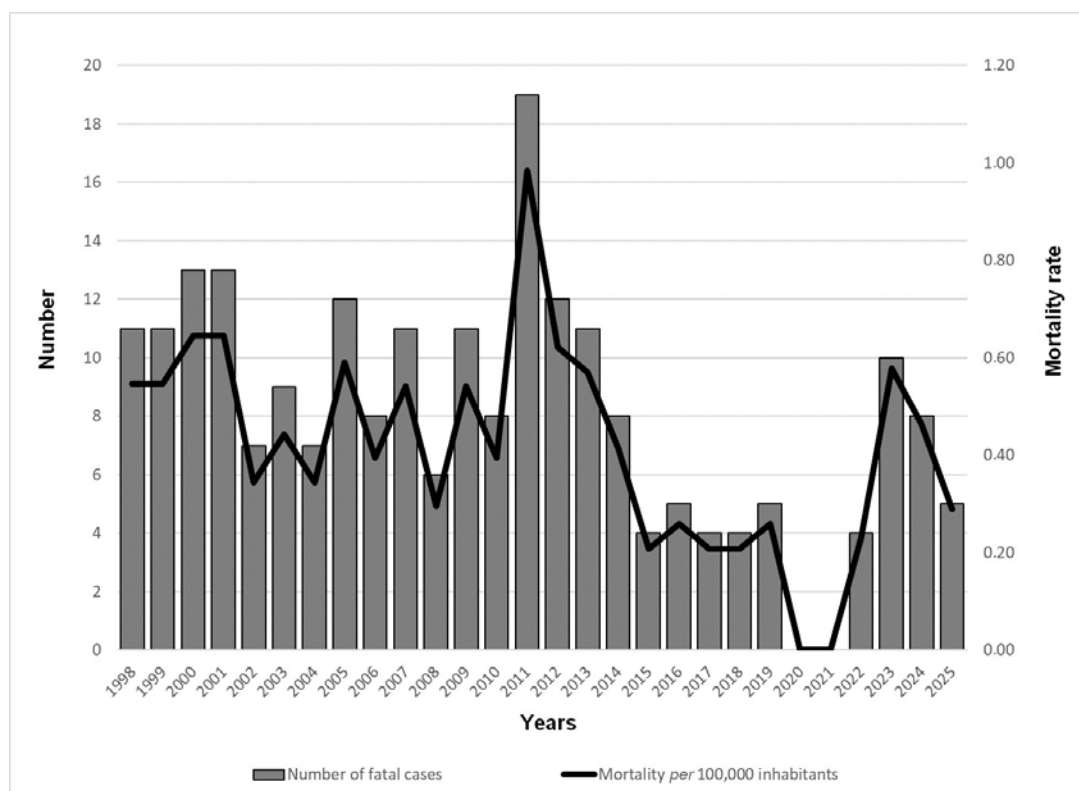


Fig. 2 – Annual number of fatal cases and mortality rate of tuberculosis in the Autonomous Province of Vojvodina, Serbia (1998–2025).

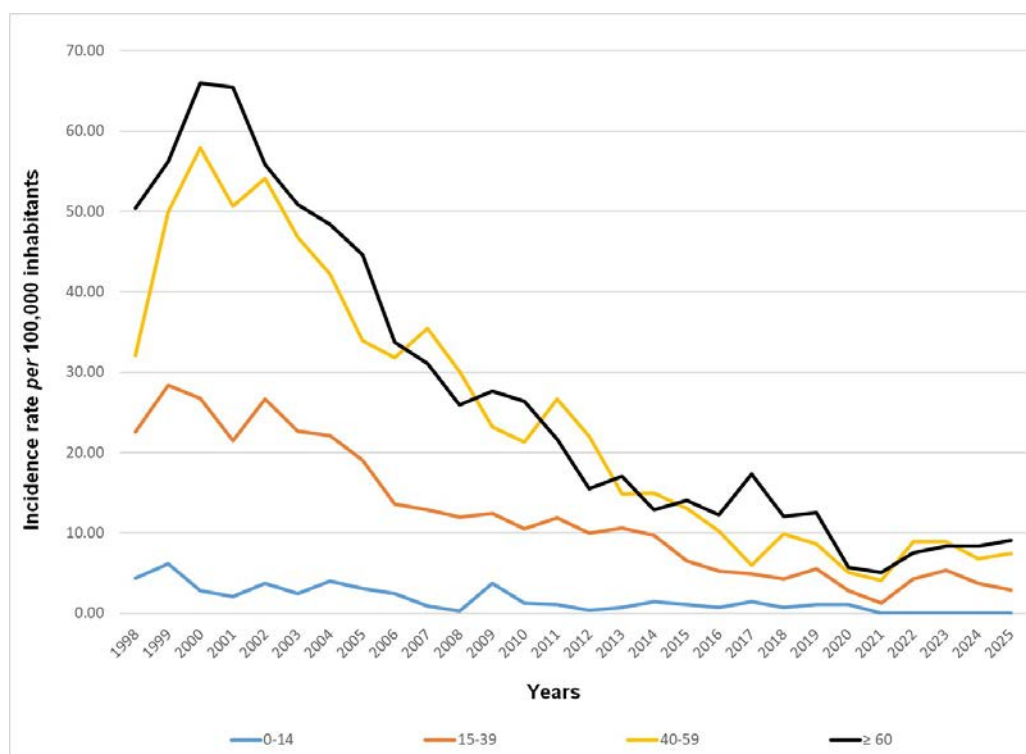


Fig. 3 – Age-specific incidence of tuberculosis in the Autonomous Province of Vojvodina, Serbia (1998–2025).

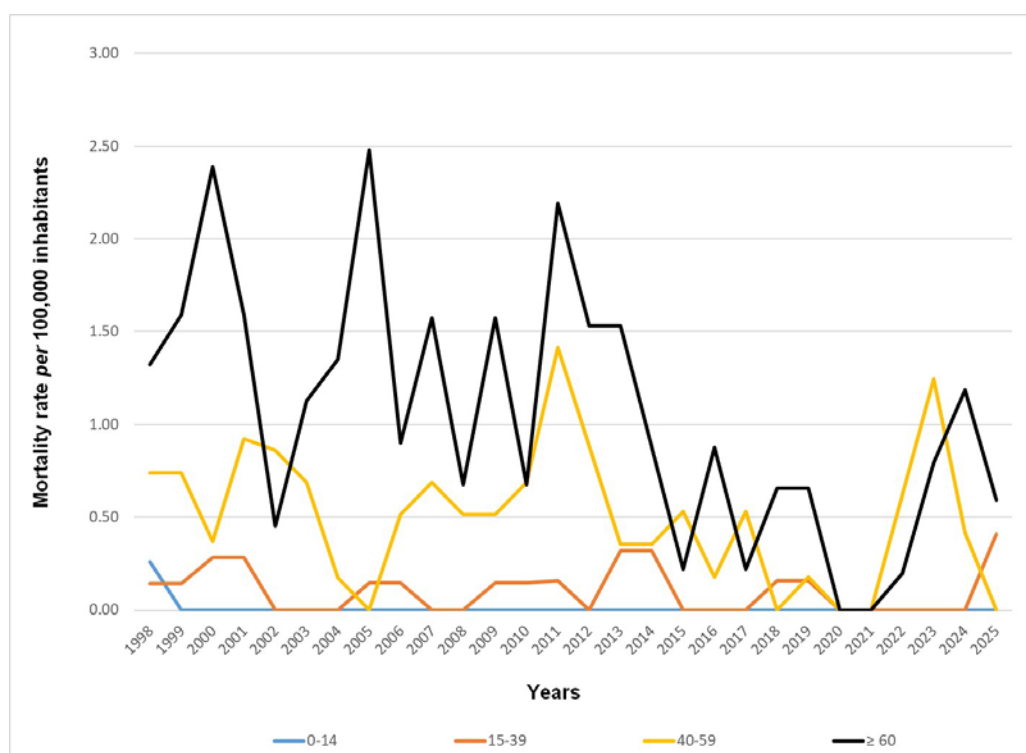


Fig. 4 – Age-specific mortality of tuberculosis in the Autonomous Province of Vojvodina, Serbia (1998–2025).

Analysis of TB cases reported during the period 1998–2025 revealed a clear seasonal pattern. The highest proportion of cases was recorded in January (22% of all notified cases), followed by a marked decline during the subsequent months. From February to September, the

monthly distribution was relatively uniform, with each month accounting for approximately 7–9% of total TB cases. In contrast, a pronounced decrease was observed in the last quarter of the year, and December accounted for the lowest proportion of notifications (2.9%) (Figure 5).

The highest number of cases was consistently reported in January, particularly among individuals in the 15–39, 40–59, and ≥ 60 -year age groups, who accounted for the majority of notifications throughout the year. From February to September, case numbers remained relatively stable across adult age groups, with moderate month-to-

month variation. A marked decline was observed during the autumn and early winter months, with the lowest numbers recorded in November and December in all age categories. TB cases among children aged 0–14 years were few throughout the year and showed no pronounced seasonal variation (Figure 6).

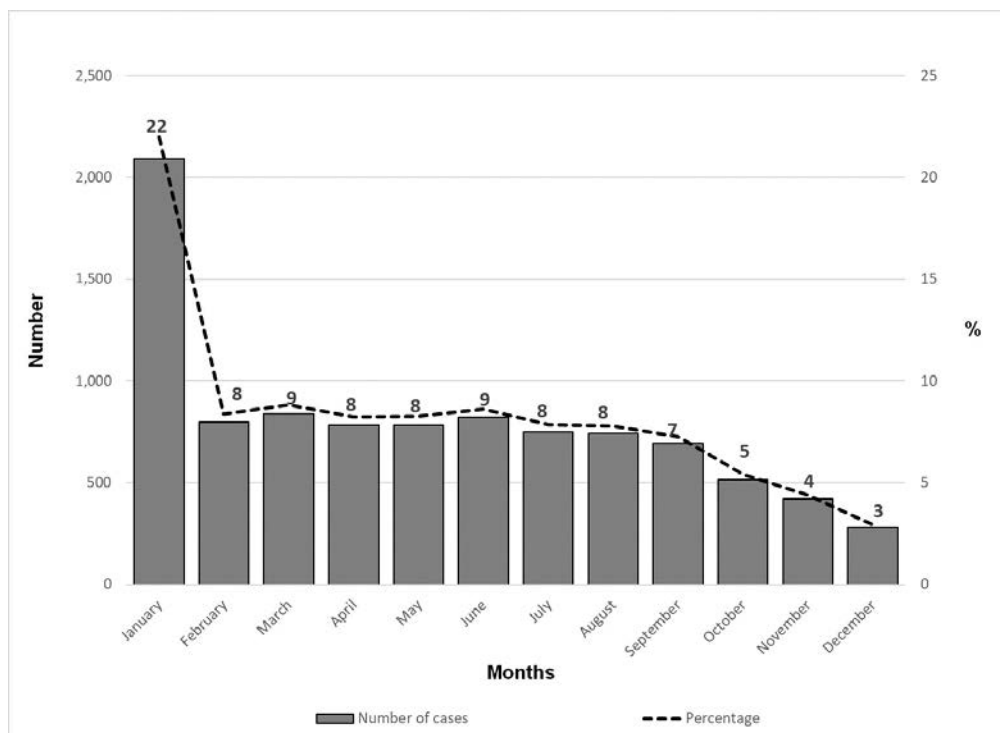


Fig. 5 – Monthly distribution of tuberculosis and percentage of total notifications in the Autonomous Province of Vojvodina, Serbia (1998–2025).

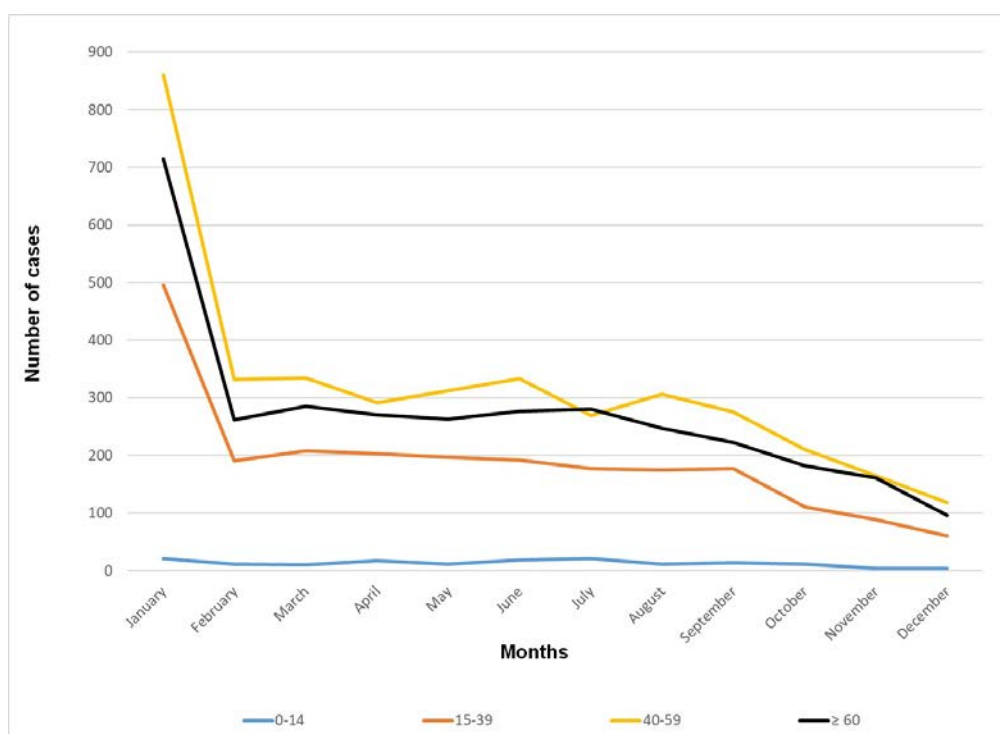


Fig. 6 – Monthly number of tuberculosis cases by age group in the Autonomous Province of Vojvodina, Serbia (1998–2025).

A total of 9,511 TB cases were registered during the study period, with 7,516 cases reported in 1998–2011 and 1,995 cases in 2012–2025.

Men predominated in both periods, accounting for 65.45% of cases in 1998–2011 and 64.46% in 2012–2025; the gender distribution did not differ significantly between periods ($p = 0.4263$). The mean age of TB cases was higher in the later period (2012–2025) compared with the earlier period (1998–2011), increasing from 50.54 years (SD ± 17.37) to 52.24 years (SD ± 17.75). This difference was statistically significant ($p = 0.0001$).

Age-specific analysis revealed a significant shift in the distribution of cases between the two periods ($p = 0.0195$). The proportion of children aged 0–14 years declined (from 1.78% to 1.20%), as did the share of individuals aged 15–39 and 40–59 years, whereas the proportion of patients aged ≥ 60 years increased from 33.62% to 36.89%.

No statistically significant difference in the distribution of TB cases by place of residence was observed between 1998–2011 and 2012–2025 ($p = 0.2825$).

In contrast, the geographical distribution by district changed significantly over time ($p < 0.001$). A higher

proportion of cases in the later period was recorded in South Bačka (from 31.85% to 38.50%) and South Banat (from 17.16% to 19.65%), while declines were observed in North Bačka, West Bačka, and North Banat.

Seasonal distribution of TB notifications remained stable, with the highest proportion of cases consistently reported in the first quarter of the year (January–March), accounting for approximately 39% of cases in both periods ($p = 0.4526$).

In 1998–2011, 2,626 cases (34.94%) were diagnosed clinically, whereas 4,890 (65.06%) cases were laboratory-confirmed. In contrast, during 2012–2025, the proportion of clinically diagnosed cases decreased to 362 (18.15%), while laboratory-confirmed cases increased to 1,633 (81.85%) ($p < 0.001$).

Treatment outcome analysis showed a significant increase in case fatality over time. While survival remained high overall, the proportion of fatal cases more than doubled, rising from 1.94% in 1998–2011 to 4.01% in 2012–2025 ($p < 0.001$) (Table 1).

During the period 2015–2025, the total number of workers undergoing routine medical examinations showed

Table 1

Distribution of tuberculosis cases in the Autonomous Province of Vojvodina, Serbia, by demographic, spatial, and temporal characteristics (1998–2025)

Variable	1998–2011 (n = 7,516)	2012–2025 (n = 1,995)	p-value
Gender			
male	4,919 (65.45)	1,286 (64.46)	0.4263
female	2,597 (34.55)	709 (35.54)	
Age, years	50.54 $\pm$ 17.37	52.24 $\pm$ 17.75	0.0001
Age, range			
0–14	134 (1.78)	24 (1.20)	0.0195
15–39	1,815 (24.15)	463 (23.21)	
40–59	3,040 (40.45)	772 (38.70)	
≥ 60	2,527 (33.62)	736 (36.89)	
Place of residence			
urban	3,573 (47.54)	976 (48.92)	0.2825
rural	3,943 (52.46)	1,019 (51.08)	
District of the AP Vojvodina			
North Bačka	631 (8.40)	128 (6.42)	< 0.001
West Bačka	838 (11.15)	180 (9.02)	
South Bačka	2,394 (31.85)	768 (38.50)	
North Banat	489 (6.51)	78 (3.91)	
Central Banat	560 (7.45)	134 (6.72)	
South Banat	1,290 (17.16)	392 (19.65)	
Srem	1,314 (17.48)	315 (15.79)	
Quarter of the year			
January–March	2,934 (39.04)	794 (39.80)	0.4526
April–June	1,903 (25.32)	487 (24.41)	
July–September	1,736 (23.10)	443 (22.21)	
October–December	943 (12.55)	271 (13.58)	
Confirmed TB			
clinically diagnosed	2,626 (34.94)	362 (18.15)	< 0.001
laboratory-confirmed	4,890 (65.06)	1,633 (81.85)	
Treatment outcome			
survived	7,370 (98.06)	1,915 (95.99)	< 0.001
fatal cases	146 (1.94)	80 (4.01)	

n – number of patients with tuberculosis.

Statistically significant values ($p < 0.05$) are marked in bold.

Values are given as mean $\pm$ standard deviation or numbers (percentages).

notable fluctuations, ranging from 3,489 in 2020 to a peak of 7,552 in 2024. TB cases among workers were reported sporadically throughout the study period. In the early years, 3 TB cases were recorded in both 2015 and 2016, followed by a decrease to 1 case annually in 2017 and 2018. No cases were reported in 2019 and 2020. Subsequently, 2 TB cases were detected in 2021 and 1 case in 2022. A further increase

was observed in 2023 (3 cases), followed by 2 cases in 2024, and a peak of 5 cases in 2025, representing the highest annual number recorded during the study period (Figure 7).

A total of 21 workers with reported TB cases were identified across a broad range of occupations, classified according to ISCO-08 of the ILO. The distribution was heterogeneous, including healthcare, service, technical, and

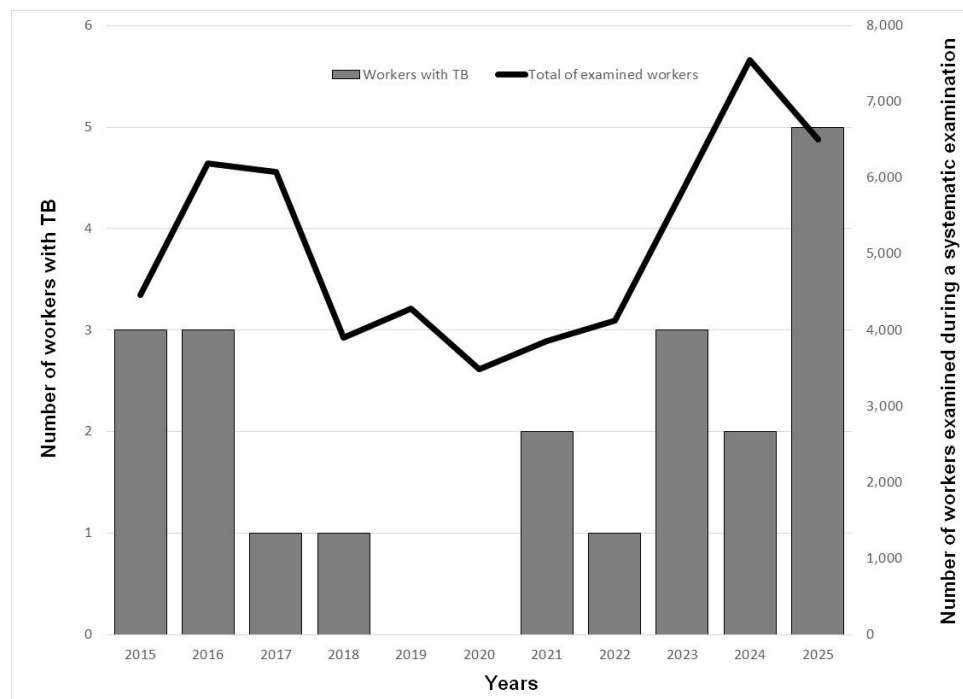


Fig. 7 – Annual number of workers examined and tuberculosis (TB) cases at the Institute of Occupational Health of Novi Sad (2015–2025).

Table 2

Occupation, gender, and age distribution of workers with tuberculosis at the Institute of Occupational Health of Novi Sad (2015–2025)

Occupations – ISCO-08 code	Gender	Age, years
Electrical technician – 3113	m	61
Nurse – 2221	f	60
Hospital cleaner / sanitation worker – 9112	f	53
Nurse – 2221	m	28
Software developer – 2512	m	64
Cashier – 5230	m	65
Petrol station attendant – 5245	f	25
Municipal services worker – 9613	m	57
Physician – 2211	f	60
Municipal services worker – 9613	f	64
Hospital cleaner / sanitation worker – 9112	m	50
Nurse – 2221	f	50
Municipal services worker – 9613	f	55
Locksmith – 7222	m	65
Plant breeding assistant – 3142	m	57
Nurse – 2221	f	43
Carpenter – 7115	m	47
Locksmith – 7222	m	51
Horticultural technician / fruit production technician – 3142	m	64
Physician – 2211	m	52
Central heating installer – 7126	m	62

ISCO – International Standard Classification of Occupations; m – male; f – female.

manual occupations. Healthcare workers were notably represented (4 nurses, 2 physicians, and 2 hospital cleaners), alongside municipal services workers ($n = 2$), and various other occupations, such as a cashier, petrol station attendant, electrical technician, software developer, skilled trades workers, and agricultural technicians. Most cases occurred among males (62%; 13/21). The age ranged from 25 to 65 years, with a median of 54 years, indicating a predominance of TB among middle-aged workers (Table 2).

Discussion

This long-term population-based study demonstrates a substantial decline in TB incidence in the AP of Vojvodina between 1998 and 2025, accompanied by persistently low mortality and a shift towards an older age distribution. These findings are consistent with broader global and regional trends reported by WHO and ECDC, reflecting overall progress in TB control over the past decades ^{1, 2, 5}.

JRA demonstrated a significant overall decline in TB incidence throughout the study period, indicating sustained progress in TB control in the AP of Vojvodina. The temporal pattern, however, was not uniform. Following a non-significant increase in incidence during the early years of observation (1998–2002), TB incidence declined markedly between 2002 and 2021, representing the most substantial period of epidemiological improvement. This prolonged decline likely reflects the combined effects of strengthened TB control measures, improved case detection and treatment, and broader socioeconomic improvements. Although a slight upward trend was observed during the final period (2021–2025), this increase was not statistically significant and should be interpreted with caution, as it may reflect year-to-year variation rather than a true reversal of the long-term declining trend.

The marked reduction in TB incidence observed from the early 2000s onwards mirrors trends reported across Europe, where improved case detection, treatment success rates, and implementation of DOT have contributed to declining transmission ^{2, 5}. In Serbia, this decline has been particularly pronounced, with national notification rates falling below 10 *per* 100,000 population in recent years ⁷. The decline in the AP of Vojvodina aligns with the country's progression towards low TB incidence.

In EU countries, in 2024, the highest TB IRs were reported in Romania (49/100,000), Latvia (17/100,000), Portugal (12/100,000), Malta (12/100,000) and Bulgaria (10/100,000), while the lowest were observed in Belgium, Denmark, Iceland, and Slovenia (2.1–2.6/100,000). Among non-EU/EEA countries, the highest IRs in 2024 were reported in Kyrgyzstan (99/100,000), Ukraine (68/100,000), Tajikistan (56/100,000), the Republic of Moldova (52/100,000), and Azerbaijan (50/100,000). On the other hand, the lowest were recorded in Israel (2/100,000) and the United Kingdom (9/100,000)—levels comparable to those observed in our country ⁵.

The exceptionally low number of reported TB cases and the absence of TB-related deaths during 2020–2021 likely

reflect the impact of COVID-19 on TB surveillance and healthcare access rather than a true reduction in transmission. Similar disruptions have been documented globally, with WHO reporting declines in TB notifications during the pandemic period due to reduced healthcare utilization and diagnostic delays ¹. The moderate increase in reported cases observed after 2021 may therefore reflect delayed diagnoses and the partial restoration of surveillance systems ⁵. Regarding fatal cases, increases in the number of deaths were observed in two years (2011 and 2023). Although a direct causal relationship cannot be confirmed, these increases may be associated with the impact of preceding public health crises, namely the 2009 H1N1 influenza pandemic (2009/10) and the COVID-19 pandemic.

Overall, the long-term decline in TB mortality observed in the AP of Vojvodina is consistent with trends reported across most European countries ⁵ and likely reflects the combined effects of sustained reductions in TB incidence, improvements in socioeconomic conditions, earlier diagnosis, standardized treatment regimens, and strengthened implementation of the WHO Directly Observed Treatment, Short-course (DOTS) strategy ^{1, 2, 5}. Improved access to microbiological diagnostics, systematic contact investigation, and effective drug supply have probably contributed to better treatment outcomes and reduced mortality over time. Nevertheless, the occurrence of occasional mortality peaks indicates that TB deaths remain sensitive to fluctuations in case detection, delays in diagnosis, and the clinical complexity of affected patients, particularly among older adults and individuals with multiple comorbidities.

A key finding of this study is the persistent age gradient in both TB incidence and mortality, with the highest burden consistently observed among older adults aged ≥ 60 years. This pattern is well recognized in both low- and high-incidence settings and reflects the combined effects of immunosenescence, reactivation of latent TB infection acquired earlier in life, reduced lung function, inflammation, adverse drug reactions, poor tolerance to anti-TB treatment, delayed or suboptimal diagnosis and management, and age-related comorbidities ^{5, 14, 15}. Similar patterns have previously been reported in Serbia for the 1992–2002 period ¹⁶, as well as in Central Serbia (1992–2006), where most patients were aged 40–60 years, but the highest IRs were observed in the oldest age group ¹⁷. Findings from another prospective study conducted at the Department of Pulmonology, Clinical Center in Kosovska Mitrovica, Serbia, which included all TB patients treated during two three-year periods (2000–2002 and 2012–2014), further indicated that social determinants, older age, and comorbidities are key risk factors contributing to the persistent burden of TB ¹⁸. We observed an increasing proportion of older TB patients in the later study period, further supporting the role of population ageing as a key driver of TB epidemiology in the AP of Vojvodina and in comparable European settings ⁵.

TB remains a major cause of both pulmonary and extrapulmonary disease, as well as mortality, among children

in TB-endemic areas. However, it is increasingly encountered in non-endemic settings due to growing international travel, population mobility, and refugee resettlement. While overdiagnosis may occur in certain contexts, underdiagnosis remains far more common in most TB-endemic regions, where access to TB care for young children is often limited to referral hospitals¹⁹. A study conducted in Serbia among children and adolescents between 2005 and 2016 reported a stable trend in TB notification rates, alongside a significant increase in the proportion of pediatric cases among all TB cases²⁰. Coverage with Bacille Calmette-Guerin – BCG vaccine among children aged ≤ 12 months in the AP of Vojvodina has traditionally been $\geq 95\%$ ⁸. In our study, incidence among children aged 0–14 years declined to below 1.5 *per* 100,000 after 2010, with no reported deaths during the study period except for a single case in 1998.

The observed increase in the proportion of reported cases in the South Bačka and South Banat districts should be interpreted with caution. In addition to differences in population size and urbanization, this pattern may partly reflect the concentration of specialized healthcare facilities for TB diagnosis and treatment located in these districts. These centers serve patients from a wider catchment area, which may influence the geographical distribution of notified cases. Therefore, the higher proportion of TB cases in these districts should not necessarily be interpreted as evidence of a higher underlying risk of TB transmission.

Overall, TB notifications were highest in winter and early spring, followed by a gradual decline towards the end of the year. These variations were largely driven by changes in case numbers among middle-aged and older adults, consistent with the age distribution of the TB burden in the population. Similar seasonal patterns have been reported across diverse settings, with peaks in late winter or early spring observed in Europe, North America, and Asia. This seasonality is commonly attributed to increased transmission during colder months, when indoor crowding is more frequent, as well as to delayed progression from infection to clinically manifest disease. Seasonal variation in host immunity, including reduced vitamin D levels during winter, may also contribute. In addition, healthcare-seeking behavior and reporting practices may have influenced the observed distribution^{21–25}.

The increasing proportion of laboratory-confirmed TB cases over time indicates improvements in diagnostic capacity and surveillance quality, in line with international recommendations promoting bacteriological confirmation wherever possible. This shift enhances the reliability of surveillance data and supports more accurate monitoring of TB trends. Similar patterns have been reported following the scale-up of improved diagnostic tools, including rapid molecular assays, which have contributed to increased case detection and confirmation^{1, 2, 5, 26–28}.

Although overall MRs declined during the study period, the proportion of fatal outcomes among notified TB cases increased significantly in the later period. This apparent paradox may partly reflect changes in the demographic

profile of TB patients, with a growing proportion of older individuals who are more likely to have multiple comorbidities, delayed clinical presentation, and poorer treatment tolerance. Because detailed information on disease severity, drug resistance, HIV status, and individual comorbidities was not available, the relative contribution of these factors could not be assessed and warrants further investigation. Maintaining low TB mortality in low-incidence settings therefore requires sustained TB control programs, timely diagnosis, prompt initiation of effective treatment, and uninterrupted TB services, particularly during public health emergencies. Particular attention should also be given to older adults with multiple comorbidities, who remain at increased risk of adverse outcomes^{1, 5, 14, 15}.

The number of TB cases detected among workers undergoing routine medical examinations remained low throughout the study period, despite fluctuations in the number of examined workers. Although a slight increase in reported TB cases was observed in the most recent years, particularly in 2025, the small number of cases precludes conclusions regarding a true temporal increase in occupational TB burden. This pattern may reflect random annual variation, changes in case detection, or differences in the number of workers undergoing routine medical examinations rather than a genuine increase in occupational transmission.

The occupational profile of TB cases was heterogeneous, encompassing healthcare workers, municipal service employees, technical personnel, skilled trades workers, and other service occupations. These findings suggest that TB among workers in the AP of Vojvodina was not restricted to a single occupational category. Healthcare workers represented the largest identifiable occupational subgroup, which is consistent with their recognized occupational exposure to *Mycobacterium tuberculosis* and their increased likelihood of being diagnosed through routine occupational health surveillance. However, given the limited number of TB cases and the absence of denominator data for individual occupational groups, the present study cannot estimate occupation-specific incidence or relative risk. Therefore, the occupational findings should be interpreted as descriptive rather than indicative of differential occupational risk. From a public health perspective, these findings underscore the importance of maintaining systematic occupational surveillance and strengthening targeted risk assessments, even in low-incidence settings. The occurrence of TB cases among healthcare personnel reinforces the continued need for strict infection prevention and control measures, regular occupational screening, prompt diagnosis, and timely initiation of treatment within healthcare facilities to minimize the risk of nosocomial transmission and protect both healthcare workers and patients. Furthermore, the occurrence of TB across diverse occupational groups highlights the importance of maintaining awareness of TB beyond traditionally recognized high-risk professions. Sustained vigilance remains essential to preserve the progress achieved in TB control and to ensure early detection of occupationally relevant cases^{29–33}.

This study has several important strengths. First, it is based on a long-term, population-level dataset spanning 28 years, enabling robust assessment of temporal trends in TB epidemiology. Such extended observation periods are rarely available and provide valuable insights into both pre- and post-transition phases in TB control. Second, the analysis relies on routine surveillance data from a mandatory notification system aligned with the WHO and ECDC standards. Third, the inclusion of multiple epidemiological dimensions—incidence, mortality, age-specific patterns, seasonality, diagnostic practices, and occupational distribution—provides a comprehensive overview of TB dynamics in a defined population. Finally, the study captures recent disruptions and subsequent recovery patterns associated with the COVID-19 pandemic, contributing to the growing body of evidence on its indirect effects on TB surveillance and control.

Limitation of the study

Several limitations should be considered when interpreting these findings. First, as a retrospective study based on routinely collected surveillance data, the analysis is subject to potential underreporting and reporting delays, particularly in earlier years when diagnostic capacity and surveillance systems were less developed. In addition, changes in case definitions, diagnostic methods (e.g., increased availability of molecular tests), and reporting practices over time may have influenced the observed trends, particularly the increase in laboratory-confirmed cases. Second, data on outbreak-related TB occurrences in hospitals, social care institutions, and similar settings were not analyzed, which may partly explain the observed year-to-year variability in age-specific MRs. Third, the absence of detailed clinical and risk-factor data—such as HIV status, diabetes, socioeconomic status, or migration background—limits the ability to fully explain the observed demographic patterns and mortality trends. Fourth, the apparent decline in TB incidence and mortality during 2020–2021 should be interpreted with caution, as it likely reflects reduced healthcare utilization and disruptions in case detection during the COVID-19 pandemic. Fifth, the occupational

analysis was based on a relatively small number of cases and a limited time period, which restricts the generalizability of these findings. Sixth, the study did not assess treatment outcomes beyond mortality in detail (e.g., treatment success, loss to follow-up), nor did it include microbiological data on drug resistance, which are important components of TB surveillance. Finally, as an ecological, population-level analysis, causal inferences cannot be established, and the observed associations should be interpreted with caution.

Given the observed fluctuations during and after the COVID-19 pandemic, further research should assess the long-term impact of healthcare disruptions on TB detection, treatment outcomes, and delayed diagnosis. Analytical studies exploring health system factors, access to care, and diagnostic delays would be particularly valuable. Moreover, the near-elimination of pediatric TB warrants continued surveillance to ensure sustained interruption of transmission. Studies focusing on occupation and specific risk groups, including healthcare workers and other vulnerable populations, should be expanded using larger datasets and longer follow-up periods. Such research would support the development of tailored screening, prevention, and intervention strategies adapted to the evolving epidemiology of TB in low-incidence settings.

Conclusion

Tuberculosis incidence and mortality in the Autonomous Province of Vojvodina have declined substantially over the past three decades, with the epidemiological profile increasingly characterized by low transmission and a predominance of cases among older adults. These findings underscore the need to adapt tuberculosis control strategies to an ageing population, ensure timely diagnosis, and maintain robust surveillance systems, particularly in the context of potential disruptions such as pandemics. Although tuberculosis cases among workers were uncommon, their occurrence across multiple occupational groups highlights the need for continued occupational health surveillance and effective infection prevention measures.

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Trends in cesarean section rates and declining birth rates in a secondary care hospital: a 20-year retrospective analysis (2005–2025)

Trendovi stopa carskog reza i opadanja broja porođaja u bolnicama sekundarnog nivoa zdravstvene zaštite: 20-godišnja retrospektivna analiza (2005–2025)

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Abstract

Background/Aim. The global rise in cesarean section (CS) rates represents a significant clinical and public health concern. Long-term monitoring of local trends provides important insight into healthcare system organization and evolving obstetric practice. The aim of the study was to analyze temporal trends in total deliveries, CS rates, and major indications for CS in a secondary care hospital over a 20-year period. **Methods.** A retrospective descriptive study was conducted using anonymized hospital records from General Hospital in Gračanica, Bosnia and Herzegovina, covering the period from 2005 to 2025. Annual data on total deliveries and CS were collected. CS rates were calculated for each year, and temporal trends were assessed using descriptive and trend analysis. In addition, a subanalysis of CS indications from 2015 to 2025 was performed. **Results.** A marked decline in total deliveries was observed, decreasing from 464 in 2005 to 214 in 2025. At the same time, CS rates demonstrated a consistent upward trend, increasing from 13.6% in 2005 to 29.4% in 2025. The peak CS rate was recorded in 2019 (31.9%), while a similarly high rate was observed in 2021 (31.8%). Lower rates were observed in 2022 and 2023, followed by an increase in the subsequent 2 years. The most frequent indication for CS was previous CS (55.5%), followed by hypertensive disorders in pregnancy (11.6%) and breech presentation of the fetus (11.5%). **Conclusion.** The simultaneous decline in birth rates and increase in CS rates reflects the combined impact of demographic changes and evolving healthcare system capacity, including improved access to operative obstetric care. The predominance of repeat CS as the leading indication further emphasizes the importance of careful evaluation of primary cesarean deliveries and adherence to evidence-based clinical guidelines.

Keywords:

birth rate; bosnia and herzegovina; cesarean section; primary health care.

Apstrakt

Uvod/Cilj. Globalni porast stopa carskog reza (*cesarean section* – CS) predstavlja značajan klinički i javnozdravstveni problem. Dugoročno praćenje lokalnih trendova pruža važan uvid u organizaciju zdravstvenog sistema i razvoj akušerske prakse. Cilj rada bio je da se analiziraju vremenski trendovi ukupnog broja porođaja, stopa CS i glavnih indikacija za CS u bolnici sekundarnog nivoa zdravstvene zaštite tokom perioda od 20 godina. **Metode.** Retrospektivna deskriptivna studija sprovedena je korišćenjem anonimizovanih bolničkih podataka iz Opšte bolnice u Gračanici, Bosna i Hercegovina, za period od 2005. do 2025. godine. Prikupljeni su godišnji podaci o ukupnom broju porođaja i CS. Stope CS izračunate su za svaku godinu, a vremenski trendovi analizirani su primenom deskriptivne analize i analize trenda. Pored toga, sprovedena je podanaliza indikacija za CS od 2015. do 2025. godine. **Rezultati.** Zapažen je izraziti pad ukupnog broja porođaja, sa 464 u 2005. godini na 214 u 2025. godini. Istovremeno, stope CS pokazale su kontinuirani porast, sa 13,6% u 2005. na 29,4% u 2025. godini. Najviša stopa CS zabeležena je 2019. godine (31,9%), a skoro identično visoka stopa zabeležena je 2021. godine (31,8%). Niže stope zabeležene su 2022. i 2023. godine, dok je u naredne 2 godine usledio porast. Najčešća indikacija za CS bio je prethodni CS (55,5%), zatim hipertenzivni poremećaji u trudnoći (11,6%) i karlična prezentacija ploda (11,5%). **Zaključak.** Istovremeni pad nataliteta i porast stopa CS odražava kombinovani uticaj demografskih promena i razvoja kapaciteta zdravstvenog sistema, uključujući bolju dostupnost operativnog akušerskog zbrinjavanja. Dominacija ponovljenog CS kao vodeće indikacije dodatno naglašava značaj pažljive procene indikacija za primarni CS i pridržavanja kliničkih smernica zasnovanih na dokazima.

Ključne reči:

natalitet; bosna i hercegovina; carski rez; zdravstvena zaštita, primarna.

Introduction

In recent decades, a significant increase in cesarean section (CS) rates has been observed worldwide, representing a major challenge for modern obstetric practice. Although CS can be a life-saving procedure in certain clinical situations, its excessive use is associated with increased risks for both the mother and the newborn^{1,2}.

The World Health Organization – WHO recommendation is that CS rates should not exceed 10–15%, while many countries report considerably higher values. Monitoring local trends is of particular importance, as it provides insight into changes in clinical practice, healthcare organization, and demographic patterns^{3–5}.

The coronavirus disease 2019 (COVID-19) pandemic further affected the organization of healthcare systems and the management of childbirth, and in some healthcare systems it was associated with changes in CS rates^{6–10}.

Although based on data from a single healthcare institution, such analyses provide valuable insights into broader demographic and clinical trends comparable to regional and global patterns. However, data from smaller healthcare facilities, particularly in transitional healthcare systems, remain underrepresented in the literature, highlighting the importance of such studies. In addition to monitoring temporal trends, evaluation of the major indications for CS may provide further insight into contemporary obstetric practice and factors contributing to the increasing CS rates.

The aim of this study was to analyze temporal trends in total deliveries, CS rates, and major indications for CS at the General Hospital in Gračanica, Bosnia and Herzegovina, during the 2005–2025 period.

Methods

Study design and data source

A retrospective, descriptive study was conducted using data on the total number of deliveries and CSs at the General Hospital in Gračanica, Bosnia and Herzegovina, from January 1, 2005, to December 31, 2025. The study was approved by the Ethics Committee of the General Hospital “Dr. Mustafa Beganović”, Gračanica, Bosnia and Herzegovina (No. 02-389-3/26, from April 30, 2026). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Data were obtained from internal hospital records. The analysis included the total number of deliveries and the number of CSs for each year of the study period. For each year, the CS rate was calculated as the percentage of CSs among all deliveries. In addition, a subanalysis of indications for CS from 2015 to 2025 was performed using aggregated institutional data. Additional demographic and obstetric characteristics, including maternal age and gestational age among women who underwent cesarean delivery, were analyzed from 2021 to 2025 using aggregated institutional records.

Statistical analysis

Data were analyzed using descriptive statistics, including absolute values and percentages. Trends over time were assessed descriptively, with graphical presentation of changes in the total number of deliveries and CS rates. Frequencies and percentages of major indications for CS between 2015 and 2025 were additionally analyzed. The analysis was descriptive in nature and did not include inferential statistical methods. All analyses were performed at the aggregate level, and no individual patient-level data were used.

Results

During the study period, the total number of deliveries declined from 464 in 2005 to 214 in 2025.

At the same time, CS rates showed a progressive increase. The rate increased from 13.6% in 2005 to values ranging between 24.3% and 29.4% in recent years. The highest rate was recorded in 2019, reaching 31.9%, while a similarly high rate of 31.8% was observed in 2021.

A temporary decline was observed in 2022, when the CS rate fell to 24.8%, compared to the previous year. Subsequently, the rates were 24.3% in 2023, 29.0% in 2024, and 29.4% in 2025 (Table 1; Figures 1–3).

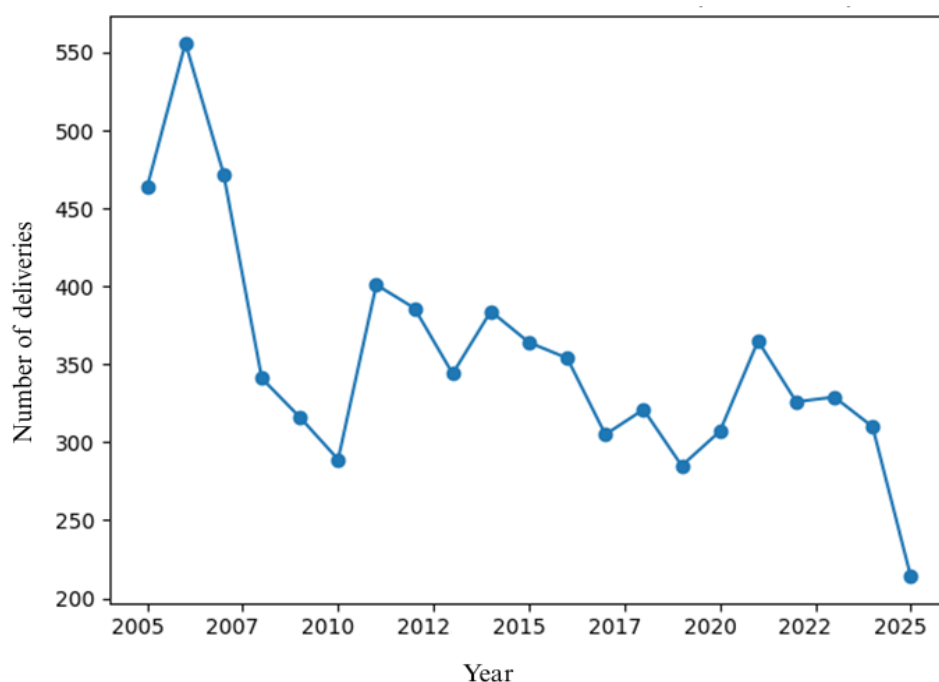
Analysis by time periods showed that the average CS rate increased from 13.3% between 2005 and 2014 to 26.3% between 2015 and 2019, and further to 27.9% between 2020 and 2025.

Table 1

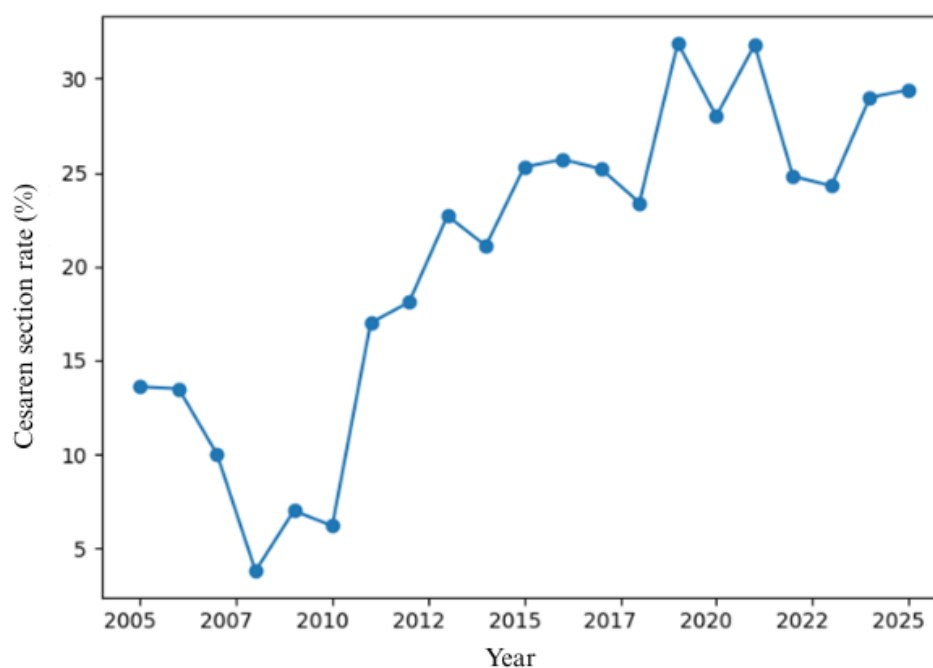
Trends in total number of deliveries and cesarean section (CS) rates from 2005 to 2025

Year	Total deliveries	Cesarean sections, rate
2005	464	63 (13.6)
2006	556	75 (13.5)
2007	472	47 (10.0)
2008	341	13 (3.8)
2009	316	22 (7.0)
2010	289	18 (6.2)
2011	401	68 (17.0)
2012	386	70 (18.1)
2013	344	78 (22.7)
2014	384	81 (21.1)
2015	364	92 (25.3)
2016	354	91 (25.7)
2017	305	77 (25.2)
2018	321	75 (23.4)
2019	285	91 (31.9)
2020	307	86 (28.0)
2021	365	116 (31.8)
2022	326	81 (24.8)
2023	329	80 (24.3)
2024	310	90 (29.0)
2025	214	63 (29.4)

Values are presented as absolute numbers and percentages. CS rate (%) represents the proportion of CS relative to total deliveries.



**Fig. 1 – Trend in the total number of deliveries (2005–2025)
at the General Hospital in Gračanica, Bosnia and Herzegovina.**



**Fig. 2 – Trend in cesarean section rate (2005–2025)
at the General Hospital in Gračanica, Bosnia and Herzegovina.**

A subanalysis of CS indications from 2015 to 2025 demonstrated that previous CS was the leading indication (55.5%), followed by hypertensive disorders in pregnancy (11.6%) and breech presentation (11.5%) (Table 2).

Additional analysis of women who underwent cesarean delivery from 2021 to 2025 showed that women aged 35 years and older accounted for 48.8% of all cesarean deliveries, while 37.9% occurred among women aged 25–34 years and 13.3% among those younger than 25 years.

Analysis of gestational age demonstrated that the majority of cesarean deliveries were performed in term pregnancies (37–40+6 weeks of gestation), accounting for 80.9% of all CSs. Preterm pregnancies (< 37 weeks of gestation) accounted for 7.7%, while 11.4% of cesarean deliveries were performed at 41 or more weeks of gestation (Table 3). These findings provide additional demographic and obstetric context to the observed CS trends.

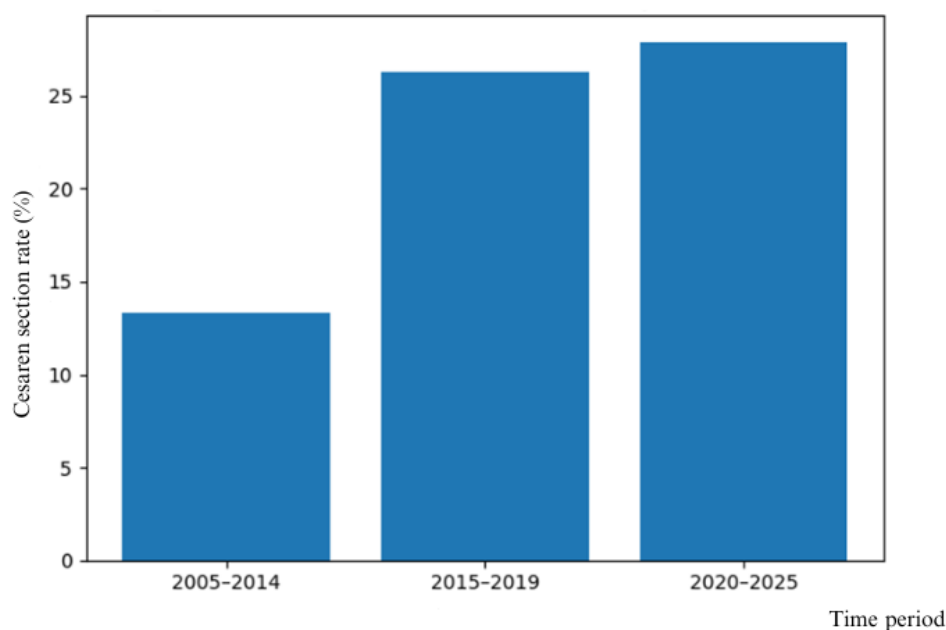


Fig. 3 – Average cesarean section rate across time periods (2005–2025) at the General Hospital in Gračanica, Bosnia and Herzegovina.

Table 2

Main indications for cesarean section (CS) in the period 2015–2025

Indication for CS	Values
Previous CS (<i>status post CS</i>)	523 (55.5)
Hypertensive disorders in pregnancy	109 (11.6)
Breech presentation (<i>presentatio pelvina</i>)	108 (11.5)
Perinatal asphyxia	51 (5.4)
IVF pregnancy	40 (4.2)
Cephalopelvic disproportion (<i>dysproportio fetopelvina</i>)	33 (3.5)
IUGR	26 (2.8)
Twin pregnancy (<i>gemelli</i>)	22 (2.3)
Previous VE (<i>status post VE</i>)	17 (1.8)
Placenta previa	11 (1.2)
Uterus duplex	2 (0.2)
Total	942 (100)

IVF – *in vitro* fertilization; IUGR – intrauterine growth restriction; VE – vacuum extraction.

All values are given as numbers (percentages).

Table 3

Distribution of maternal and gestational age among women who underwent cesarean delivery between 2021 and 2025, at the General Hospital in Gračanica, Bosnia and Herzegovina

Variable	Values
Age group, years	
< 25	57 (13.3)
25–34	163 (37.9)
≥ 35	210 (48.8)
Gestational age, weeks	
< 37	33 (7.7)
37–40+6	348 (80.9)
≥ 41	49 (11.4)
Total	430 (100)

Values are given as numbers (percentages).

Preterm: < 37 weeks; term: 37–40+6 weeks; post-term: ≥ 41 weeks.

Discussion

The present study demonstrates two consistent and interrelated trends: a long-term decline in the total number of deliveries and a parallel increase in CS rates over a 20-year period. The observed decline refers to the annual number of deliveries recorded at our institution rather than to a population-based birth rate. These findings are in line with global and regional patterns, where declining fertility rates, population migration, and changes in reproductive behavior have significantly influenced birth trends¹⁻³.

The observed increase in CS rates reflects a well-documented global phenomenon, commonly attributed to evolving clinical practice, advances in surgical safety, and medico-legal considerations^{2, 4, 5}. However, in the context of this study, the increase should be interpreted within a broader health-system perspective. Changes in institutional organization and referral patterns over time may have contributed to the observed differences in CS rates.

These findings underscore the importance of considering structural and organizational factors when interpreting CS trends, particularly in smaller healthcare systems undergoing transition. In such settings, rising CS rates may represent a phase of system development and strengthening of obstetric services, rather than unequivocal overuse.

The similarly high CS rate observed in 2021 (31.8%) coincides with the COVID-19 pandemic, suggesting a potential association with changes in healthcare organization and obstetric care during that period. Similar increases have been reported globally, often linked to a more cautious and controlled approach to delivery management during the pandemic⁶⁻¹³. In contrast, the decrease in CS rates in 2022 likely reflects the reorganization of healthcare services in the later phase of the pandemic and changes in referral patterns¹⁴⁻¹⁶.

Despite following global trends, the results highlight specific local characteristics related to healthcare organization and capacity building. In addition, broader demographic changes and declining fertility trends observed in many transitional healthcare systems may have further contributed to the reduction in total deliveries during the study period¹⁷. Additional analysis of cesarean deliveries from 2021 to 2025 revealed that women aged 35 years and above accounted for nearly half of all cases, with the majority of procedures performed in term pregnancies. These findings provide additional demographic and obstetric context to the observed trends. Advanced maternal age has been recognized as a factor associated with an increased likelihood of CS and may have contributed, at least in part, to the rising CS rates observed in our population¹⁸⁻²⁰.

From a clinical and public health perspective, the continuous rise in CS rates observed in this study highlights the necessity for systematic monitoring, critical evaluation

of indications, and adherence to evidence-based guidelines. Continued monitoring is important to ensure that increasing access to operative care remains aligned with appropriate clinical indications. The additional analysis of CS indications demonstrated that previous CS was the leading indication, followed by hypertensive disorders in pregnancy and breech presentation. These findings are consistent with contemporary obstetric practice, where repeat CS remains one of the major contributors to rising CS rates worldwide¹⁸. Similar findings have been reported in recent studies, where previous CS, hypertensive disorders in pregnancy, and malpresentation remain among the leading indications for CS¹⁸⁻²⁰.

Limitations of the study

This study has several limitations. As a retrospective, single-center analysis, its findings may have limited generalizability. The retrospective design limited the possibility of more detailed evaluation of factors associated with changing CS rates. Detailed maternal age and gestational age data were available only from 2021 to 2025 and could therefore not be analyzed for the entire study period.

Nevertheless, the strength of this study lies in its long observation period and consistent data collection, providing valuable insight into temporal trends in obstetric practice.

Conclusion

Over the 20-year study period, a marked decline in birth rates accompanied by a sustained increase in cesarean section rates was observed. These trends reflect the combined effects of demographic changes and progressive development of healthcare system capacity, including improved access to operative obstetric care.

The findings highlight the importance of continuous surveillance of cesarean section rates and critical evaluation of clinical indications. Furthermore, they emphasize the need to balance improved accessibility of surgical care with the prevention of unnecessary interventions. The predominance of repeat cesarean section as the leading indication further underscores the importance of reducing unnecessary primary cesarean deliveries in contemporary obstetric practice. From a broader health system perspective, these results may inform strategic planning, resource allocation, and optimization of obstetric services, particularly in secondary care settings and transitional healthcare systems. Future research incorporating detailed clinical variables is warranted to further elucidate the determinants of increasing cesarean section rates.

Conflict of interest

The author declares no conflict of interest.

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Serum neurofilament light chain as a biomarker for monitoring the therapeutic response of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis

Laki lanac neurofilamenta u serumu kao biomarker za praćenje terapijskog odgovora na lekove koji modifikuju tok bolesti kod obolelih od relapsno-remitentne multiple skleroze

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Abstract

Background/Aim. Serum neurofilament light chain (sNfL) is a sensitive biomarker of neuroaxonal damage and disease activity in multiple sclerosis (MS). The aim of this study was to investigate changes in sNfL levels following initiation of different disease-modifying therapies (DMTs) in treatment-naïve patients with relapsing-remitting MS (RRMS), and to explore potential sex-related differences in treatment response. **Methods.** The longitudinal study analyzed 78 treatment-naïve RRMS patients (40 males, 38 females) initiating their first DMT [injectable (n = 37): interferon beta-1a: Rebif®, interferon beta-1b: Betaferon®, glatiramer acetate: Copaxone®, or oral (n = 41): sphingosine 1-phosphate receptor (S1PR) modulators: fingolimod, ozanimod, ponesimod]. Concentrations of sNfL were measured using enzyme-linked immunosorbent assay – ELISA prior to therapy initiation and after 6 months. Disability was assessed at baseline using Expanded Disability Status Scale – EDSS and Multiple Sclerosis Severity Score – MSSS. Repeated measures analysis was used to evaluate longitudinal

changes. **Results.** A significant reduction in sNfL levels was observed after 6 months of DMT therapy in the examined patients ($p < 0.001$; partial $\eta^2 = 0.358$). A significant interaction between sex and treatment response was found ($p = 0.003$), with a more pronounced reduction in sNfL levels observed in females. No significant difference in sNfL reduction was found between injectable therapies and S1PR modulators ($p = 0.092$), although baseline sNfL levels were higher in the S1PR group ($p < 0.001$). **Conclusion.** Initiation of DMTs in RRMS patients was associated with a significant decrease in sNfL levels, suggesting reduced neuroaxonal damage following treatment introduction. Higher baseline sNfL levels in females may indicate potential sex-related differences in neuroaxonal injury. Monitoring sNfL may represent a useful non-invasive biomarker of biological treatment response in RRMS patients.

Keywords: biomarkers; drug administration routes; immunotherapy; multiple sclerosis, relapsing-remitting; neurofilament proteins; sex factors.

Apstrakt

Uvod/Cilj. Laki lanac neurofilamenta u serumu (*serum neurofilament light chain* – sNfL) je osetljiv biomarker neuroaksonalnog oštećenja i aktivnosti bolesti kod multiple skleroze (MS). Cilj rada bio je da se ispituju promene nivoa sNfL posle započinjanja različitih terapija koje modifikuju tok bolesti (*disease-modifying therapies* – DMT) kod prethodno nelečenih, obolelih od relapsno-remitentne MS (RRMS), kao i da se u terapijskom odgovoru analiziraju potencijalne razlike povezane sa polom. **Metode.** Longitudinalnom studijom analizirano je 78 obolelih od

RRMS (40 muškaraca i 38 žena) koji ranije nisu bili lečeni a koji su započeli DMT prvi put [injekciono (n = 37): interferon beta-1a: Rebif®, interferon beta-1b: Betaferon®, glatiramet acetat: Copaxone® ili oralno (n = 41): modulatori sfingozin-1-fosfat receptora (*sphingosine 1-phosphate receptor* – S1PR): fingolimod, ozanimod i ponesimod]. Koncentracije nivoa sNfL određene su metodom *enzyme-linked immunosorbent assay* – ELISA na početku i posle 6 meseci terapije. Step onespoboljenosti procenjen je na početku studije, primenom *Expanded Disability Status Scale* – EDSS i *Multiple Sclerosis Severity Score* – MSSS. Za procenu longitudinalnih promena primenjena je analiza ponovljenih

merjenja. **Rezultati.** Zabeleženo je značajno sniženje nivoa sNfL kod ispitivanih bolesnika 6 meseci nakon primene DMT ($p < 0,001$; delimični $\eta^2 = 0,358$). Nađena je značajna interakcija pola i terapijskog odgovora ($p = 0,003$), sa izraženijim sniženjem nivoa sNfL kod žena. Nije utvrđena statistički značajna razlika u sniženju nivoa sNfL između injekcione terapije i S1PR modulatora ($p = 0,092$), mada su početne vrednosti sNfL bile značajno više u grupi bolesnika lečenih S1PR modulatorima ($p < 0,001$). **Zaključak.** Započinjanje DMT kod obolelih od RRMS bilo je povezano sa značajnim sniženjem nivoa sNfL, što ukazuje na

smanjeno neuroaksonalno oštećenje posle uvođenja terapije. Viši početni nivoi sNfL kod žena mogu ukazivati na razlike u neuroaksonalnom oštećenju povezane sa polom. Praćenje nivoa sNfL može predstavljati koristan neinvazivan biomarker biološkog odgovora na terapiju kod obolelih od RRMS.

Ključne reči:
biomarkeri; lekovi, putevi primene; imunoterapija; multipla skleroza, relapsno-remitentna; proteini, neurofilament; pol, faktor.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease of the central nervous system characterized by inflammation, demyelination, and axonal loss¹. The most common form is relapsing-remitting MS (RRMS), characterized by relapses followed by periods of remission. Functional disability is commonly assessed using the Expanded Disability Status Scale (EDSS)². A better parameter for estimating the severity of the disease is the Multiple Sclerosis Severity Score (MSSS), which includes disease duration³.

Neurofilament light chain (NfL) is a structural protein released during axonal damage^{4, 5}. Serum NfL (sNfL) has emerged as a promising biomarker reflecting disease activity and therapeutic response in MS⁵⁻⁷. Increased sNfL levels correlate with inflammatory activity and risk of disability progression^{5, 8}.

In addition, oxidative stress contributes to neuroaxonal damage in MS, leading to increased release of NfL into the circulation. Therefore, sNfL can also reflect oxidative stress-related neuronal injury^{8, 9}.

Although disease-modifying therapies (DMTs) reduce relapse rates and slow down disease progression, reliable biomarkers for monitoring therapeutic response in clinical practice remain of great importance¹⁰.

The aim of this study was to investigate the effect of initiating different DMTs [interferon beta-1a: Rebif®, interferon beta-1b: Betaferon®, glatiramer acetate: Copaxone®, and sphingosine 1-phosphate receptor (S1PR) modulators: fingolimod, ozanimod, ponesimod] on sNfL levels in RRMS patients after 6 months of follow-up, as well as to explore potential sex-related differences in treatment response.

Methods

Design and participants

This longitudinal interventional study included 78 treatment-naïve RRMS patients who initiated their first DMT at study entry. They were recruited at the Neurology Clinic of the Military Medical Academy, Belgrade, Serbia, between March 2018 and July 2019. Diagnosis was established according to the 2017 McDonald criteria¹¹. The study was

approved by the Ethics Committee of the Military Medical Academy (from June 12, 2018) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

All patients initiated DMT at study entry. Baseline blood samples were obtained prior to the first dose of therapy. Disability was evaluated using EDSS and MSSS. The injectable therapy group included patients who had been receiving interferon beta-1a (Rebif®), interferon beta-1b (Betaferon®), and glatiramer acetate (Copaxone®), whereas the S1PR modulator group included patients who had been receiving fingolimod, ozanimod, and ponesimod. Baseline blood samples were obtained prior to the first dose of DMT, and follow-up samples were collected 6 months after therapy initiation.

Inclusion and exclusion criteria

The study included patients diagnosed with RRMS according to the 2017 McDonald criteria¹¹.

Patients with acute infections, severe systemic diseases, or other medical conditions potentially affecting serum biomarker levels at the time of sampling were not included in the study.

Comorbidity data were not systematically collected for all participants and therefore could not be analyzed as potential confounders.

Biochemical analysis

Concentrations of sNfL were measured using a commercial sandwich enzyme-linked immunosorbent assay (ELISA) kit (NEFL-BioAssay™, US Biological) according to the manufacturer's instructions. Serum samples were stored at -80 °C until analysis.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Normality of data distribution was assessed using the Shapiro-Wilk test and Kolmogorov-Smirnov tests. Although several variables showed moderate deviations from normality, mixed-design repeated measures analysis of variance – ANOVA was applied because of its robustness to

such deviations and its suitability for longitudinal repeated measures designs. Non-parametric tests were used where appropriate. Appropriate paired and unpaired statistical tests were applied to assess differences between measurements. Continuous variables were presented as mean $\pm$ standard deviation to facilitate comparison with previous studies.

A value of $p < 0.05$ was considered statistically significant. A formal power analysis was not performed prior to the study because it was exploratory; however, the sample size was comparable to that of similar studies in the field.

Results

Demographic and clinical characteristics

Demographic and clinical characteristics are presented in Table 1. Females had significantly higher baseline sNfL levels than males ($p < 0.001$). This sex-related difference

was observed among younger patients (< 30 years), with females showing higher sNfL levels than males ($p = 0.027$), and also among older patients (> 30 years) ($p < 0.001$). Younger patients (< 30 years) showed higher sNfL levels compared with older patients (> 30 years) ($p = 0.003$).

Demographic and baseline clinical characteristics of study patients according to the route of administration (injectable vs. oral) are presented in Table 2. No statistically significant differences were observed between patients receiving injectable therapies and those treated with S1PR modulators in terms of age, disease duration, baseline EDSS, or MSSS scores (all $p > 0.05$). However, baseline sNfL levels were significantly higher in patients treated with S1PR modulators compared to those receiving injectable therapies ($p < 0.001$).

No significant correlation was observed between body mass index (BMI) and sNfL levels (Spearman's $\rho = -0.168$, $p = 0.140$).

Table 1

Demographic and clinical characteristics of patients with RRMS receiving DMT according to gender

Parameter	Total (n = 78)	Males (n = 40)	Females (n = 38)	*p-value
Age, years	42.26 $\pm$ 8.67	42.95 $\pm$ 8.11	41.53 $\pm$ 9.28	0.472
MS duration, years	8.72 $\pm$ 5.70	9.15 $\pm$ 4.93	8.26 $\pm$ 6.45	0.496
EDSS	2.62 $\pm$ 1.21	2.67 $\pm$ 1.22	2.56 $\pm$ 1.22	0.693
MSSS	3.84 $\pm$ 2.15	3.80 $\pm$ 2.25	3.89 $\pm$ 2.07	0.853
sNfL, pg/mL [#]	13.09 $\pm$ 3.20	11.63 $\pm$ 1.90	14.62 $\pm$ 3.59	< 0.001
sNfL (pg/mL) by age group, years [#]				
< 30	15.43 $\pm$ 2.45**	13.06 $\pm$ 1.95	16.61 $\pm$ 1.74 **	0.027
> 30	12.78 $\pm$ 3.17	11.51 $\pm$ 1.87	14.21 $\pm$ 1.09	< 0.001

RRMS – relapsing-remitting multiple sclerosis; DMT – disease-modifying therapy; n – number; MS – multiple sclerosis; EDSS – Expanded Disability Status Scale; MSSS – Multiple Sclerosis Severity Score; sNfL – serum neurofilament light chain.

All values of continuous variables are given as mean $\pm$ standard deviation.

Note: *gender-related differences; **age-related differences; [#]statistical analysis performed: Student's *t*-test and Mann-Whitney *U* test. Parameter sNfL represents the levels of sNfL before the patients received DMTs. The age groups are as follows: < 30 years – total (n = 9); males (n = 3), females (n = 6); and > 30 years – total (n = 69), males (n = 37), females (n = 32).

Table 2

Demographic and baseline clinical characteristics of patients with RRMS according to the route of administration of DMT (injectable vs. oral)

Parameter	Injectable therapies (n = 37)	S1PR modulators (n = 41)	p-value
Age, years	43.67 $\pm$ 9.03	40.59 $\pm$ 9.33	0.089
MS duration, years	9.02 $\pm$ 5.16	7.90 $\pm$ 5.39	0.288
EDSS	2.53 $\pm$ 1.09	2.52 $\pm$ 1.29	0.939
MSSS	3.62 $\pm$ 2.31	3.69 $\pm$ 2.04	0.878
Baseline sNfL, pg/mL	10.21 $\pm$ 1.04	13.24 $\pm$ 1.69	< 0.001

RRMS – relapsing-remitting multiple sclerosis; DMT – disease-modifying therapy; n – number; S1PR – sphingosine 1-phosphate receptor; MS – multiple sclerosis; EDSS – Expanded Disability Status Scale; MSSS – Multiple Sclerosis Severity Score; sNfL – serum neurofilament light chain. All values of continuous variables are given as mean $\pm$ standard deviation.

Note: Statistical analysis performed – Student's *t*-test and Mann-Whitney *U* test.

Effects of disease-modifying therapies on serum neurofilament light chain levels

Repeated measures analysis showed a significant decrease in sNfL levels after 6 months of DMT therapy in the RRMS population ($p < 0.001$; partial $\eta^2 = 0.358$). A significant sex-related difference in treatment response was observed ($p = 0.003$; partial $\eta^2 = 0.107$), with a more pronounced reduction of sNfL in females (Figure 1).

When patients were grouped according to therapeutic category (injectable therapies vs. S1PR modulators), no

statistically significant difference in sNfL reduction was observed between groups ($p = 0.092$; partial $\eta^2 = 0.037$), although patients treated with S1PR modulators showed a trend toward greater reduction (Figure 2).

Discussion

Intensive investigation of MS pathophysiology has led to the development of DMTs that reduce inflammation and delay disease progression¹⁰. In parallel, significant efforts have focused on identifying and validating diagnostic and

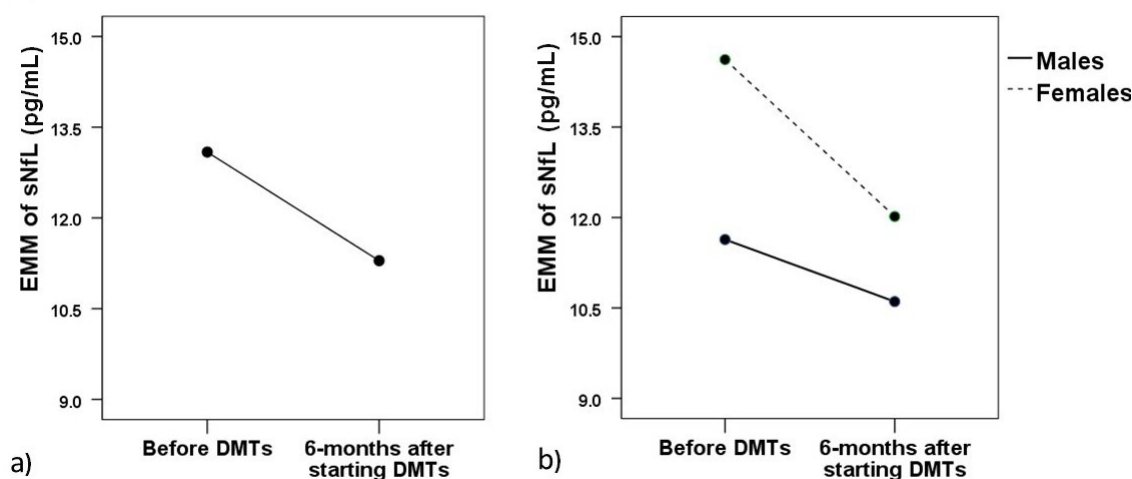


Fig. 1 – Estimated marginal means (EMM) of sNfL before and 6 months after initiation of DMTs in patients with RRMS: a) overall RRMS patient group (n = 78); b) gender-related RRMS subgroup analysis (males, n = 40; females, n = 38). sNfL – serum neurofilament light chain; DMT – disease-modifying therapies; RRMS – relapsing-remitting multiple sclerosis.

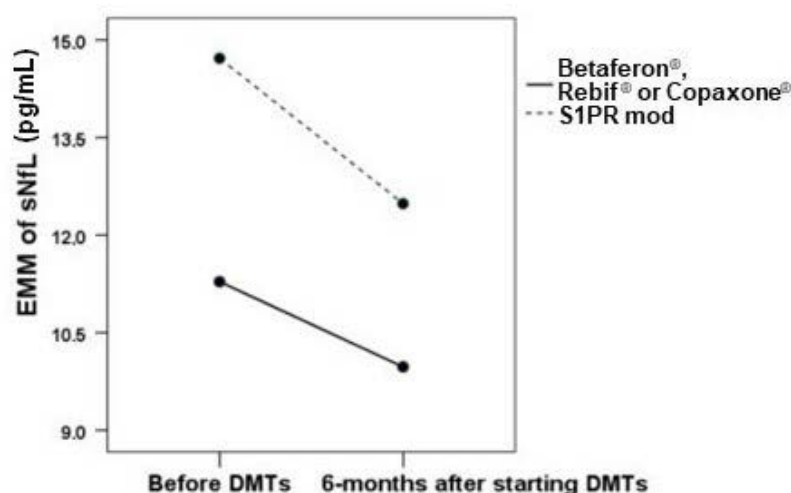


Fig. 2 – Effects of DMTs on sNfL levels after 6 months of follow-up in patients who have been receiving injectable therapies (Betaferon®, Rebif®, or Copaxone®) (n = 37) and those treated with S1PR modulators (n = 41). EMM – estimated marginal means; sNfL – serum neurofilament light chain; DMT – disease-modifying therapies; S1PR – sphingosine 1-phosphate receptor; mod – modulators; n – number.

prognostic biomarkers capable of detecting neuronal damage and monitoring therapeutic response in patients with MS. Among circulating biomarkers, sNfL has emerged as a sensitive indicator of recent neuroaxonal damage and is particularly valuable in “clinically silent disease” where overt clinical changes may be difficult to interpret⁶.

A previous study has shown that chronic white matter inflammation is associated with increased sNfL levels and greater disease severity in MS¹². Furthermore, elevated baseline sNfL concentrations have been reported as a potential prognostic marker of brain lesion development and brain atrophy in patients with RRMS¹³.

In the present study, we evaluated longitudinal changes in sNfL levels following the initiation of DMTs. A significant reduction in sNfL concentrations was observed after 6 months of therapy in the overall RRMS population. These findings are consistent with a previous report demonstrating lower sNfL levels under DMTs¹⁴.

Recent evidence from routine clinical practice and systematic reviews reinforces the role of sNfL as a biomarker of disease activity and therapeutic response in MS^{15, 16}. In line with these findings, our longitudinal data demonstrate a significant reduction in sNfL levels following DMT initiation, further supporting its utility in monitoring treatment response.

MS is characterized by demyelination and axonal injury, leading to increased release of neurofilament proteins into the circulation. Therefore, the observed decrease in sNfL following treatment initiation likely reflects reduced neuroaxonal damage after therapeutic intervention¹⁴.

Our results showed that females had significantly higher baseline sNfL levels compared to males. This finding may indicate greater susceptibility of females to neuroaxonal injury, emphasizing the importance of early therapeutic intervention. However, a previous study has not consistently demonstrated the effect of gender on the level of sNfL in patients with MS¹⁴. Additionally, younger female patients showed higher sNfL levels compared with older female patients, whereas such age-related differences were not observed in males. In contrast, previous studies have reported no significant influence of age on sNfL concentrations^{16, 17}. Further studies are warranted to clarify the combined effects of age and sex on sNfL levels in RRMS.

Although BMI has been reported to influence sNfL levels in some studies¹⁶, we did not observe a significant association in our cohort.

After 6 months of follow-up, sNfL levels were significantly reduced in patients receiving DMTs, both in the overall RRMS population and within sex-based subgroups. The 6-month follow-up period was selected to capture early biological changes in sNfL levels following DMT initiation. A previous study has shown that sNfL responds relatively rapidly to treatment, reflecting acute neuroaxonal damage¹⁴. However, longer follow-up may be necessary to fully capture the maximal effects of certain

DMTs on sNfL levels and long-term clinical outcomes^{13, 14}. This approach may help bridge the gap between early biological responses reflected by sNfL changes and long-term clinical outcomes¹⁴. In addition, therapies were grouped into injectable treatment and S1PR modulators based on their distinct mechanisms of action. Injectable therapies primarily exert immunomodulatory effects, while S1PR modulators act by preventing lymphocyte egress from lymph nodes, potentially leading to differential effects on neuroaxonal damage and sNfL levels¹⁰. When patients were divided according to therapeutic group (injectable therapies vs. S1PR modulators), no statistically significant difference in sNfL reduction was observed between groups, although a slightly greater decrease was noted in patients treated with S1PR modulators.

Patients receiving S1PR modulators had significantly higher baseline sNfL levels compared with those treated with injectable therapies. This difference likely reflects greater pre-treatment neuroaxonal activity and may partly explain variations in observed treatment responses. Previous literature suggests that sNfL concentrations above approximately 16 pg/mL may indicate active disease in patients with MS¹⁸. In our study population, baseline sNfL values were within the range consistent with ongoing neuroaxonal damage prior to treatment initiation, supporting the biological relevance of the observed reduction after therapy.

These findings are in line with studies reporting decreased sNfL levels following treatment with interferon-beta and fingolimod^{14, 19, 20}.

Limitations of the study

Limitations of this study include the absence of a healthy control group and the lack of longitudinal clinical disability assessment. This limits the ability to directly correlate biological changes in sNfL with clinical outcomes. EDSS was evaluated only at baseline and was not reassessed after 6 months of follow-up. Therefore, we were unable to directly correlate changes in sNfL concentrations with clinical improvement. Another limitation of the study was that comorbidities were not systematically collected, although they may act as potential confounding factors influencing sNfL levels. In addition, sNfL concentrations were measured using ELISA, which is less sensitive than newer ultrasensitive platforms such as single-molecule array; however, all samples were analyzed using the same standardized protocol, minimizing intra-study variability.

The study primarily focused on longitudinal changes within patients following DMT initiation, without comparisons with healthy controls.

An additional limitation of this study is that potentially important factors influencing sNfL concentrations were not evaluated. Specifically, patients were not stratified according to BMI, and comorbid conditions were not systematically recorded. Both factors may have contributed to the interindividual variability in

sNfL concentrations²¹ and should be taken into account in future studies.

Conclusion

This study demonstrated a significant reduction in circulating serum neurofilament light chain levels following disease-modifying therapy initiation in patients with relapsing-remitting multiple sclerosis, suggesting

decreased neuroaxonal damage after treatment introduction. Higher baseline serum neurofilament light chain levels observed in females indicate potential sex-related differences in neuroaxonal injury; however, further investigation is needed to clarify their clinical implications. Monitoring serum neurofilament light chain levels may serve as a useful non-invasive biomarker for assessing biological response to therapy in relapsing-remitting multiple sclerosis.

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Beyond expectations – malignant pleural mesothelioma in a patient with Bardet-Biedl syndrome

Izvan granica očekivanog – maligni pleuralni mezoteliom kod obolelog od Bardet-Biedl-ovog sindroma

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Abstract

Introduction. Bardet-Biedl syndrome (BBS) is a rare autosomal recessive ciliopathy caused by structural and functional abnormalities of primary cilia, leading to disruption of key signaling pathways. It is clinically characterized by progressive retinal degeneration, polydactyly, early-onset obesity, cognitive impairment, hypogonadism, and renal abnormalities. Malignant mesothelioma (MM) is a malignant tumor of mesothelial cells that most commonly affects the pleura and is strongly associated with asbestos exposure and poor prognosis. In addition to environmental factors, genetic predisposition may contribute to its pathogenesis. **Case report.** We present a 27-year-old male with BBS who was evaluated for chest pain and progressive dyspnea. Pleural fluid analysis and video-assisted thoracoscopic pleural biopsy confirmed epithelioid pleural MM. The patient received systemic chemotherapy with pemetrexed and cisplatin, together with palliative treatment for recurrent pleural effusions. Therapeutic options were further limited by the underlying genetic disorder. Despite advanced disease and limited treatment options, the patient achieved unexpectedly prolonged overall survival of 7 years from the time of MM diagnosis. **Conclusion.** This case illustrates the diagnostic and therapeutic complexity of managing malignancies in patients with rare genetic syndromes and emphasizes the importance of an individualized multidisciplinary approach. It also raises the possibility that ciliary dysfunction may contribute to mesothelioma pathogenesis, warranting further molecular and clinical investigation.

Keywords:

bardet-biedl syndrome; diagnosis; palliative care; survival; antineoplastic agents.

Apstrakt

Uvod. Bardet-Biedl-ov sindrom (BBS) je retka autozomno recesivna ciliopatija, nastala usled strukturnih i funkcionalnih poremećaja primarnih cilija, što dovodi do narušavanja ključnih signalnih puteva. Klinički se karakteriše progresivnom degeneracijom retine, polidaktilijom, ranom gojaznošću, kognitivnim poremećajem, hipogonadizmom i bubrežnim poremećajima. Maligni mezoteliom (MM) je maligni tumor mezotelijalnih ćelija koji najčešće zahvata pleuru i usko je povezan sa izloženošću azbestu i nepovoljnom prognozom. Pored faktora sredine, genetska predispozicija može doprineti njegovoj patogenezi. **Prikaz bolesnika.** Prikazujemo 27-godišnjeg muškarca obolelog od BBS koji je ispitivan zbog bolova u grudima i progresivne dispneje. Analizom pleuralnog izliva i biopsijom pleure, dobijenom video-asistiranom torakoskopijom, potvrđen je epitelioidni MM pleure. Bolesnik je lečen sistemskom hemioterapijom, pemetreksedom i cisplatinom, zajedno sa palijativnim lečenjem ponavljajućih pleuralnih izliva. Terapijske mogućnosti bile su dodatno ograničene prisutnim genetskim poremećajem. Uprkos uznapredovaloj bolesti i ograničenim mogućnostima lečenja, bolesnik je postigao neuobičajeno dugo ukupno preživljavanje od 7 godina od trenutka dijagnostikovanja MM. **Zaključak.** Prikazani slučaj ukazuje na složenost dijagnostike i lečenja maligniteta kod bolesnika sa retkim genetskim sindromima i naglašava značaj individualizovanog multidisciplinarnog pristupa. Slučaj ukazuje i na moguću ulogu disfunkcije cilija u patogenezi mezotelioma, što upućuje na potrebu za daljim molekularnim i kliničkim istraživanjima.

Ključne reči:

bardet-biedl sindrom; dijagnoza; lečenje, palijativno; preživljavanje; antineoplastici.

Introduction

Bardet-Biedl syndrome (BBS) is a rare multisystem autosomal recessive ciliopathy caused by structural and functional abnormalities of primary cilia, leading to disrupted cellular signaling and multisystem dysfunction. Historically classified within Laurence-Moon-Biedl syndrome, BBS is clinically characterized by cone-rod retinal dystrophy, post-axial polydactyly, early-onset truncal obesity, learning difficulties, hypogonadism, genitourinary anomalies, and frequent renal involvement ranging from congenital abnormalities to progressive tubulointerstitial disease¹⁻³.

BBS is associated with mutations in more than 25 genes, particularly *BBS1* and *BBS10*, which are involved in ciliary trafficking and signaling pathways⁴⁻⁶.

Inheritance is typically autosomal recessive, and molecular diagnosis requires identification of biallelic pathogenic variants in a known *BBS* gene. Modifier loci are thought to contribute to the marked phenotypic variability observed among affected individuals⁷. Clinical manifestations usually begin in childhood with night blindness, followed by progressive visual impairment, obesity, and developmental abnormalities, while renal disease often emerges later and represents a major determinant of morbidity and prognosis^{8,9}.

Life expectancy largely depends on the severity of renal and cardiometabolic complications^{10,11}.

Malignant mesothelioma (MM) is an aggressive malignancy arising from mesothelial surfaces, most commonly the pleura. Although rare worldwide, pleural MM accounts for approximately 85% of all mesothelioma cases, with an estimated global incidence of 0.3 per 100,000 population^{12,13}. Histologically, MM is classified into epithelioid, sarcomatoid, and biphasic subtypes. The principal etiologic factor is asbestos exposure, while additional risk factors include erionite exposure, prior therapeutic radiation, and inherited genetic susceptibility^{14,15}. A key pathogenic alteration involves BAP1 (*BRCA1*-associated protein 1), a tumor-suppressor deubiquitinating enzyme whose inactivation disrupts chromatin regulation, cell-cycle control, and deoxyribonucleic acid – DNA repair processes, contributing to tumor predisposition and the development of multiple malignancies. Prognosis remains poor and is strongly influenced by disease stage and histologic subtype. Current management includes surgical resection in selected early-stage cases, platinum-pemetrexed chemotherapy, immune checkpoint inhibitors, and palliative interventions for recurrent pleural effusions^{16,17}.

Although no direct association between BBS and MM has been established, ciliary dysfunction may represent a potential mechanistic link. Impaired mucociliary clearance may facilitate retention of inhaled carcinogens, including asbestos fibers, within the pleural environment and contribute to mesothelial carcinogenesis.

We present an exceptionally rare coexistence of BBS and pleural MM, highlighting the diagnostic challenges, therapeutic limitations, and unexpectedly prolonged patient survival.

Case report

A 27-year-old male with genetically confirmed BBS, harboring pathogenic variants in *BBS1*, was under longitudinal follow-up for cone-rod dystrophy and obesity. He had no documented occupational or familial exposure to asbestos. The patient presented with subacute pleuritic pain localized to the right hemithorax, accompanied by a nonproductive cough and progressively worsening exertional dyspnea over a period of 4 to 6 weeks.

Phenotypically, the patient showed characteristic features of BBS including truncal obesity with relatively slender extremities, postaxial polydactyly, brachydactyly, broad feet with *pes planovalgus*, and hypogonadism. Mild craniofacial dysmorphism was also present, including a broadened nasal root and subtle midfacial flattening. The overall phenotype was consistent with the typical skeletal and metabolic manifestations of BBS. The patient's physical appearance is illustrated in Figures 1 and 2.

Physical examination demonstrated diminished breath sounds at the right lung base. Resting peripheral oxygen saturation was 95%, and the Eastern Cooperative Oncology Group – ECOG scale¹⁸ performance status was 1 (that means the patient is symptomatic but fully ambulatory and capable of self-care).

Laboratory testing revealed mild thrombocytosis with a platelet count of $480 \times 10^9/L$ (reference range $150\text{--}400 \times 10^9/L$) and elevated C-reactive protein of 68 mg/L (upper limit less than 5 mg/L). Tumor markers showed no characteristic pattern.

Chest X-ray and multidetector computed tomography revealed a right-sided pleural effusion with diffuse irregular thickening of the parietal and diaphragmatic pleura without an identifiable pulmonary parenchymal mass (Figures 3 and 4).

The patient's mother was his legal guardian because of his longstanding physical and cognitive developmental impairments. He had previously been assessed as unable to make independent medical decisions and had a documented mild intellectual disability, with an intelligence quotient of 60. Following a detailed discussion with the patient's mother, informed consent was obtained for the performance of invasive diagnostic procedures and, if clinically indicated, surgical intervention.

An ultrasound-guided thoracentesis was performed under procedural sedation and analgesia. The procedure produced an exudative pleural effusion that on macroscopic examination appeared serous to serosanguineous. Cytologic analysis revealed atypical mesothelial cells and reactive mesothelial proliferations. The findings were inconclusive and did not allow determination of a definitive underlying etiology. Given the persistent clinical suspicion of a neoplastic process, additional diagnostic evaluation was required.

Video-assisted thoracoscopic (VATS) pleural biopsy was then performed. During the procedure, a total of 2,000 mL of pleural effusion was evacuated, allowing complete inspection of the pleural cavity. Thoracoscopic examination

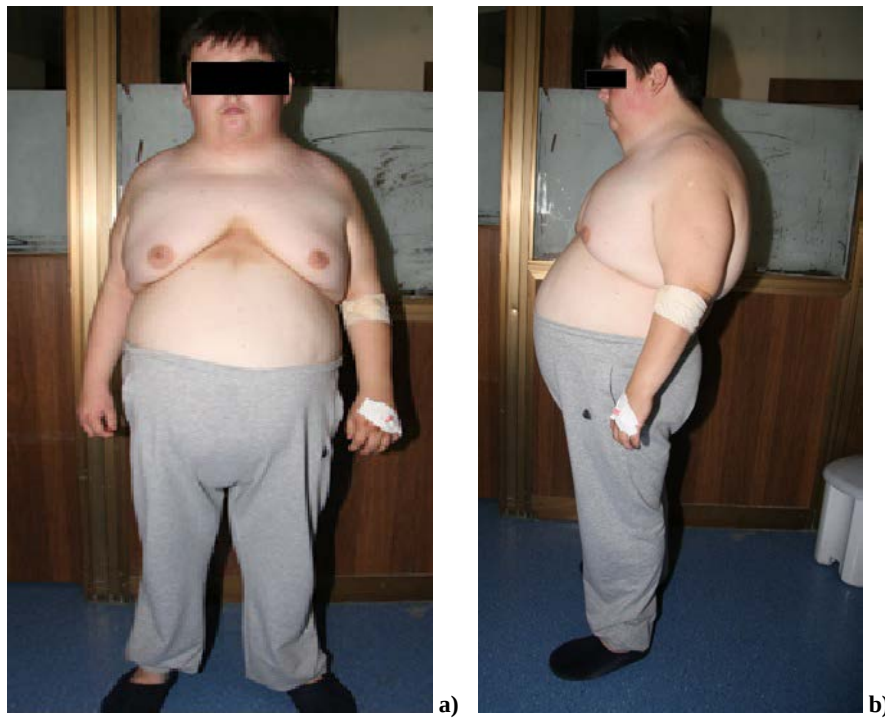


Fig. 1 – Characteristic Bardet-Biedl syndrome phenotype habitus with central obesity and typical body disproportions: a) anterior view; b) profile view.



Fig. 2 – Postaxial polydactyly of the foot with shortened toes (brachydactyly) and morphologically irregular toes representing a typical manifestation of Bardet-Biedl syndrome.

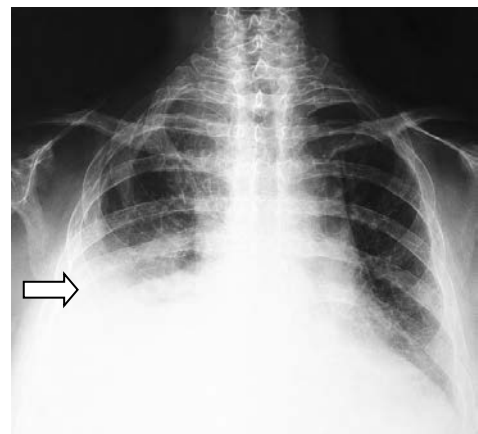


Fig. 3 – Chest X-ray showing a right-sided pleural effusion (arrow).

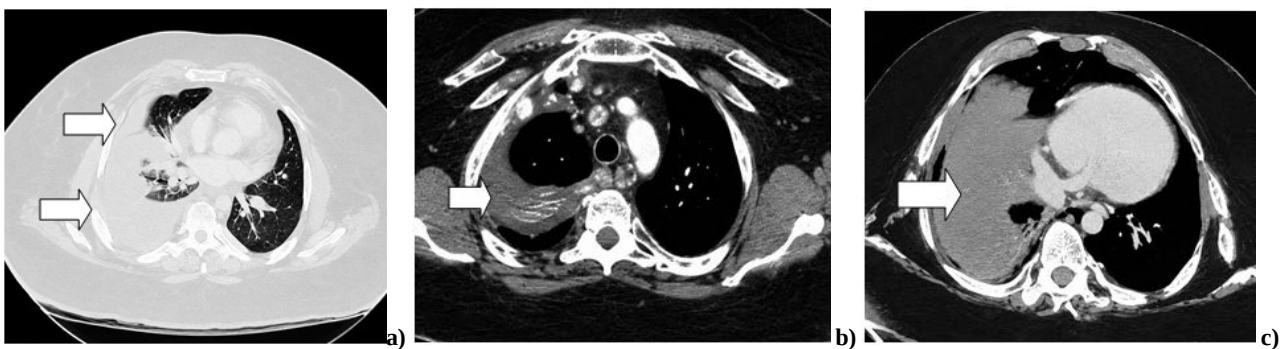


Fig. 4 – Multidetector computed tomography of the chest in the axial plane (a–c) demonstrating a large right-sided pleural effusion and thickening of the costal and diaphragmatic pleura (arrowed).

revealed diffuse thickening of the parietal pleura with nodular deposits distributed across its entire surface, as well as nodular involvement of the diaphragmatic and visceral pleura. Representative biopsy specimens were obtained from multiple areas of the parietal, diaphragmatic, and visceral pleura. Samples were taken from macroscopically suspicious regions whenever technically feasible. The procedure was completed without intraoperative or delayed complications. Histopathologic evaluation confirmed epithelioid MM supported by a characteristic immunohistochemical profile demonstrating diffuse positivity for calretinin, Wilms tumor 1 (WT1), podoplanin (D2-40), and cytokeratin 5/6 (CK5/6),

with negative staining for epithelial cell adhesion molecule BerEP4 and epithelial-related antigen MOC31. The immunophenotypic profile was consistent with epithelioid MM and argued against metastatic adenocarcinoma, including primary pulmonary adenocarcinoma. In combination with radiologic evidence of diffuse pleural involvement without an identifiable pulmonary parenchymal mass, the overall clinicopathologic findings supported the diagnosis of epithelioid pleural MM.

Histopathologic and immunohistochemical samples were analyzed using a microscope equipped with a Leica ICC50 W digital camera (Figures 5–8).

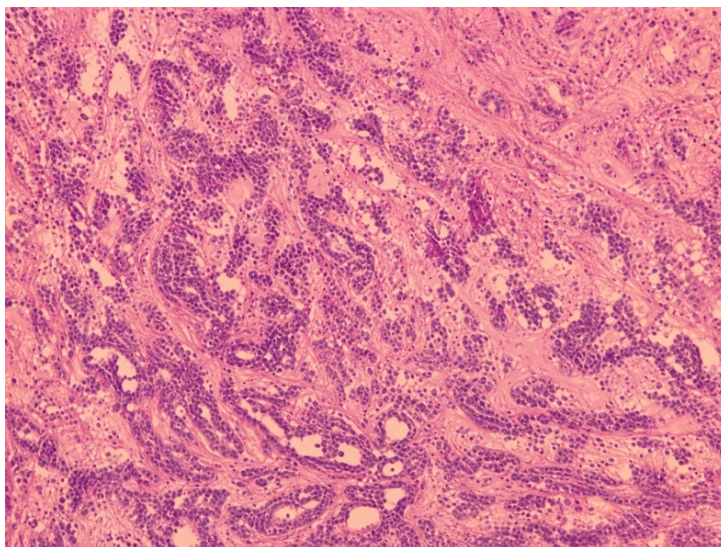


Fig. 5 – Epithelioid malignant mesothelial cells infiltrating connective and adipose tissue with tubulopapillary architecture (hematoxylin-eosin staining, magnification $\times 20$).

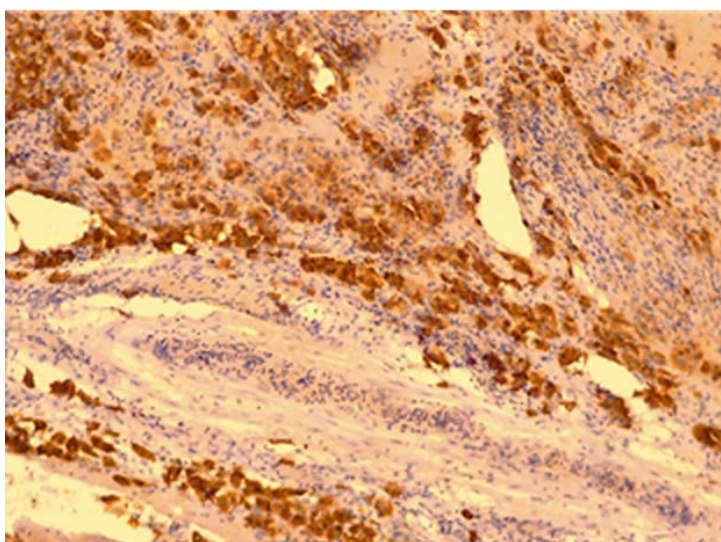


Fig. 6 – Tumor cells demonstrate strong cytoplasmic and membranous positivity for calretinin, with nuclei counterstained blue with hematoxylin. The positive cells are arranged in irregular clusters and cords within a fibrous stromal background (immunohistochemical staining for calretinin, magnification $\times 50$).

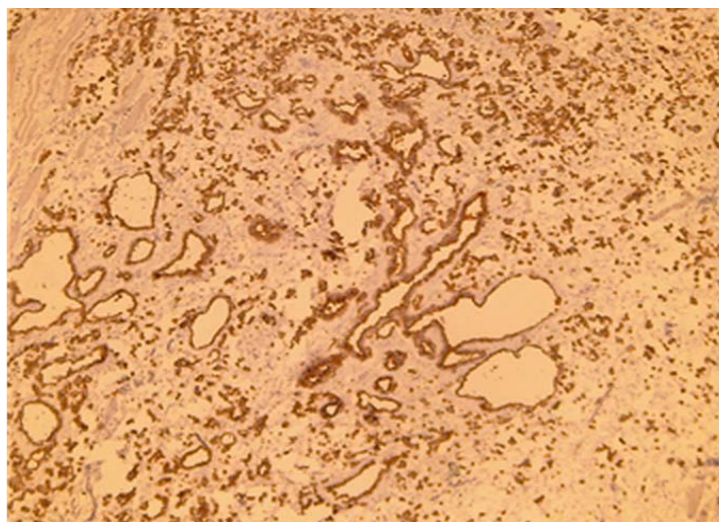


Fig. 7 – Tumor cells demonstrate strong membranous and cytoplasmic positivity for D2-40, evidenced by dark brown staining. The positive cells line tubulopapillary and irregular luminal structures within a fibrous stromal background containing scattered negative cells. Nuclei are counterstained blue with hematoxylin (immunohistochemical staining for D2-40, magnification $\times 10$).

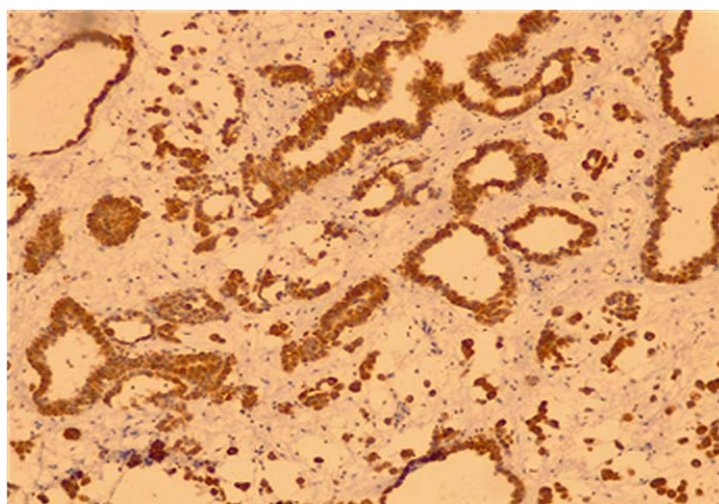


Fig. 8 – Tumor cells demonstrate strong cytoplasmic and membranous positivity for cytokeratin 5/6 (CK5/6), highlighted by dark brown staining. The positive cells form prominent tubulopapillary and trabecular structures within a fibrous stromal background. Nuclei are counterstained blue with hematoxylin (immunohistochemical staining with CK5/6, magnification $\times 50$).

As the patient was treated 8 years ago, disease staging was determined according to the International Association for the Study of Lung Cancer – IASLC 8th edition tumor-node-metastasis – TNM classification for malignant pleural mesothelioma, which was valid at that time ¹⁹. Based on diffuse parietal pleural thickening with nodularity involving the parietal, diaphragmatic, and visceral pleura, in the absence of regional lymph node involvement or distant metastases, the disease was classified as T3N0M0, corresponding to stage III pleural MM.

A multidisciplinary tumor board comprising thoracic surgery, medical oncology, radiology, and pathology rec-

ommended a cytoreductive surgical strategy consisting of pleurectomy and decortication, with the option of pericardial reconstruction, based on the locally advanced yet predominantly epithelioid disease and the absence of distant metastases.

Despite comprehensive counseling regarding the therapeutic objectives, potential risks, and expected outcomes, the patient's family, including his legal guardian and mother, declined surgical intervention, and surgery was not performed. The patient underwent additional evaluation by the oncology tumor board. In accordance with the standard treatment protocol at that time, a nonsurgical multimodal approach was

recommended, consisting of first-line systemic chemotherapy with pemetrexed (500 mg/m²) and cisplatin (75 mg/m²) administered every 21 days with appropriate vitamin supplementation, combined with integrated palliative and supportive measures to control pain, dyspnea, and pleural effusions.

He completed six cycles of pemetrexed-cisplatin chemotherapy without significant adverse effects. Imaging performed during and after treatment showed a favorable tumor response, with a partial response according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST)²⁰.

The patient was followed regularly with scheduled clinical and radiologic evaluations. Two years later, radiologic assessment revealed disease progression according to mRECIST criteria, accompanied by recurrent right-sided pleural effusion. Reinduction systemic chemotherapy was recommended by the multidisciplinary team. However, consent from the legal guardian was not obtained, and additional systemic treatment was not initiated.

Recurrent symptomatic pleural effusions were initially treated with four therapeutic thoracenteses, followed by talc pleurodesis, resulting in sustained control of pleural fluid recurrence. Overall survival was 7 years from the time of MM diagnosis. The final 9–12 months were characterized by gradual disease progression with moderate but symptomatic pleural effusions, managed with repeated drainages and a second pleurodesis procedure. The patient remained independent in activities of daily living until the late stage of the disease, with effective palliative control of pain and dyspnea.

Discussion

This report presents a complex and unusual case of coexistence of two rare conditions, BBS and MM, highlighting possible biological links and the associated diagnostic and therapeutic challenges.

A previous report has described various malignancies in individuals with BBS, including renal, hepatic, and gastrointestinal tumors, suggesting a potentially increased oncologic risk within this population²¹.

A review of the available literature revealed no previously reported cases of this highly unusual coexistence, underscoring the uniqueness of the present case.

Despite advances in diagnostic methods and the introduction of novel systemic therapies, the median overall survival of MM remains between 12–18 months in most reported series, particularly in advanced stages of the disease and in the absence of surgical management²². In this context, the prolonged survival of our patient, well beyond the expected median survival, represents an exceptional clinical course.

Several factors may have contributed to the unexpectedly prolonged survival observed in our patient. First, the tumor was of the epithelioid subtype, which is associated with a more favorable prognosis than sarcomatoid or biphasic mesothelioma. Second, despite locally advanced disease, there was no evidence of distant metastatic spread or lymph node involvement at diagnosis. Third, the patient achieved a

partial response to first-line pemetrexed-cisplatin chemotherapy, followed by prolonged disease control. In addition, effective management of recurrent pleural effusions with repeated thoracenteses and talc pleurodesis contributed substantially to symptom control, preservation of functional status, and maintenance of quality of life. Finally, it remains speculative whether underlying molecular or biologic characteristics associated with BBS-related ciliary dysfunction may have influenced tumor behavior and contributed to a less aggressive clinical course.

Establishing the diagnosis was particularly challenging. The subacute presentation with chest pain and dyspnea was nonspecific and could resemble benign pleuropulmonary disorders. Although the presence of pleural effusion and diffuse pleural thickening on imaging raised suspicion for MM, these findings were insufficient to definitively distinguish it from chronic inflammatory conditions or secondary malignant involvement.

As in most published series, cytological evaluation of the pleural effusion was nondiagnostic, consistent with the well-recognized limitation of cytology in the assessment of MM^{23, 24}.

VATS pleural biopsy and, less frequently, open surgical biopsy can provide representative tissue samples from multiple pleural regions, enabling definitive histologic and immunohistochemical confirmation of MM, although open surgical biopsy is rarely required in contemporary clinical practice²⁵.

The differential diagnosis of epithelioid mesothelioma primarily includes metastatic adenocarcinomas, particularly primary lung adenocarcinoma²⁶. In our case, the combination of positive mesothelial markers (calretinin, WT1, D2-40, CK5/6) and negative epithelial markers (BerEP4 and MOC31), together with the absence of a pulmonary parenchymal mass on imaging, strongly supported the diagnosis of malignant pleural mesothelioma.

The presence of BBS further complicated both the diagnostic evaluation and therapeutic decision-making. As a prototypical ciliopathy, it is characterized by primary ciliary dysfunction leading to widespread disturbances in cellular signaling and a multisystem phenotype that includes retinopathy, obesity, skeletal and renal abnormalities, and often cognitive impairment²⁷.

In our patient, the presence of intellectual disability, which had resulted in legal incapacity and guardianship, substantially influenced the process of obtaining informed consent, particularly in relation to invasive diagnostic procedures and therapeutic options.

From a therapeutic standpoint, cytoreductive surgery (pleurectomy/decortication) within a multimodal treatment strategy was recommended, which was consistent with treatment recommendations at that time for selected patients with locally advanced epithelioid MM. In the absence of consent from the legal guardian, surgical intervention could not be performed, restricting management to systemic chemotherapy and palliative measures. Treatment with the standard pemetrexed-cisplatin regimen achieved a partial response, consistent with the established benefit of

this combination demonstrated in randomized clinical trials²⁸.

At the time treatment was initiated, immunotherapy with immune checkpoint inhibitors (nivolumab and ipilimumab) was neither available nor recommended as first-line therapy. Evidence supporting this approach emerged later, when the CheckMate 743 trial²⁹ demonstrated improved overall survival compared with chemotherapy in patients with unresectable MM. Effective control of recurrent pleural effusions through thoracenteses and talc pleurodesis played an important role in symptom relief, preservation of functional status, and maintenance of quality of life³⁰. Together with the partial response achieved with pemetrexed-cisplatin chemotherapy and the epithelioid histologic subtype, these factors may have contributed to the unusually prolonged survival observed in our patient.

Pathogenetically, this case raises the question of a potential link between ciliopathy and the development of MM. Primary cilia function as cellular signaling organelles involved in the regulation of proliferation, differentiation, and responses to the microenvironment, and their dysfunction is increasingly implicated in the pathogenesis of various malignancies³¹.

At the same time, the role of genetic predisposition in MM has already been well established, particularly through the BAP1 tumor predisposition syndrome, in which germline *BAP1* mutations markedly increase the risk of mesothelioma as well as other malignancies³².

An additional potential pathogenetic mechanism may involve impaired mucociliary clearance. Beyond asbestos exposure, various environmental factors have been implicated in MM development. It is therefore conceivable that impaired mucociliary clearance, resulting in reduced elimination of potential etiologic agents from the airways, may contribute to disease initiation.

In our case, a germline *BAP1* mutation was not identified, yet the occurrence of MM in a young patient with a confirmed ciliopathy raises the hypothesis that ciliary dysfunction may create a microenvironment more permissive to malignant transformation of mesothelial cells, even in the absence of classical asbestos exposure.

Although isolated malignancies have been reported in patients with BBS, a definitive association between BBS and increased cancer predisposition has not been established²¹.

Conclusion

Although a single case cannot establish a causal relationship between Bardet-Biedl syndrome and mesothelioma, it raises the possibility of a pathogenetic link that warrants further investigation. This case also highlights important diagnostic and therapeutic challenges, including nonspecific clinical presentation, limitations related to cognitive impairment and legal guardianship, and the need for an individualized multidisciplinary treatment approach. Further studies, particularly those incorporating molecular profiling in patients with ciliopathies, may help clarify the role of ciliary dysfunction in mesothelioma pathogenesis and identify potential therapeutic targets.

Conflicts of interest

The authors declare no conflict of interest.

Informed consent statement

As the patient was deceased, written informed consent for publication was obtained from the patient's legal representative (mother), who was authorized to access the medical records and pictures.

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Based on the decision of the Editorial Board of *Vojnosanitetski pregl*, made at its meeting on September 23, 2026, the following article has been retracted from the journal because it was previously published in an almost identical form ("duplicate publication"):

Taotao Luo, Xuezhi Zhang, Yating Luo, Boqi He, Yongle Xie. Protective effect of dexmedetomidine combined with remifentanyl on perioperative brain tissue in patients with severe traumatic brain injury and its influence on serum inflammatory markers. *Vojnosanit Pregl* 2025; 82(6): 325–334 (DOI: 10.2298/VSP241231037L)

Previously published article:

Wu Xiaoxia, Zhou Hu. Application of remifentanyl in postoperative ICU sedation and analgesia in patients with severe craniocerebral trauma. *Chin J Clin Pharmacol Ther* 2022; 27(10): 1119–1124 (DOI: 10.12092/j.issn.1009-2501.2022.10.006) (Chinese).

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Authors who have used any AI tools are required to submit an [AI Use Statement](#) when submitting the manuscript.

TYPES OF MANUSCRIPTS

VSP publishes the following categories and types of manuscripts and communications: Editorial, Original Article, Preliminary Report, Short Report, Case Report and Case Series, General (Narrative) Literature Review, Mini-Review, Systematic Literature Review, Meta-Analysis, Systematic Literature Review with Meta-Analysis, Current Topic, In Focus, Article on the History of Medicine/Dentistry/Pharmacy, Letter to the Editor, Research Letter, Clinical Research, Congress and Scientific Meeting Report, Book Review, In Memoriam, and other contributions.

ORIGINAL ARTICLE

An Original Article presents new and significant findings in a specific field, with a detailed description of the research methods used, the results obtained, and the conclusions drawn. The reference list should include the most recent and most relevant references in the field.

PRELIMINARY REPORT

A Preliminary Report presents research that has not yet been completed, with findings that require further investigation and validation before final conclusions can be drawn, but where the obtained information is of interest to the scientific and professional community. It contains all sections of an Original Article, but in a substantially abbreviated form. Authors are encouraged to subsequently publish a full Original Article with complete, validated data and a comprehensive analysis.

SHORT REPORT

A Short Report presents a completed research study that is small in scope, narrowly focused, and has clear conclusions based on the presented results. It includes all sections of an Original Article, but in a substantially abbreviated form. It is considered the final publication of that specific, limited study and cannot be republished as a full-length article (although follow-up research building on it is encouraged).

REVIEW ARTICLES

GENERAL (NARRATIVE) LITERATURE REVIEW

A General (Narrative) Literature Review provides a review, critical analysis, and synthesis of existing scientific knowledge on a selected topic. Authors cover all available relevant literature over a defined time period, present the results of relevant studies, identify gaps, limitations, or controversies, and indicate directions for future research, offering their own perspective on the issue in the form of concluding remarks.

Authors of this category of article should have published at least five papers in peer-reviewed journals (M20) in the field of the review topic.

MINI-REVIEW ARTICLE

A Mini-Review provides a concise overview of the existing literature and the most recent advances within defined aspects of a particular research field, as well as its new and/or current directions of development.

SYSTEMATIC LITERATURE REVIEW

A Systematic Literature Review synthesizes previously published studies on a specific topic using clearly defined and pre-established methodological procedures for study selection and evaluation. The author must use relevant databases, define inclusion and exclusion criteria, and apply a transparent methodology.

META-ANALYSIS

A Meta-Analysis uses statistical methods to combine quantitative data from multiple primary studies in order to identify overall trends and assess the strength of evidence on a specific topic. Authors must use relevant databases, define inclusion and exclusion criteria, and apply a transparent and reproducible methodology. The research question must be clearly defined using the PICOS framework, and selection guidelines and a study flow diagram (PRISMA) must be provided.

SYSTEMATIC LITERATURE REVIEW WITH META-ANALYSIS

A Systematic Literature Review with Meta-Analysis combines qualitative and quantitative synthesis, using statistical techniques to summarize quantitative results and qualitative synthesis for descriptive/narrative findings. Authors must use relevant databases, clearly define inclusion and exclusion criteria, and apply a transparent and reproducible methodology. The research question must be clearly defined according to the PICOS framework, with specification of the reporting guidelines used (e.g., PRISMA) and inclusion of a PRISMA flow diagram showing study selection.

CURRENT TOPIC

A Current Topic addresses a contemporary, unresolved, or controversial issue of theoretical and practical importance, presenting the authors' own research

results or the most recent important data from the literature. The structure of the article is flexible, and brief concluding remarks with a clear message are encouraged.

IN FOCUS

An In Focus article provides a thematic, focused analysis or a brief overview of a scientific issue within the journal's scope, addressing a topic of significance for the scientific community and broader professional audience.

CASE REPORTS

CASE REPORT and CASE SERIES (≥4, ≤9)

Case reports or case series present cases with rare or unusual diagnoses, diagnostic processes, treatment strategies, clinical courses, or treatment outcomes that may be useful for clinical practice and medical education. The CARE guidelines should be followed when preparing the manuscript (<https://www.care-statement.org/writing-a-case-report>). Written informed consent from the patient is mandatory.

EDITORIAL

Editorials are non-peer-reviewed texts written by the Editor-in-Chief and/or members of the Editorial Board, intended to announce a new volume, special issues, or content of significance for the profession and/or institutions served by the journal, as well as invited editorial texts. Editorials should not contain unpublished or original data, and must include a statement of conflict of interest.

LETTER TO THE EDITOR

A non-peer-reviewed comment or critique of a paper published in VSP. It is written in a free format, with optional citation of relevant literature, and must not contain unpublished results. It is published at the discretion of the Editor-in-Chief.

RESEARCH LETTER

A Research Letter is a short report of original research, containing Introduction, Methods, Results, and Discussion in a condensed form (without separate sections or subheadings) and up to 2 supplementary items (tables/figures). It does not include an abstract or keywords, but must meet all general manuscript requirements for consideration, including the peer-review process.

HISTORY OF MEDICINE/STOMATOLOGY/PHARMACY

Manuscripts presenting material relevant to elucidating specific events and/or portraying notable figures in the history of medicine/stomatology/pharmacy, with particular emphasis on military medicine/stomatology/pharmacy.

CLINICAL RESEARCH

Clinical Research includes original randomized controlled trials and observational studies assessing the impact of one or more interventions or measures on human health outcomes, clinical practice, or health policy.

Manuscripts must be prepared in accordance with international guidelines (e.g., CONSORT – <https://www.consort-statement.org/> or STROBE – <https://www.strobe-statement.org/>) and be registered in a recognized public registry (e.g., ClinicalTrials.gov).

BOOK REVIEW

A Book Review includes bibliographic details of the publication (authors, original title, publisher, place, and year of publication), a brief summary, and critical comments on the content, style, and significance of the book in the relevant field. The manuscript must not exceed 2 pages.

SCIENTIFIC MEETING REPORT

A Scientific Meeting Report presents the activities of a scientific or professional meeting, highlighting the most important presentations, conclusions, or recommendations relevant to the wider readership of VSP.

MANUSCRIPT LENGTH

A complete manuscript consists of: title page, abstracts in Serbian and English with keywords, main text, acknowledgements (if applicable), reference list, and supplementary material (tables, figures, charts, diagrams, drawings).

For Original Article, General (Narrative) Literature Review, Systematic Literature Review, Meta-Analysis, and Systematic Literature Review with Meta-Analysis, the manuscript length may not exceed 5,000 words.

For Mini-Review, Preliminary Report, Short Report, Case Report, Case Series, Current Topic, Clinical Research, and History of Medicine/Stomatology/Pharmacy, the manuscript length may not exceed 3,000 words.

Manuscripts in other categories/sections may have a maximum of 1,500 words.

MANUSCRIPT PREPARATION

TITLE PAGE

The first page of the manuscript should include the following:

1. Title of the manuscript without abbreviations;
2. Full names of all authors (without academic titles, but with ORCID numbers included for those who have them) with symbols assigned in the following order: *, †, ‡, §, ||, ¶, **, ††... etc.;
3. Full official names of the institutions where the authors work, including city and country of the institution (the symbols *, †, ‡, §, ||, ¶, **, ††... etc. correspond to the institutions of each author);
4. At the bottom of the page, provide the name and surname, postal address, email address, and phone number (mobile/Viber or WhatsApp) of the author responsible for correspondence.

ABSTRACT

The abstract and keywords should be provided on the second page of the manuscript. The abstract should be written in short and clear sentences. For the

categories Original Article, Preliminary Report, Short Report, Systematic Literature Review, Systematic Literature Review with Meta-Analysis, Meta-Analysis, and Clinical Research, the abstract must be structured and include the following sections: Introduction/Aim, Methods, Results, Conclusion. Each section should be written as a separate paragraph beginning with a bolded heading. The most important results should be presented, including numerical values and the level of statistical significance. The conclusion must be directly related to the study results. The abstract must not exceed 300 words.

For the categories Case Report and Case Series, the abstract should have the following structure: Introduction (with the aim stated in the last sentence), Case Report, Conclusion. Each section should be written as a separate paragraph beginning with a bolded heading. The abstract must not exceed 250 words.

For all other manuscript categories: General (Narrative) Literature Review, Mini Review, Current Topic, In Focus, and History of Medicine/Stomatology/Pharmacy, the abstract is unstructured and must not exceed 200 words.

Care should be taken in ensuring that the Serbian and English versions of the abstract are accurate and precise translations of each other. No sentence may appear in one version without being translated into the other.

KEYWORDS

Below the abstract, list five to seven relevant keywords or phrases that indicate the content of the manuscript. It is recommended to avoid repeating words from the title of the paper. When selecting keywords, use Medical Subject Headings (MeSH) (<https://www.nlm.nih.gov/mesh/meshhome.html>).

STRUCTURE OF THE MAIN TEXT

Original Articles, Preliminary Reports, Short Reports, Meta-Analyses, Systematic Literature Review, Systematic Literature Reviews with Meta-Analysis, and Clinical Research papers must include the following sections: Introduction (a brief overview of the research topic, with the study aim stated in the final paragraph); Methods (a precise description of participant selection and applied methods, including statistical methods, and the approval number of the competent Ethics Committee); Results (presented in a logical order, without duplicating the same results in multiple forms); Discussion (without repeating data already presented in the Results section; only the obtained findings should be discussed, placing them in the context of other relevant studies; the discussion and conclusions should be linked to the study aims, and study limitations should be highlighted if necessary); Conclusion (derived directly from the study results); Acknowledgements (if applicable); References.

Manuscripts in the categories General (Narrative) Literature Review, Mini-Review, Current Topic, and In Focus should contain the following sections: Introduction (with appropriate subheadings), Conclusion, and References.

Manuscripts in the categories Case Report and Case Series should include the following sections: Introduction (the aim of the paper should be stated in the final paragraph of the Introduction), Case Report (the patient's identity must remain anonymous), Discussion, and References.

A Case Report must not have more than five authors.

QUESTIONNAIRES

All questionnaires used as measurement instruments for any of the investigated parameters must be translated into the language spoken by the study participants, with evidence provided of their validation and cultural adaptation to the participants' setting.

TABLES AND FIGURES

Tables and figures, the number of which should be appropriate to the length of the text, should be placed at the end of the main manuscript text, after the References. The exact position of each item should be clearly indicated in the text. The final placement of tables and figures will be determined during manuscript preparation for publication.

Tables

The title should be placed above the table, and explanations (the legend) below it. Tables should be numbered with Arabic numerals in the order in which they appear in the text. Tables must be created exclusively in the Microsoft Word program using the menu Table-Insert-Table, with the exact number of rows and columns defined. Use Times New Roman font, 12-point size, single spacing. Tables must be clear and include all elements necessary for the proper interpretation of the data presented. If the displayed values have ranges or reference values, these must be specified.

In the legend below the table, all abbreviations used in the table and all symbols (e.g., superscript letters or bolded values) must be explained. In addition, the applied statistical methods must be clearly specified.

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Figures include all forms of graphical material (photographs, drawings, diagrams, and graphs). Figures should be embedded in the manuscript at the end of the text, after the References and after the Tables (if any). Figures should be numbered with Arabic numerals in the order in which they appear in the text. Capital letters A, B, C, etc., should be used to designate parts of multipart figures. Letters, numbers, and symbols must be clear, consistent, and of sufficient size to remain legible after reduction. All elements shown in figures must be saved as images (not as editable graphic objects) so that their position cannot be altered, ensuring the accuracy of the data presented. Only digital images with a minimum resolution of 300 dpi and in JPEG, PNG, or PDF format are accepted. Figures that do not meet these requirements will not be accepted for publication. The dimensions of submitted figures should be approximately the same as the dimensions at which they will be published. If authors are unable to provide digital photographs, original images should be scanned at a resolution of 300 dpi and at their original size and submitted in that form. All text in diagrams and graphs should be written in a sans-serif font for

better readability (e.g., Arial, Helvetica), with a font size of no less than 10 pt. Measurement units and scales must be clearly indicated. Decimal numbers in graphs must be presented with a decimal point, and thousands should be separated by a comma (e.g., 1,234.56).

Video supplements (illustrations of the manuscript) may last 1–3 minutes and should be submitted in AVI or MP4 (FLV) format. A separate still image representing the video (video thumbnail) must also be provided for use in the electronic edition and publication in the printed edition, along with a link to the platform where the video is already hosted.

In the legend below each illustration, all abbreviations, symbols, numbers, or letters used to explain individual parts of the figure must be defined. For graphs, the applied statistical methods should be specified where appropriate; for photomicrographs, details of the staining method and magnification must be provided.

If photographs of persons (patients) are presented, the face must be blurred or written consent must be obtained from the person depicted. In imaging materials (X-rays, CT scans, ultrasound images, etc.), all information that could identify the patient must be removed. If a figure has been previously published, the source must be cited, and written permission must be obtained if the material is protected by copyright.

ABBREVIATIONS

Abbreviations should be used only when necessary, primarily for very long names of chemical compounds or for terms that are already widely recognized in abbreviated form (e.g., DNA). For each abbreviation—except standard units of measurement—the full term must be given at its first occurrence in the text (including the abstract). The use of abbreviations should be avoided in the title and abstract; in the title, abbreviations should be used only if absolutely necessary. For terms mentioned more than 3 times in the text, introducing appropriate abbreviations is recommended.

DECIMAL NUMBERS

In manuscripts written in English, decimal numbers should be written with a decimal point (e.g., 22.7), whereas in manuscripts written in Serbian, a comma should be used (e.g., 22,7). Whenever possible, numbers should be rounded to one decimal place and reported consistently throughout the manuscript (e.g., if one value is 32.2, all others should also be rounded to one decimal place, e.g., 32.0).

UNITS OF MEASUREMENT

Length, height, weight, and volume should be expressed in metric units (meter – m, kilogram (gram) – kg (g), liter – L) or their subunits. Temperature should be expressed in degrees Celsius (°C), and blood pressure in millimeters of mercury (mm Hg). Results of clinical and biochemical measurements should be reported in metric units according to the International System of Units (SI).

ACKNOWLEDGEMENTS

The contributions of individuals who should be acknowledged but do not meet the criteria for authorship should be stated. Financial support (sponsorships, grants, equipment, etc.) should be disclosed, as well as the name of the project within which the research was conducted.

STATISTICAL ANALYSIS

In the Methods section, the applied statistical methods should be described in sufficient detail to allow verification of their correct use and reproduction of the analysis. Results must be presented numerically and clearly, with appropriate measures of variability and reliability (e.g., standard deviation, standard error, confidence interval). The type of study should be specified, and the manner in which it was conducted should be described. Inclusion and exclusion criteria must be stated. The software and the version of the computer program used for statistical data analysis should be reported. In the Results section, as well as in the legends of tables and/or figures, the statistical method used to analyze the presented results must be indicated. The *p* values should always be written with a leading zero (e.g., *p* > 0.05, not *p* > .05).

REFERENCES

References should be numbered with Arabic numerals according to the order of their first appearance in the text (including tables and figure legends). It is recommended that the majority of cited references be published within the last ten years. At least 80% of the cited references should be original research articles, while books, book chapters, and review articles should account for no more than 20% of the total number of references. All references, regardless of the language of the original source, must be cited in English, with the original language indicated in parentheses after the reference.

All data on the references must be accurate, and the cited works should be easily accessible to readers. A DOI number must be provided for each reference. Citation of articles published in journals indexed in Current Contents, Index Medicus (MEDLINE), Excerpta Medica, Scopus, and Web of Science is recommended.

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References should be formatted according to the Vancouver style established by the ICMJE (https://connect.ebsco.com/s/article/Citing-Articles-in-Vancouver-ICMJE-Style?language=en_US).

Citation examples:**Article with 1 to 6 authors**

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Article with more than 6 authors

Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2017; 13(3): 479–504. DOI: 10.5664/jcsm.6506

Volume with a Supplement

Smith JA, Brown LM. Effects of vitamin D on immune response. *J Nutr Sci* 2024; 15(Suppl 2): S45–53.

Issue with a Supplement

Zhou Q, Shi R, Kopjar B, Wang H, Chen D, Li H, et al. Adjacent Intervertebral Disc Changes in Patients with Isobar Semirigid Dynamic Stabilization System. *Global Spine J* 2017; 4(1 Suppl): s-0034-1376699.

Volume with Part (Pt)

Ozben T, Nacitarhan S, Tuncer N. Plasma and urine sialic acid in non-insulin dependent diabetes mellitus. *Ann Clin Biochem* 1995; 32(Pt 3): 303–6.

Issue with Part (Pt)

Poole GH, Mills SM. One hundred consecutive cases of flap lacerations of the leg in ageing patients. *N Z Med J* 1994; 107(986 Pt 1): 377–8.

Issue with no Volume

Turan I, Wredmark T, Fellander-Tsai L. Arthroscopic ankle arthrodesis in rheumatoid arthritis. *Clin Orthop* 1995; (320): 110–4.

No Volume or Issue

Browell DA, Lennard TW. Immunologic status of the cancer patient and the effects of blood transfusion on antitumor responses. *Curr Opin Gen Surg* 1993; 325–33.

Pagination with Roman numerals

Fisher GA, Sikic BI. Drug resistance in clinical oncology and hematology. Introduction. *Hematol Oncol Clin North Am* 1995; 9(2): xi–xii.

Book**Printed Book**

Ritter JM, Flower RJ, Henderson G, Loke YK, MacEwan D, Robinson E, et al. Rang & Dale's Pharmacology. 10th ed. London: Elsevier; 2023. p. 3630.

Book in electronic format

Shreeve DF. Reactive attachment disorder: a case-based approach [Internet]. New York: Springer; 2012 [cited 2012 Nov 2]. 85 p. Available from: <http://dx.doi.org/10.1007/978-1-4614-1647-0>

Chapter**In an edited book**

Metcalfe CS, Smith MD, Wilcox KS. Pharmacotherapy of the Epilepsies. In: Brunton LL, Knollmann BC, editors. Goodman & Gilman's The pharmacological basis of therapeutics. 14th ed. NY: McGrawHill; 2023. p. 385–411.

In an edited electronic (online) book

Halpen-Felsher BL, Morrell HE. Preventing and reducing tobacco use. In: Berlan ED, Bravender T, editors. Adolescent medicine today: a guide to caring for the adolescent patient [Internet]. Singapore: World Scientific Publishing Co.; 2012 [cited 2012 Nov 3]. Chapter 18. Available from: http://www.worldscientific.com/doi/pdf/10.1142/9789814324496_0018

Website**Homepage**

Diabetes Australia. Diabetes globally [Internet]. Canberra ACT: Diabetes Australia; 2012 [updated 2012 June 15; cited 2012 Nov 2]. 85 p. Available from: <http://www.diabetesaustralia.com.au/en/Understanding-Diabetes/Diabetes-Globally/>

Part of a website

Australian Medical Association [Internet]. Barton ACT: AMA; c1995-2012. Junior doctors and medical students call for urgent solution to medical training crisis; 2012 Oct 22 [cited 2012 Nov 2]; [about 3 screens]. Available from: <https://ama.com.au/media/junior-doctors-and-medical-students-call-urgent-solution-medical-training-crisis>

Conference Proceedings

Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996.

Article from Conference Proceedings

Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6–10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561–5.

Dissertation

Knežević D. The importance of decontamination as an element of complex therapy of poisoning with organophosphorous compounds [Ph.D. Thesis]. Belgrade: School of Veterinary Medicine; 1988. (Serbian)

Other published articles**News article**

Vujadinović J. The inconsistency between federal and republican regulation about pharmacies. In between double standards. *Borba* 2002 February 28; p. 5. (Serbian)

Holy Bible

Serbian Bible. Belgrade: British and Foreign Biblical Society; 1981. Book of Isaiah 2: 19–22. (Serbian)

Dictionaries and similar references

Kostić AD. Multilingual Medical Dictionary. 4th Ed. Belgrade: Nolit; 1976. Erythrophobia; p. 173–4.

Other examples of citing publications can be seen at https://www.nlm.nih.gov/bsd/uniform_requirements.html

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УПУТСТВО ЗА АУТОРЕ

Пре подношења рукописа за разматрање за објављивање у часопису „Војносанитетски преглед“ (ВСП) неопходно је да аутори пажљиво прочитају Упутство за ауторе, како би рукопис припремили у складу са пропозицијама часописа.

Рад који не испуњава услове овог упутства не може бити разматран и биће враћен ауторима да га допуне и исправе.

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ВСП је доступан у режиму отвореног приступа. Сви чланци могу се бесплатно преузети са сајта часописа и користити у складу са лиценцом **Creative Commons Autorstvo-Deliti pod istim uslovima (CC BY-SA)** (<https://creativecommons.org/licenses/by-sa/4.0/deed.en>).

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Рукопис рада и сви прилози уз рад достављају се **као један документ** (прилози су инкорпорирани у текст и позиционирани на крају рукописа иза одељка Литература) искључиво електронски преко система за пријављивање *Asestant*. Ради очувања квалитета фотографија, препоручује се достављање слика и као посебних фајлова, јер Word може смањити њихову резолуцију, како би се избегла компресија слика и евентуални губитак квалитета.

Сви аутори и рецензенти морају бити регистровани корисници система са јединственом е-маил адресом. Регистрацију је могуће извршити на: <http://asestant.ceon.rs/index.php/vsp/user>. Техничко упутство за коришћење система електронске пријаве доступно је на: <http://asestant.ceon.rs/index.php/vsp/about/submissions>.

Уколико имате проблем са подношењем рукописа путем платформе *Asestant* можете се обратити за помоћ Редакцији часописа слањем е-мејла на адресу: vsp@vma.mod.gov.rs.

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Уколико је део резултата поднетог рукописа претходно саопштен на научном/стручном скупу или је део докторске дисертације, у Пропратном писму Уредништву потребно је навести званичан назив скупа, место и време одржавања, и да ли су саопшћени резултати публиковани и у којој форми (нпр. исти или другачији наслов или сажетак), а у Напомени на крају рукописа то треба посебно назначити.

Радови се објављују на енглеском језику. Поједине категорије радова (нпр. историја медицине/стоматологије/фармације) се по одлуци Уредништва ВСП могу објавити и на српском језику. Све категорије рукописа осим категорија уводник, писмо уреднику, истраживачко писмо, приказ књиге, извештај са научног или стручног скупа се објављују са апстрактима на српском и енглеском језику (у склопу рукописа). О структури и обиму апстракта видети детаљније у одељку Апстракт овог Упутства.

За писање рукописа користити програм *Word*, фонт *Times New Roman*, величину слова 12, проред 1,5. Величину странице подесити на формат А4, са левом маргином од 4 cm а преостале три 2 cm. Текст куцати без дељења речи (хифенирације), а после сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*.

Подаци о коришћеној литератури у тексту означавају се арапским бројевима у суперскрипту, редоследом којим се појављују у тексту.

Странице нумерисати редом у доњем десном углу, почев од прве стране (изузимајући насловну страну).

При писању текста на енглеском језику придржавати се језичког стандарда *American English*. Обавезно је коришћење међународног система мера (SI). Изузетак чине крвни притисак (mm Hg) i temperatura (°C).

Приликом писања користе се стандардне скраћенице. Избежавати скраћенице у наслову и апстракту осим уколико је неопходно. Пун назив са скраћеницом у загради наводи се у њеном првом помињању, а даље у тексту само скраћенице, како у апстракту тако и у главном тексту. У закључку рада (не апстракта) нема скраћеница.

Не користити комерцијална имена лекова и других препарата, а уколико је то неопходно уз њихове називе обавезно навести и генеричка имена. Уређаји (апарати) се означавају фабричким називима, а податке о произвођачу (назив и место) навести у обилм заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или субскрипту.

Избежавати фонтове **bold** и курзив (*italic*) јер су резервисани за поднаслове. Изузети су обавезно писање курзивом оних назива који се тако морају писати (нпр. гени или стране речи - латински).

Групе испитаника морају бити јасно дефинисане и доследно именоване кроз цео рад. За исти појам користити један, јединствен термин кроз цео рад. У одељку Резултати избежавати реченице које почињу са: „Табела X показује“ или „Слика X приказује“. Реченица треба да опише резултат, а ознака

табеле или слике да стоји у загради на крају описа. Реченице не би требало почињати скраћеницом, бројем или датумом. Избежавати предугачке реченице које умањују јасноћу текста и дати предност краћим јасним реченицама. Закључак формулисати новим реченицама, без преписивања већ изречених. Превод радова на енглески језик посредством *Google Translate* може изазвати неразумевање текста и стога се не препоручује.

У избору кључних речи користити *Medical Subject Headings* – *MeSH* (<https://www.nlm.nih.gov/mesh/meshhome.html>). Кључне речи у прихваћеном рукопису не подлежу ауторској коректури, пошто су оне дескриптори из Тезауруса које одређују стручни индекси.

ОБЈАВНА ПРАТЕЋА ДОКУМЕНТА

ИЗЈАВА АУТОРА И АУТОРСТВО

За сваки рукопис који се подноси на разматрање за објављивање у ВСП неопходно је да аутор(и) достави(е) **Образац за изјаву о ауторству (Изјаву аутора)** да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, да су рукопис прочитали и одобрили сви аутори који испуњавају критеријуме ауторства, и контакт податке свих аутора у раду (имејл адресу, број мобилног телефона). У овом обрасцу се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. Сви аутори морају Изјаву аутора потписати својеручно.

За додатне информације о различитим врстама сукоба интереса видети препоруке Светског удружења уредника медицинских часописа (*World Association of Medical Editors* – *WAME*; <http://www.wame.org>).

ВСП поштује препоруке критеријума за ауторство које даје ICMJE (<https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>). Ауторство се заснива на испуњењу сва четири критеријума: значајном доприносу концепцији рада, добијању резултата или анализи/тумачењу резултата; критичкој ревизији рукописа од знатног интелектуалног значаја; одобрењу финалне верзије рукописа која ће бити објављена и преузимању одговорности за све аспекте објављеног садржаја. Сви други учесници који су допринели изради рада, али нису испунили прописане критеријуме требало би да буду наведени у Захвалници уз прецизирање доприноса раду. Потребно је да особе наведене у Захвалници дају писмену сагласност.

ЕТИЧКА САГЛАСНОСТ

Сва истраживања која укључују људе и/или хумани материјал морају бити спроведена у складу са препорукама ICMJE (<https://www.icmje.org/recommendations/browse/roles-and-responsibilities/protection-of-research-participants.html>) и Хелсиншком декларацијом, ревизија 2024 (<https://www.wma.net/policies-post/wma-declaration-of-helsinki/>). Скенирану страну дозволе Етичке комисије (ЕК) надлежне институције које је одобрила истраживање, на којој се види датум издавања и предмет истраживања, аутори су у обавези да доставе истовремено са рукописом. Дозвола ЕК се доставља на језику на коме је издата и енглеском језику (може и оверена копија).

У одељку Методе мора бити наведено да је студија одобрена од стране надлежног ЕК, уз навођење назива институције и броја одлуке, као и да је спроведена у складу са етичким принципима за истраживања која укључују људе и/или хумани материјал.

Анонимност пацијената мора бити заштићена у складу са ICMJE препорукама. За сва истраживања која укључују податке о пацијентима који омогућавају директну или индиректну идентификацију, аутори су обавезни да прибаве писану пристанак информисаног пацијента, да у рукопису назначе да је пристанак пацијента прибављен, и да га по потреби доставе Уредништву.

У случају истраживања на животињама, аутори су дужни да доставе одобрење надлежног ЕК који води бригу о поштовању међународних стандарда о употреби лабораторијских животиња у истраживачке сврхе.

Уредништво може одбити радове за које процени да нису изведени у складу са међународним етичким стандардима.

РЕПРОДУКОВАЊЕ ПРЕТХОДНО ОБЈАВЉЕНОГ ЗАШТИЋЕНОГ МАТЕРИЈАЛА И/ИЛИ НЕОБЈАВЉЕНОГ ТУЂЕГ МАТЕРИЈАЛА

Уколико се користе претходно објављене илустрације (фотографије, схеме) уз обавезно цитирање извора преузимања потребно је доставити дозволу (писано одобрење часописа у коме су објављене) за њихову објаву у ВСП. Уколико се користе туђе необјављене илустрације (фотографије, схеме) потребно је доставити дозволу аутора илустрација, за њихову објаву у ВСП.

ПЛАГИЈАРИЗАМ

Од 2012. године сви рукописи достављени на разматрање у ВСП подвргавају се провери на потенцијални (ауто)плагијаризам посредством *SCIndex Assistant – Cross Check (iThenticate)*. Рукописи код којих се докаже (ауто)плагијаризам биће одбијени. У зависности од степена и врсте утврђеног (ауто)плагијаризама ауторима се може изрећи забрана објављивања у ВСП-у (различите дужине трајања), уз обавештење надлежних тела у институцијама у којима аутори раде и релевантних професионалних удружења.

КОРИШЋЕЊЕ AI

Генеративна вештачка интелигенција (*artificial intelligence-AI*) или технологије које користе помоћ AI (AI-потпомогнуте) могу се користити само уз поштовање начела транспарентности (употреба AI мора бити јасно наведена у рукопису), одговорности (аутори остају у потпуности одговорни за тачност и оригиналност садржаја), проверљивости (сви учесници у публицистичком процесу морају проверити да AI није унела измишљене податке, цитате или тврдње) и поверљивости (ауторима и рецензентима је забрањено учитавање рукописа поднетих у ВСП у јавне AI сервисе).

Употреба AI алата је допуштена само за ограничене језичке и техничке интервенције у тексту рукописа: исправку граматике и правописа, стилско дотеривање ауторског текста, помоћ при формирању, техничку асистенцију (попут исправљања кода). Аутори могу користити AI алате искључиво за креирање AI-потпомогнутог, али не и AI -генерисаног садржаја.

Аутори који су користили AI-потпомогнут садржај у обавези су да потпуно и тачно наведу употребу AI алата (тачан назив AI алата, датум приступа, коришћене упите и сврху употребе), гарантују оригиналност научног доприноса, избегавају било какву фабрикацију или манипулацију и поштују правила научне етике. Информације о коришћењу AI се наводе у одељку Методе или Захвалница.

Забрањено је користити AI алате за генерисање већег дела садржаја рукописа, креирање научних идеја, података и резултата, анализу и интерпретацију резултата, формирање закључака, измену слика, табела или графикона (укључујући графичке сажетке), измену података или референци.

Недовислено утврђена недопуштена употреба AI за последицу има одбијање рада.

AI ни у ком случају не може бити аутор или коаутор рада, нити може као аутор бити цитиран у одељку Литература.

Ради заштите поверљивости, ниједан део необјављеног истраживања достављеног ВСП не сме бити унет у велики језички модел од стране аутора или рецензента.

Аутори који су користили неки од AI алата су у обавези да приликом подношења рукописа поднесу и [Изјаву о коришћењу AI](#).

ТИПОВИ РУКОПИСА

У ВСП се објављују следеће категорије и типови рукописа и саопштења: уводник, оригинални рад, претходно саопштење, кратко саопштење, приказ случаја и серија случајева, општи (наративни) преглед литературе, мини преглед, систематски преглед литературе, мета-анализа, систематски преглед литературе са мета-анализом, актуелна тема, у фокусу, рад из историје медицине/стоматологије/фармације, писмо уреднику, истраживачко писмо, клиничко истраживање, извештај са конгреса и научног скупа, приказ књиге, *In memoriam* и други прилози.

ОРИГИНАЛНИ ЧЛАНАК

Приказује нова и значајна открића у одређеној области уз детаљан опис коришћених метода истраживања, добијених резултата и изведених закључака. Листа референци треба да укључи најновије и најважније референце из области рада.

ПРЕТХОДНО САОПШТЕЊЕ

Представља приказ истраживања која нису завршена, са налазима који захтевају додатна истраживања и валидацију пре коначних закључака, али су добијене информације од интереса за научну и стручну јавност. Садржи сва поглавља као оригинални научни чланак, али у знатно скраћеном обиму. Аутори се подстичу да касније објаве пуну оригиналну научну студију са комплетним, валидираним подацима и свеобухватном анализом.

КРАТКО САОПШТЕЊЕ

Представља завршено истраживање које је мало по обиму, уско фокусирано са јасним закључцима на основу представљених резултата. Садржи сва поглавља као оригинални научни чланак, али у знатно скраћеном обиму. Сматра се коначном публикацијом тог специфичног, малог истраживања. Не може се поново објавити као чланак пуног обима (иако се подстиче накнадно истраживање које се надовезује на њега).

ПРЕГЛЕДНИ ЧЛАНЦИ

ОПШТИ (НАРАТИВНИ) ПРЕГЛЕД ЛИТЕРАТУРЕ

Преглед, критичка анализа и синтеза постојећих научних сазнања о изабраној теми. Аутори обухватају сву доступну припадајућу литературу за одређени временски период, приказују резултате релевантних истраживања, идентификују недостатке, ограничења или контроверзе и указују на правце будућих истраживања, дајући своје виђење проблема у виду закључног става. Аутори чланка ове категорије могу бити они који су објавили минимално пет радова публикованих у часописима са рецензијом (M20) из области прегледног рада.

МИНИ ПРЕГЛЕДНИ ЧЛАНАК

Сажет преглед постојеће литературе и најновијих достигнућа унутар дефинисаних аспеката одређене истраживачке области и њени нови и/или актуелни правци развоја.

СИСТЕМАТСКИ ПРЕГЛЕД ЛИТЕРАТУРЕ

Синтеза претходно објављених истраживања о одређеној теми коришћењем јасно дефинисаних и унапред одређених методолошких поступака за селекцију и евалуацију. Аутор мора да користи релевантне базе података, постави критеријуме укључивања и искључивања студија и примени транспарентну методологију.

МЕТА-АНАЛИЗА

Користи статистичке методе за комбиновање квантитативних података из више примарних студија како би се идентификовали општи трендови и проценила снага доказа о одређеној теми. Аутор мора да користи релевантне базе података, дефинише критеријуме за укључивање и искључивање и примени транспарентну и репродукцибилну методологију. Неопходно је јасно дефинисање истраживачког питања (PICOS оквир), навођење смерница за одабир и дијаграма тока за селекцију студија (PRISMA).

СИСТЕМАТСКИ ПРЕГЛЕД ЛИТЕРАТУРЕ СА МЕТА-АНАЛИЗОМ

Комбинује квалитативну и квантитативну синтезу, користећи статистичке технике за сумирање квантитативних резултата а квалитативну синтезу за описне/наративне налазе. Аутор мора користити релевантне базе података, јасно дефинисати критеријуме за укључивање и искључивање студија, и применити транспарентну и репродукцибилну методологију. Истраживачко питање мора бити јасно дефинисано према PICOS оквиру, уз навођење коришћених смерница за извештавање (нпр. PRISMA) и укључивање PRISMA дијаграма тока за приказ селекције студија.

АКТУЕЛНА ТЕМА

Разматра савремено, нерешено или контрадикторно питање од теоријског и практичног значаја, уз изношење сопствених резултата истраживања или најновијих важних података из литературе. Конструкција чланка је слободна а пожељне су кратке закључне напомене са јасном поруком.

У ФОКУСУ

Тематска, фокусирана анализа и/или кратак осврт на научни проблем који је у тематској области часописа, а који обрађује питање од значаја за научну заједницу и ширу стручну јавност.

КАЗУИСТИКА

ПРИКАЗ СЛУЧАЈА И СЕРИЈА СЛУЧАЈЕВА (≥4, ≤9)

Приказ случајева са ретком и необичном дијагнозом, дијагностичким процесом, стратегијама лечења, клиничким током, или исходом лечења, који могу бити од користи за клиничку праксу и медицинско образовање. Приликом писања потребно је користити CARE смернице (<https://www.care-statement.org/writing-a-case-report>). Неопходан је пристап информисаног пацијента.

УВОДНИК

Уводници су нерцензирани текстови главног и одговорног уредника и/или чланова Уредништва намењени најави новог волумена, тематског броја, садржаја који су од значаја за струку и/или институције чијим члановима је часопис намењен као и уреднички текстови по позиву. Уводници не треба да садрже необјављене или оригиналне податке, а морају укључити изјаву о сукобу интереса.

ПИСМО УРЕДНИКУ

Нерцензирани коментар/критика текста објављеног у ВСП. Пишу се у слободној форми, уз евентуално навођење података из литературе. Не смеју садржати необјављене резултате. Објављују се према одлуци главног и одговорног уредника.

ИСТРАЖИВАЧКО ПИСМО

Кратки приказ оригиналног истраживања, који садржи увод, методе, резултате и дискусију у сажетом облику (без поделе у посебне целине са поднасловима) и максимално до 2 прилога (табеле/слике). Не садржи апстракт и кључне речи али мора да испуни све опште услове за разматрање рукописа (укључујући процес рецензије).

ИСТОРИЈА МЕДИЦИНЕ/СТОМАТОЛОГИЈЕ/ФАРМАЦИЈЕ

Материјал значајан за расветљавање појединих догађаја и/или приказ значајних личности из историје медицине/стоматологије/фармације, а посебно војне медицине/стоматологије/фармације.

КЛИНИЧКО ИСТРАЖИВАЊЕ

Оригинална рандомизована контролисана испитивања и опсервационе студије утицаја једног или више средстава или мера на исход здравља људи, клиничку праксу и здравствену политику. Рукописи морају бити припремљени у складу са међународним смерницама (нпр. CONSORT – <https://www.consort-spirit.org/> или STROBE – <https://www.strobe-statement.org/>) и регистрована у неком од међународно признатих јавних регистара (нпр. ClinicalTrials.gov).

ПРИКАЗ КЊИГЕ

Садржи библиографске податке о публикацији (аутори, изворни наслов, издавач, место и година издања), њен кратак садржај и критичке коментаре садржаја, стила и значаја књиге у датој области. Рукопис не сме бити дужи од 2 странице.

ИЗВЕШТАЈ СА НАУЧНОГ ИЛИ СТРУЧНОГ СКУПА

Приказ активности научног или стручног скупа, уз истацање најважнијих реферата или закључака, односно препорука од значаја за шири круг читалаца ВСП.

ОБИМ РУКОПИСА

Целокупни рукопис рада чине: насловна страна, апстракти на српском и енглеском језику са кључним речима, главни текст рада, захвалност (по потреби), списак литературе, прилози (табеле, слике, графикони, схеме, цртежи).

Обим рукописа за категорије оригинални рад, општи (наративни) преглед литературе, систематски преглед литературе, мета-анализа, систематски преглед литературе са мета-анализом износи до 5 000 речи.

Обим рукописа за категорије мини преглед, претходно саопштење, кратко саопштење, приказ случаја, серија случајева, актуелна тема, клиничко истраживање, историја медицине/стоматологије/фармације износи до 3 000 речи.

Рукописи за остале категорије/рубике могу имати највише 1 500 речи.

ПРИПРЕМА РАДА

НАСЛОВНА СТРАНА

На првој страници рукописа треба навести следеће:

1. Наслов рада без скраћеница;
2. Пуна имена и презимена аутора (без титула, уз навођење ORCID броја за све ауторе који га имају) са ознакама следећим редом *, †, ‡, §, ||, ¶, **, †† ... итд.
3. Пун званичан назив установа у којима аутори раде, место и државу у којој се установе налазе (значи *, †, ‡, §, ||, ¶, **, †† ... итд. показују редом установе у којима аутори раде);
4. На дну стране навести име и презиме, адресу за контакт, е-маил адресу и број телефона (мобилног/Viber или WhatsApp) аутора задуженог за кореспонденцију.

АПСТРАКТ

На другој страни рада пишу се апстракт и кључне речи. Апстракт се пише кратким и јасним реченицама. За категорије оригинални рад, претходно саопштење, кратко саопштење, систематски преглед литературе, систематски преглед литературе са метаанализом, мета-анализа, клиничко истраживање, апстракт је структурисан и треба да има следеће делове: Увод/Циљ, Методе, Резултати, Закључак. Сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) и ниво статистичке значајности. Закључак мора бити директно повезан са резултатима рада. Обим апстракта не сме да пређе 300 речи.

За категорије приказ случаја и серија случајева апстракт има следећу структуру: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак. Сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Обим апстракта не сме да пређе 250 речи.

За остале категорије радова, општи (наративни) преглед литературе, мини преглед, актуелна тема, у фокусу, историја медицине/стоматологије/фармације апстракт нема посебну структуру и не сме да пређе 200 речи.

Водити рачуна да српска и енглеска верзија апстракта буду међусобно тачни и прецизни преводи. Ниједна реченица не сме постојати у једној верзији а да није преведена у другој.

КЉУЧНЕ РЕЧИ

Испод апстракта навести пет до седам релевантних кључних речи или израза који указују на садржај рада. Препорука је да се не понављају речи из наслова рада. У избору кључних речи користити *Medical Subject Headings – MeSH* (<https://www.nlm.nih.gov/mesh/meshhome.html>).

СТРУКТУРА ГЛАВНОГ ТЕКСТА РАДА

Неопходно је да оригинални рад, претходно саопштење, кратко саопштење, мета-анализа, систематски преглед литературе, систематски преглед литературе са мета-анализом, клиничко истраживање садрже поглавља: Увод (кратак приказ предмета истраживања уз навод циља рада у последњем пасусу), Методе (прецизан опис одабира испитаника и примењених метода, укључујући статистичке методе, број дозволе сагласности надлежног ЕК), Резултати (приказани логичким редоследом без дуплирања приказа истих резултата на више начина), Дискусија (без понављања података који су већ наведени у одељку Резултати; дискутовати само добијене налазе довођењем у везу са другим релевантним студијама, повезати дискусију и закључке са циљевима рада, по потреби нагласити лимитације истраживања), Закључак (који проистиче из резултата датог истраживања), Захвалница (по потреби), Литература.

Рукописи из категорија општи (наративни) преглед литературе, мини преглед, актуелна тема, у фокусу садрже следеће целине: Увод (са одговарајућим поднасловима), Закључак, Литература.

Рукописи из категорије приказ случаја, серија случајева садрже следеће целине: Увод (циљ рада навести као последњи пасус Увода), Приказ болесника (идентитет болесника мора остати анониман), Дискусија, Литература.

Приказ болесника не сме имати више од пет аутора.

УПИТНИЦИ (Questionnaires)

Сви коришћени упитници који су употребљени као мерни инструменти за било који од испитиваних параметара, морају бити преведени на језик говорног подручја испитаника уз навођење доказа о извршеној валидацији и културолошкој адаптацији поднебљу испитаника.

ПРИЛОЗИ

Прилоге чији број треба да буде усклађен са дужином текста поставити на крај главног текста рукописа иза Литературе, а у самом тексту јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публикавање.

Табеле

Наслов треба написати изнад табеле, а објашњења (легенду) испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле израдити искључиво у програму Word, кроз мени *Table-Insert-Table*, уз дефинисање тачног броја колона и редова који ће је чинити. Куцати фонтом *Times New Roman*, величином слова 12, с једностраним поредом. Табеле морају бити јасне и имати све елементе неопходне за правилно разумевање шта је у њима приказано. Уколико приказане вредности имају „опсег“ или „референтне вредности“, то се мора додати.

У легенди испод табеле треба објаснити све скраћенице наведене у табели и све ознаке (нпр. слова у суперскрипту или болдоване вредности). Такође, неопходно је прецизирати примењене статистичке методе.

Слике (илустрације)

Под сликама подразумевамо све облике графичких прилога (фотографије, цртежи, схеме и графикони). Слике треба уградити у рукопис на крају текста, после литературе и после табела (ако их има). Слике се означавају арапским бројевима према редоследу навођења у тексту. Велика слова А, Б, Ц итд. треба користити за означавање делова вишеделних слика. Слова, бројеви и симболи треба да су јасни и уједначени, а довољне величине да приликом умањивања буду читљиви. Додаци приказани на сликама морају бити сачувани као фотографије (не као измењиви графички елементи), тако да се њихов положај не може мењати, како би се обезбедила тачност података приказаних на слици. Примају се искључиво дигиталне фотографије са минималном резолуцијом од 300 dpi и формата JPEG, PNG или PDF. Слике које не задовољавају наведене услове неће бити прихваћене за објаву. Димензије достављених слика би требало да буду приближне димензијама у којима ће слика бити објављена. Уколико аутори нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 dpi и у оригиналној величини и као такве их доставити. Сви подаци на схемама и графиконима треба да буду исписани безсерифним фонтом ради лакше читљивости (нпр. *Arial*, *Helvetica*), величина слова не мања од 10 pt. Мерне јединице и скале морају бити јасно назначене. Децимални бројеви на графиконима морају бити приказани са тачком, а раздвајање хиљада мора бити означено резом (нпр. 1,234.56).

Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi*, *mp4(flv)*. Уз видео доставити посебно слику која би била илустрација видео-приказа у е-издању и објављена у штампаном издању, као и линк ка платформи где је видео већ постављен.

У легенди испод илустрација треба објаснити све скраћенице, симболе, бројеве или слова који се користе за објашњење појединих делова слике. У случају графикаона прецизирати примењене статистичке методе (по потреби), а код фотомикрографије навести детаље о врсти коришћеног бојења и увећању.

Уколико се приказују фотографије особа (болесника), лик мора бити „замућен“ или је потребно обезбедити писану дозволу лица са фотографије за њено коришћење. На прилозима (снимци рендгена, скенера, ултразвука, итд.) потребно је уклонити све што може да идентификује болесника. Уколико је слика већ негде објављена потребно је цитирати извор уз писано одобрење ако се ради о заштићеном материјалу.

СКРАЋЕНИЦЕ

Скраћенице користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (нпр. ДНК). За сваку скраћеницу, осим стандардне јединице мере, навести пун назив при првом навођењу у тексту (укључујући апстракт). У наслову и апстракту избежавати коришћење скраћеница, у наслову их користити само ако су неопходне. За појмове који се у тексту помињу више од три пута препоручује се увођење одговарајућих скраћеница.

ДЕЦИМАЛНИ БРОЈЕВИ

У тексту рада на енглеском језику децималне бројеве писати са тачком (нпр. 22.7), а у тексту на српском језику са резом (нпр. 22,7). Кад год је то могуће, број заокружити на једну децималу и писати доследно кроз цео рад (нпр. ако је једна вредност 32.2, све остале морају имати једну децималу, нпр. 32.0).

ЈЕДИНИЦЕ МЕРА

Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – m, килограм (грам) – kg (g), литар – L) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), притисак крви у милиметрима живиног стуба (mm Hg). Резултате клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (SI).

ЗАХВАЛНИЦА

Изнети допринос особе којој треба одати признање, али која не испуњава критеријуме за ауторство. Навести финансијску помоћ (спонзорства, стипендије, опрема и друго), као и назив пројекта у оквиру кога је истраживање спроведено.

СТАТИСТИЧКА АНАЛИЗА

У одељку Методе детаљно описати примењене статистичке методе како би била омогућена провера исправности њихове примене и репродукција анализе. Резултати морају бити нумерички јасно приказани уз одговарајуће показатеље варијабилности и поузданости (нпр. стандардна девијација, стандардна грешка, интервал поверења). Прецизирати тип студије и описати начин на који је изведена. Навести критеријуме укључења и искључења. Навести софтвер и верзију компјутерског програма у коме је извршена статистичка обрада података. У одељку Резултати као и у легендама табела и/или прилога навести статистички метод који је коришћен за анализу приказаних резултата. Вредности *p* се увек пишу са почетном нулом (нпр. *p* > 0.05 а не *p* > .05).

ЛИТЕРАТУРА

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту (укључујући табеле и легенде прилога). Препоручује се да већина цитираних радова буде млађа од десет година. Препоручује се да број цитираних оригиналних радова буде најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Сви радови, без обзира на језик извора, цитирају се на енглеском језику, а изворни језик наводи се у загради, иза цитиране референце.

Сви подаци о цитирању литературе морају бити тачни, а цитирани радови лако приступачни читаоцима. Уз сваку референцу навести DOI број. Препоручује се цитирање само радова објављених у часописима које индексирају *Current Contents*, *Index Medicus (Medline)*, *Excerpta Medica*, *Scopus*, *Web of Science*.

Није дозвољено цитирање апстраката, секундарних публикација, усмених саопштења, необјављених радова, службених и поверљивих докумената, Википедије, препринт објава и *in press* чланака, повучених радова (*retracted article*), радова објављених у предаторским часописима.

Приликом цитирања сајтова, не може се цитирати насловна страна већ се мора цитирати она страна са које је информација преузета. Свака наведена референца мора бити доступна за проверу *online*. Уколико референца не постоји на интернету (нпр. архивски материјал и сл.), аутор мора да достави извор одакле је преузео цитирану литературу односно може сликати или скенирати документ и послати на е-мејл: strliteratura@gmail.com.

Референце се цитирају према Ванкуверском стилу који је успоставио ICMJE (https://connect.ebsco.com/s/article/Citing-Articles-in-Vancouver-ICMJE-Style?language=en_US).

Примери цитирања:

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Nikolić A, Biočanin V, Rančić N, Dušpara M, Đurić D. Serbian translation and validation of the SF-36 for the assessment of quality of life in patients with diagnosed arterial hypertension. *EABR Exp Appl Biomed Res* 2023; 24(3): 227–34. DOI: 10.2478/sjcr-2020-0073

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